TITLE:	**A Phase Ib/II Clinical Study of BBI608 Administered with Paclitaxel in Adult Patients with Advanced Malignancies**
PROTOCOL NUMBER:	**BBI608-201**
STUDY DRUG:	**BBI608**
IND #:	**100,887**
SPONSOR:	**Boston Biomedical, Inc.** **640 Memorial Drive** **Cambridge, MA 02139** **Telephone:** [redacted] **Fax:** [redacted]
MEDICAL MONITOR:	[redacted]
SAFETY FAX:	[redacted]
SAFETY CONTACT:	[redacted]
DATE OF PROTOCOL:	**24 November 2010**
DATE OF AMENDMENT 1:	**20 March 2013**
DATE OF AMENDMENT 2:	**27 March 2015**
DATE OF AMENDMENT 3:	**13 April 2018**
DATE OF AMENDMENT 4:	**10 May 2018**

SYNOPSIS

Study Title:	**A Phase Ib/II Clinical Study of BBI608 Administered with Paclitaxel in Adult Patients with Advanced Malignancies**
Study Number:	BBI608-201
Study Phase:	Ib/II
Study Drug	BBI608, an investigational small molecule anticancer drug, that is hypothesized to affect multiple oncogenic cellular pathways, including inhibition of the STAT3 pathway, which has been implicated in cancer stem cells viability.
Primary Objective:	To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of BBI608 when administered with paclitaxel in adult patients with advanced malignancies
Secondary Objectives:	To determine the pharmacokinetic profile of BBI608 and paclitaxel when administered in combination. To assess the preliminary anti-tumor activity of BBI608 when administered in combination with paclitaxel in patients with advanced malignancies. To assess the objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), and overall survival (OS) of patients with selected tumor types treated with BBI608 in combination with paclitaxel. To determine the pharmacodynamics (biomarkers) of BBI608 when tumor biopsy is possible.
Study Design:	This is an open label, multi-center, dose escalation study of BBI608 administered in combination with a fixed dose of paclitaxel administered IV weekly at 80 mg/m^2 given as a 1 hour infusion; A cycle will consist of daily and continuous oral administration of BBI608 for four weeks in combination with paclitaxel administered IV weekly on day 3, 10 and 17 of each 28 day cycle. If administration of paclitaxel is discontinued due to paclitaxel-related toxicities, the administration of BBI608 will be continued until disease progression if tolerated. The doses of BBI608 will escalate in three patient cohorts until a RP2D is reached. Pharmacokinetics (PK) will be performed for patients enrolled at selected study sites in the first cycle of the study. Pharmacodynamic assessments will be performed in patients with accessible tumors when tumor biopsy is possible. Safety and tolerability of BBI608 in combination with paclitaxel will be assessed for the duration of study treatment. Evaluation of preliminary anti-tumor activity of BBI608 in combination with paclitaxel will be performed at regular intervals while patients remain on study.
Study Population:	This study is conducted in patients with advanced solid tumors for whom weekly paclitaxel is an acceptable option; including, ovarian cancer, cancer, breast cancer, NSCLC, melanoma, and gastric and esophageal adenocarcinoma. Currently the study is only enrolling patients with thymic carcinoma. All patients must have a histologically or cytologically confirmed malignancy that is locally advanced, unresectable, metastatic, or recurrent. Other inclusion criteria for all patients include: age > 18 yrs.; ECOG performance status of 1 or 0; measurable disease; and adequate hepatic, renal, and bone-marrow function. Patients with the tumor types below must also meet the following tumor-type-specific inclusion criteria:

	Ovarian Cancer	Patients must have epithelial ovarian, fallopian tube or primary peritoneal cancer that also meets one of the following definitions: • Platinum resistant: a response to platinum therapy followed by progression within 6 months after completing therapy • Platinum refractory: best response of stable disease or progression during platinum therapy AND • Must have had prior systemic treatment with a taxane • Must have received no more than 5 prior systemic cytotoxic regimens in the metastatic setting with an up-front regimen counted if there is recurrence within 6 months.
	Melanoma	Patients with BRAF wild-type melanoma, or with BRAF mutations that are not amenable to BRAF inhibitor therapy, who are candidates for immunotherapy: • Must have received ipilimumab. Patients with melanoma positive for the V600E or V600K BRAF mutation: • Must have received at least one line of prior therapy with a BRAF-specific inhibitor; either alone or in combination.
	Breast Cancer (Triple Negative)	Patients with estrogen receptor-negative (ER-), progesterone receptor-negative (PR-), and human epidermal growth factor receptor 2-negative (Her2-) breast cancer: • Must have received at least one prior chemotherapy regimen for locally advanced or metastatic disease
	Non Small-Cell Lung Cancer	Patients with NSCLC (adenocarcinoma, squamous, or adenosquamous histopathology) that is specifically, stage IIIB not curable by surgery or radiotherapy, or stage IV: • Must have received at least one prior chemotherapy regimen for locally advanced or metastatic disease. • EGFR-positive or ALK-positive patients must have received at least one line of EGFR-directed therapy or ALK-directed therapy, respectively. • Must have received prior taxane therapy.
	Esophageal/GEJ/ Gastric Adenocarcinoma	Patients with adenocarcinoma arising from the esophagus, gastro-esophageal junction, or stomach:

		• Must have received prior treatment with a platinum/fluoropyrimidine-based therapy with or without an anthracycline in the metastatic setting; or, in the adjuvant setting if recurrence occurred within 6 months of completing systemic adjuvant treatment. Patients with HER2 positive tumors: • Must have had prior treatment with a Her2 inhibitor (e.g. traztuzumab or lapatinib) Patients who have received prior taxane therapy may be enrolled.
	Thymic Carcinoma	Patients with thymic carcinoma: • Must have received at least one prior systemic chemotherapy regimen for metastatic, recurrent, locally advanced or otherwise unresectable disease.
	In the phase 2 portion of the study up to 570 patients with selected tumor types may be enrolled. This total includes patients previously enrolled under prior amendments and up to 15 total patients with thymic carcinoma will be enrolled to complete the study. Patient accrual will occur over a period of time dependent upon the number of cohorts enrolled.	
Test Product, Dose, and Mode of Administration:	Patients in this trial will receive BBI608 orally at dose levels specified for their respective dose cohorts. Administration of BBI608 bid will begin at 500 mg for a total daily dose of 1000 mg/day (first cohort) and escalate until the RP2D or MTD is determined. When BBI608 is administered tid, the dose will start at 200 mg for a total daily dose of 600mg/day and escalated until the RP2D or MTD is determined. In each cycle BBI608 will be taken daily for 4 weeks (28 days). BBI608 will be administered twice daily, one hour prior or two hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours. On days 3, 10, and 17 of each 28 day cycle, patients will receive the 1 hour infusion of paclitaxel at 80 mg/m^2 at 3 hours after taking the first morning dose of BBI608. Cycles will be repeated until progression of disease, unacceptable toxicity, or another discontinuation criterion is met. In the case of toxicity, adjustment is permitted. If administration of paclitaxel is discontinued due to paclitaxel-related toxicity, the administration of BBI608 will be continued until disease progression if tolerated.	

Criteria for Dose Escalation:	Enrollment at the next dose level and/or additional patients into the ongoing cohort will occur according to the following criteria: ● If zero treated patients experience a DLT (defined below) by Day 28 of continuous daily dosing, then dose escalation will occur. ● If one treated patient experiences a DLT (defined below) by Day 28 of continuous daily dosing, then an additional three patients will be enrolled for a total of six patients treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (one of six patients). ● If two or more treated patients at a dose level experience a DLT by Day 28 of continuous daily dosing, dose escalation will stop and an additional three patients will be enrolled for a total of six patients treated at the prior dose level. The MTD is defined as the dose level at which no more than one out of six patients has an observable DLT.
Duration of Treatment:	For an individual patient, treatment with BBI608 and paclitaxel will continue until unacceptable toxicity, disease progression or another discontinuation criterion is met. It is expected that the majority of patients will receive between one and four cycles of BBI608 and paclitaxel for a treatment period of four to 16 weeks. Patients may continue protocol therapy or BBI608 alone beyond radiologic progression provided there is no clinical deterioration.
Criteria for Determination of Dose-Limiting Toxicity:	A DLT is defined by the occurrence of any of the following toxicities possibly or probably related to BBI608, or BBI608 in combination with paclitaxel within 28 days of treatment: ● CTCAE (Common Terminology Criteria for Adverse Events) Grade 4 hematological toxicity ● Grade 3 or 4 non-hematological toxicity, except Grade 3 or 4 nausea/vomiting/anorexia, diarrhea or fatigue will be considered a DLT only if it persists more than three (3) days despite optimal medical management; and alopecia will not be considered a DLT ● Any other toxicity that in the view of the Principal Investigator represents a clinically significant hazard to the patient. Whether a DLT has occurred will be assessed for each patient at Day 29 following the first 28 days of BBI608 therapy. DLT will be determined from adverse events, changes from baseline in physical examination findings and laboratory parameters. The incidence of adverse events and DLTs will be evaluated for each dose level and for all patients. Adverse events considered related to paclitaxel will not be considered DLTs.
Pharmacokinetic and Pharmacodynamic Variables:	Pharmacokinetic variables to be determined include maximum plasma drug concentration (Cmax), volume of distribution, area under the time-concentration curve (AUC), distribution half-life, and terminal half-life. For patients enrolled at select study sites, blood samples for PK determination will be drawn on Day 16 and Day 17 during the first cycle for each dose level. Response (increase or decrease) of several biomarkers from biopsied tumors following BBI608 administration will be examined in patient with accessible tumors for biopsy. Tumor biopsies will be collected prior to the first dose of BBI608 and on day 17 of the first cycle for patients with accessible tumors and who have signed the optional tumor biopsy consent.
Statistical Methods:	All patients receiving at least one daily dose of BBI608 will be considered evaluable for safety analyses. In addition to the evaluation and categorization of adverse events, listings of laboratory test results collected at baseline and during

	the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented. Patients who have received at least one cycle of BBI608 and have had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics. For each tumor type, the following endpoints will be summarized: Objective response rate (ORR), defined as the proportion of patients with a documented complete response (CR) or partial response (PR) based on RECIST 1.1; Disease Control Rate (DCR), defined as the proportion of patients with documented CR, PR and stable disease (SD) based on RECIST 1.1; progression free survival (PFS); and overall survival (OS). There is no statistical hypothesis testing in the Phase II part and the planned sample size of Phase II (20 - 40 per cohort) is considered to be clinically adequate to assess tolerability, safety, and preliminary anti-cancer activity of study drugs of interest, and actual sample size depends on the actual enrollment in each arm. Sample Size Justification for Thymic Carcinoma Cohort: A total of 10 (minimum) to 15 (maximum) patients will be targeted to this cohort and a Bayesian posterior probability approach will be employed to monitor the enrollment based on the overall response rate (ORR) by Week 16. After the first 10 patients have response evaluation, or withdraw, or die by Week 16, the Bayesian posterior probability of the ORR being greater than a target value will be continuously evaluated. If the posterior probability is greater than 70% or less than 20%, then further enrollment may be stopped. Otherwise enrollment will continue until the enrollment cap of 15 is reached. The targeted ORR is set to be 0.45 for the thymic carcinoma cohort. The Bayesian approach incorporates the historical data into the decision process by employing a weakly informative beta prior on the ORR by Week 16 where the beta prior is chosen to have the mean equal to the historically observed ORR of 0.22 (Lemma 2011).

DOSE ESCALATION SCHEME

Phase Ib – Three-subject Cohort Dose Escalation

Group	No. Subjects[#]	Dose Level	Total Daily Dose of BBI608**	Pharmacokinetics (Week)
I-b	3	Level 1b	1000 mg[+]	1*, 2, 3*, 4
II-b	3	Level 2b	1500 mg	1*, 2, 3*, 4
III-b	3	Level 3b	2000 mg	1*, 2, 3*, 4

* Pharmacokinetic monitoring.
# Groups may be expanded to six subjects, as provided in the protocol.
**The total daily dose will be split into two approximately equal sub-doses

In the absence of disease progression and unacceptable toxicity, weekly dosing may continue. Restaging will occur after every 8 weeks of treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine transaminase (SGPT)
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate transaminase (SGOT)
AUC	Area under the time-concentration curve
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CDER	Center for Drug Evaluation and Research
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
Cru	Complete response / unconfirmed
CRF	Case report form
CT	Computed tomography
CV	Coefficient of variation
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit
HED	Human equivalent dose
Hgb	Hemoglobin
HGF	Hepatocyte growth factor
HIPAA	Health Information Portability and Accountability Act
IC_{50}	Inhibitory concentration, 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest diameter
LDH	Lactic dehydrogenase
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute

NOAEL	No observable adverse effect level
NOEL	No observable effect level
ORR	Overall response rate
PD	Progressive disease
PK	Pharmacokinetic
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 Dose
RBC	Red blood cell (count)
SAE	Serious adverse event
sCR	Stringent complete response
SD	Stable disease
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SPEP	Serum protein electrophoresis
Tmax	Time to maximum plasma concentration
TNM scale	Tumor node metastases scale
ULN	Upper limits of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WBC	White blood cell (count)

1 PRECLINICAL SUMMARY AND STUDY RATIONALE

1.1 Scientific Background of BBI608

Recent studies have uncovered the presence of cancer stem cells (CSC, also called tumor initiating cells or cancer stem-like cells) which have self-renewal capability and are considered to be potentiallyresponsible for malignant growth, relapse and metastasis. Importantly, CSCs are inherently resistant to conventional therapies. Therefore, a targeted agent with activity against cancer stem cells for cancer patients is being explored (Lobo, Shimono et al. 2007; Boman and Wicha, 2008; Please find a list of updated reviews on cancer stem cells in all major cancer types in the special issue of *Journal of Clinical Oncology* on cancer stem cells (J Clin Oncol. 2008 Jun 10;26(17)).

BBI608 is a small molecule that is hypothesized to affect multiple oncogenic cellular pathways, including inhibition of the STAT3 pathway.

STAT3 is an oncogene that belongs to a family of transcription factors activated in response to cytokines and/or growth factors to promote proliferation, survival, and other biological processes. STAT3 activates certain genes involved in tumorigenesis, invasion, and metastasis, including Bcl-xl, Akt, c-Myc, cyclin D1, VEGF, and survivin. STAT3 is aberrantly active in a variety of human cancers, including in more than half of breast and lung cancers, hepatocellular carcinomas, and multiple myelomas and more than 95% of head/neck cancers. STAT3 ablation by gene targeting blocks cancer cell proliferation, survival, and metastasis.

While essential for embryonic development, the deficiency of STAT3 seems well tolerated in adult mice. Patients with Job's syndrome survive into adulthood with STAT3 dominant negative mutations. In a French registry study of 60 patients with Job's syndrome, 93% were alive at age 50 (Chandesris et al, 2012).

Therefore, blocking STAT3 may target cancer stem cells as well as the bulk of the heterogeneous cancer cells while potentially spare normal cells and normal adult stem cells

1.2 Preclinical Efficacy

Cancer stem cells are intrinsically resistant (more than 5 to 10 fold) to chemotherapeutic drugs. BBI608 has activity (~100 to 500 nM) against cancer stem cells *in vitro* while sparing normal hematopoietic stem cells (IC_{50} not reached at 30 μM) in vitro. BBI608 has demonstrated *in vitro* activity in human cancer cell lines derived from multiple tumor types with IC_{50}s ranging from 0.300 μM to 14 μM..

1.3 GLP Toxicology

Please refer to the Investigator Brochure for further details on the GLP toxicology studies performed to date.

Briefly, the no observable adverse effect level (NOAEL, based on clinical observation, laboratory tests, gross and histopathological changes) for rats administered BBI608 daily orally over 28 days was 30 mg/kg/day (human equivalent dose: 180 mg/m^2) and the NOAEL in dogs administered BBI608 daily orally over 28 days was 30 mg/kg/day (human equivalent dose: 600 mg/m^2).

1.4 Safety and Signs of Antitumor Activity in Phase I

A phase 1 dose escalation study (BBI608-101) in adult patients with advanced cancer was initiated to determine the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics and preliminary anti-tumor activity of BBI608. A modified Simon accelerated titration scheme was used for dose escalation, with a cycle consisting of twice-daily oral administration of BBI608 for 4 weeks, and was repeated every 4 weeks (28 days) until progression of disease, unacceptable toxicity, or other discontinuation criteria were met.

The dose of BBI608 has been escalated from 20 mg to 2000 mg/day when BBI608 was taken bid, and MTD is not reached. The total daily dose has been escalated to 1500 mg (total daily dose) when BBI608 was taken tid, and MTD is not reached. Further dose escalation is limited by pill burden and gastrointestinal events.

Please refer to the Investigator's Brochure (version 6.3) for current clinical data.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of study is:

- To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of BBI608 when administered orally daily in combination with paclitaxel in adult patients with advanced malignancies.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To determine the pharmacokinetic profile of BBI608 and paclitaxel when administered in combination.
- To assess the preliminary anti-tumor activity of BBI608 when administered in combination with paclitaxel in patients with advanced malignancies.
- To assess the objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), and overall survival (OS) of patients with selected tumor types treated with BBI608 in combination with paclitaxel.
- To determine the pharmacodynamics (biomarkers) of BBI608.

3 SELECTION OF STUDY POPULATION

This study will be conducted in patients with advanced solid malignancies primarily of the following histologies for whom weekly paclitaxel is an acceptable option.

Ovarian cancer

Breast cancer

NSCLC

Melanoma

Gastric/GEJ/Esophageal Adenocarcinoma

Inclusion of other tumor types may be permitted upon agreement between investigators and the sponsor. The study is currently enrolling only patients with thymic carcinoma. Specific enrollment criteria for this cohort is detailed in section 3.1.

The study will be conducted at multiple sites in Canada and the United States.

3.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Signed written informed consent must be obtained and documented according to International Conference on Harmonization (ICH)- Good Clinical Practice (GCP), the local regulatory requirements, and permission to use private health information in accordance with the Health Insurance Portability and Accountability Act (HIPAA) prior to study-specific screening procedures
2. A histologically or cytologically confirmed ovarian, breast, non-small cell lung, melanoma, gastric/GEJ/esophageal or other type of advanced cancer* that is metastatic, unresectable, or recurrent and for which weekly paclitaxel is an acceptable therapeutic option.
3. Patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer must also meet the following criteria:
    a. Must be either platinum-resistant or platinum-refractory according to the following definitions:
        1. Platinum-resistant: a response to platinum therapy followed by progression within 6 months after completing therapy
        2. Platinum-refractory: best response of stable disease or progression during platinum therapy
    b. Must have had prior systemic treatment with a taxane
    c. Must have received no more than 5 prior systemic cytotoxic regimens in the metastatic setting, with an up-front or adjuvant regimen counted if there is recurrence within 6 months.
4. Patients with melanoma must also meet the following criteria:
    a. If melanoma is BRAF wild-type or has BRAF mutations that are not amenable to BRAF inhibitor therapy, and the patient is a candidate for immunotherapy, must have received ipilimumab.
    b. If melanoma is positive for the V600E or V600K BRAF mutation, must have received at least one line of prior therapy with a BRAF-specific inhibitor; either alone or in combination.
5. Patients with triple negative breast cancer (estrogen receptor-negative (ER-), progesterone receptor-negative (PR-), and human epidermal growth factor receptor 2-negative (Her2-) must also meet the following criteria:
    a. Must have received at least one prior chemotherapy regimen for locally advanced or metastatic disease.
6. Patients with NSCLC (adenocarcinoma, squamous, or adenosquamous histopathology) must also meet the following criteria:
    a. Must have disease that is stage IIIB, not curable by surgery or radiotherapy, or stage IV.
    b. Must have received at least one prior chemotherapy regimen for locally advanced or metastatic disease.
    c. EGFR-positive or ALK-positive patients must have received at least one line of EGFR-directed or ALK-directed therapy, respectively.
    d. Must have received prior taxane therapy.

7. Patients with adenocarcinoma arising from the esophagus, gastro-esophageal junction, or stomach must also meet the following criteria:
    a. Must have received prior treatment with a platinum/fluoropyrimidine-based therapy with or without an anthracycline in the metastatic setting; or, in the adjuvant setting if recurrence occurred within 6 months of completing systemic adjuvant treatment.
    b. Patients with HER2 positive tumors must have had prior treatment with a Her2 inhibitor (e.g. traztuzumab or lapatinib)
    c. Patients who have received prior taxane therapy may be enrolled.
8. Patients with thymic carcinoma must also meet the following criteria:
    a. Must have received at least one prior systemic chemotherapy regimen for metastatic, recurrent, locally advanced, or otherwise unresectable disease.
9. ≥ 18 years of age
10. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1, see Section 9)**
11. ECOG performance Status 0 or 1 (Section 15)
12. Male or female patients of child-producing potential must agree to use contraception or avoidance of pregnancy measures during the study and for 30 days after the last BBI608 dose
13. Females of childbearing potential must have a negative serum pregnancy test
14. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 × upper limit of normal (ULN), or ≤ 3.5 × ULN with metastatic liver disease.
15. Hemoglobin (Hgb) ≥ 9 g/dl
16. Total bilirubin ≤ 1.5 × ULN
17. Creatinine ≤ 1.5 × ULN or creatinine clearance > 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
18. Absolute neutrophil count ≥ 1.5 x 10^9/L
19. Platelets ≥ 100 x 10^9/L, patients with hepatocellular carcinoma (HCC) may enroll provided they have platelets ≥ 75 x 10^9/L
20. Life expectancy ≥ 3 months

*Patients must have only one malignancy diagnosis at the time of enrollment. A history of curatively resected non-melanoma skin cancer or curatively treated cervical carcinoma in situ is permitted. A history of another primary solid tumor is permitted provided there is no known active disease present and the investigator and medical monitor for the sponsor agree that the history will not affect patient outcome in the setting of the current malignancy.

**Patients may be enrolled provided disease can be objectively measured using another disease-specific standard (e.g., tumor marker elevation).

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. Anti-cancer chemotherapy, radiotherapy, immunotherapy, or investigational agents within 7 days of first dose provided all treatment-related adverse events have resolved or have been deemed irreversible, with the exception for a single dose radiation up to 8 Gray (equal to 800 RAD) with palliative intent for pain control up to 7 days before beginning the administration of BBI608.
2. Surgery within 4 weeks prior to first dose
3. Any known symptomatic brain metastases requiring steroids. Patients with treated brain metastases must be stable for 4 weeks after completion of that treatment, with image documentation required. Patients must have no clinical symptoms from brain metastases and must be either off steroids or on a stable dose of steroids for at least 2 weeks prior to protocol enrollment. Patients with known leptomeningeal metastases are excluded, even if treated.
4. Pregnant or breastfeeding
5. Significant gastrointestinal disorder(s), in the opinion of the Principal Investigator, (e.g., Crohn's disease, ulcerative colitis, extensive gastric and small intestine resection)
6. Unable or unwilling to swallow BBI608 capsules daily
7. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements
8. Known severe hypersensitivity to paclitaxel
9. Abnormal ECGs (ie, QT prolongation – QTc > 480 msec, signs of cardiac enlargement or hypertrophy, bundle branch block, signs of ischemia or necrosis and Wolff Parkinson White patterns)*

*Patients with abnormal ECG findings may enroll provided the findings do not represent clinically significant heart disease, and provided there is agreement between the principal investigator and medical monitor for the sponsor.

3.3 Number of Patients

The exact number of patients estimated for this trial is dependent on the number of patient cohorts investigated based on the toxicity encountered. In the phase 2 portion of the study up to 550additional patients may be enrolled. It is expected that up to approximately 570 patients will be enrolled for this study. Patient accrual will occur over a period of time dependent upon the number of cohorts enrolled.

Under protocol amendment 3.0, only 10 to 15 patients with thymic carcinoma may be enrolled.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open-label, multicenter Phase Ib study of oral BBI608 administered with paclitaxel to patients with advanced malignancies. The study is designed to explore the safety, tolerability and pharmacokinetics of BBI608 and paclitaxel and define a recommended Phase 2 dose.

Treatment will be initiated at a dose level of 1000 mg total daily dose of BBI608 for BID regimen and escalate until the RP2D or MTD is determined. In each cycle, BBI608 will be taken daily continuously for 4 weeks (28 days). BBI608 will be administered daily one hour prior or two hours after meals with the first dose taken in the morning. On day 3, 10, and 17 of each 28 day cycle, patients will receive paclitaxel at 80 mg/m^2 given as a 1 hour infusion at 3 hours after taking the first morning dose of BBI608.

Cycles (28 days) will be repeated until progression of disease, unacceptable toxicity, or another discontinuation criterion is met. In the case of toxicity, adjustment is permitted.

Dose escalation will be performed using three-patient cohorts as shown in the table below

Phase Ib Dose escalation scheme for BBI608

Cohort	Total Daily Dose (mg)	Number of Patients
Ib	1000	3[a]
IIb	1500	3[a]
IIIb	2000	3[a]

[a] If a DLT is observed, an additional 3 patients will be enrolled at the same dose

If no DLT is seen, three additional patients will be enrolled and treated at the next BBI608 dose level. If one of the three patients in a cohort shows a DLT in the first cycle of therapy, an additional three patients will be enrolled at the same dose level.

The MTD is defined as the dose level at which no more than one patient with DLT is observed among six patients. If MTD is not reached, the recommended Phase 2 dose (RP2D) of BBI608 will be determined by the maximally administered dose or a dose level which gives the best exposure.

Phase Ib will end when there are < 2 patients with DLT out of 6 evaluated for DLT at the regimen selected for use as RP2D.

Number of Subjects with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
1 out of 3	Enter at least 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the recommended phase 2 dose.

4.2 Rationale for Study Design

Considerable data has been collected from the Phase I monotherapy study of BBI608 (Protocol BBI608-101) conducted in advanced oncology patients who have failed multiple previous regimens. Dose escalation for BBI608 has been successfully conducted from a total daily dose of 20 mg to 2000 mg total daily dose. Further dose escalation is limited by pill burden. MTD is not reached.

Combination of cancer stem cell therapeutics with chemotherapy would allow simultaneous inhibition of cancer stem cells as well as non-stem regular cancer cells. Accordingly, preclinical xenografted models in mice treated with BBI608 in combination with paclitaxel showed dramatic synergy with tumor regression or cure observed in mice.

4.3 Selection of Dose

The dose escalation of BBI608 in the BBI608-101 Phase I study has reached a total daily dose of 2000 mg without dose-limiting toxicity. No MTD was reached and further dose escalation above 2000 mg total daily dose is limited by pill burden. Adverse events observed in the BBI608-101 phase I trial have been generally mild with the most common being: diarrhea, nausea, and fatigue. Grade 3 events include: fatigue or diarrhea. No bone marrow suppression or neuropathy was observed.

In the BBI608-201 study, dose escalation of BBI608 will be begin at a dose of 500 mg bid with a total daily dose of 1000 mg, in combination with 80 mg/m^2 of paclitaxel weekly. The starting dose of BBI608 will be at 600 mg (total daily dose) for tid regimen. The dose escalation schedule of BBI608 is presented in Section 4.1.

4.4 Risk Benefit Assessment

Cancer stem cell inhibitors offer one approach to the treatment of advanced malignancies. Preclinical studies of BBI608 indicate that the drug is active against a range of solid tumors. Signs of antitumor activity have been observed in the BBI608-101 phase I trial.

BBI608 has been well tolerated in phase I trials. MTD was not reached in the BBI608-101 Phase I study with doses escalated from 20 mg up to 1000 mg bid (2000 mg total daily dose). Further dose escalation above 2000 mg/day is limited by pill burden.

Adverse events observed in the BBI608-101 phase I trial have been generally mild with the most common being: diarrhea, nausea, and fatigue. Grade 3 events include: fatigue or diarrhea. There is no clinically significant overlap between adverse events observed for BBI608 and the adverse effects of paclitaxel.

The sponsor believes that the proposed study is acceptable in the context of its risks and benefits.

4.5 Criteria for Dose Escalation and Determination of Dose-Limiting Toxicity

Evaluable patients are defined as having been exposed to at least 28 days of continuous daily administration of BBI608. Based on the tolerability and safety of evaluable patients, enrollment at the next dose level and/or additional patients into the ongoing cohort will occur according to criteria described below:

- If zero treated patients experience a DLT (defined below) by Day 28, then dose escalation will occur.
- If one treated patient experiences a DLT by Day 28, then an additional three patients will be enrolled for a total of six patients treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (one out of six patients)
- If two or more treated patients at a dose level experience a DLT by Day 28, dose escalation will stop and this dose level will be considered the maximally administered dose.

The BBI medical Monitor and Principal Investigator will review all significant relevant toxicities to determine if the dose escalation schedule requires modification. Intermediate doses may be assigned to a cohort after agreement between the BBI Medical Monitor and the Principal Investigator.

4.6 Dose-Limiting Toxicity

Dose-limiting toxicity is defined by the occurrence of any of the following toxicities possibly or probably related to BBI608 within 28 days of treatment. DLT will be scored during the 28 days of BBI608 treatment.

- Grade 4 hematological toxicity
- Grade 3 or 4 non-hematological toxicity, except:
    - Grade 3 or 4 nausea/vomiting/anorexia, diarrhea or fatigue will be considered a DLT only if it persists more than three (3) days despite optimal medical management
    - Alopecia will not be considered a DLT

Adverse events considered related to paclitaxel will not be considered DLTs

4.7 Study Duration

Patients will receive treatment with BBI608 and paclitaxel until progression of disease, unacceptable toxicity or another of the discontinuation criteria is documented (see Section 5.6). It is expected that most patients will receive between one and four cycles of BBI608 and paclitaxel for a treatment period of four to 16 weeks.

5 STUDY VISITS

Study Visits will consist of a Pre-Study Evaluation, during which the patient is evaluated to determine suitability for entry into the study; Cycle 1 Evaluations which will be performed on Week 1, 2 and 3 of the first cycle only; Evaluations in Cycle 2 and beyond, which will be performed in Week 1 of each cycle; and an End-of-Study Evaluation. (See Section 14 for a schedule of Assessments)

Following the Pre-Study Evaluation and a determination by a Principal Investigator that the patient meets all inclusion/exclusion criteria and signs the informed consent, the patient will be considered entered into the study.

5.1 Informed Consent

Patients who agree to participate will sign the approved informed consent and will be provided a copy of the signed document.

5.2 Pre-Study Evaluations (Baseline) (up to 1 week ±3 days prior to the first dose of BBI608*)

After written informed consent is obtained according to ICH-GCP and local regulations, the patient will be evaluated for inclusion and exclusion criteria according to the eligibility criteria listed in Section 3.

The following will be evaluated and documented within seven days prior to first dose of BBI608:

- Medical history
- Physical examination
- ECOG performance status (see Section 15)
- Vital signs (weight, temperature, blood pressure, height, respiration and pulse)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- Urinalysis (see Section 6.3)
- Serum pregnancy test (if applicable)
- Tumor markers if applicable
- Tumor biopsy, if applicable (see Section 6.5.1)
- 12-lead electrocardiogram (ECG)
- Tumor measurement and staging[computed tomography (CT) or magnetic resonance imaging (MRI) acceptable] *

*All CT and MRI scans can be used as the baseline assessment if they were performed within three weeks prior to the first scheduled dose of BBI608.

Archival tissue samples from a prior biopsy or surgery should be collected from all patients enrolled in the clinical trial if they are available (See Section 17: Appendix E).

5.3 On-Study Assessments

5.3.1 Cycle 1

5.3.1.1 Week 1 (Cycle 1, Day 1)

- Dispense BBI608 (three day supply)
- 12-lead electrocardiogram (2 hours after first BBI608 dose)

- Provide instructions for patient to administer anti-diarrheal pre-medication 24 hours prior to the date of first dose of protocol therapy, provided there is no medical contraindication (see section 7.2.2).

5.3.1.2 Week 1 (Cycle 1, Day 3)

- ECOG performance status
- Vital signs (weight, pulse)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- Urinalysis (see Section 6.3)
- Assess AEs
- Record concomitant medication
- Paclitaxel IV infusion over 1 hour, starting 3 hours after first BBI608 dose
- The second dose of BBI608 will be taken approximately 12 hours after the first dose.
- Dispense BBI608 (one week supply)

5.3.1.3 Week 2 (Cycle 1, Day 10)

The following assessments will be made during this visit:

- ECOG performance status
- Vital signs (weight, pulse)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- Assess AEs
- Paclitaxel IV infusion over 1 hour, starting at 3 hours after first morning dose of BBI608,
- Dispense BBI608 (one week supply)

5.3.1.4 Week 3 (Cycle 1, Day 16)

- The second dose of BBI608 will be taken approximately 12 hours after the first dose.
- Blood samples for pharmacokinetics [select study sites only], (see Section 6.4)

For patients enrolled at select study sites, blood samples for pharmacokinetics will be collected immediately prior to the first dose of BBI608 on Cycle 1 Day 16 and Day 17, and will continue through 12 hours after administration of the first dose of BBI608. Specific details for the collection of blood samples for pharmacokinetics can be located in Sections 6.4 and Section 16.

5.3.1.5 Week 3 (Cycle 1, Day 17)

The following assessments will be made during this visit:

- ECOG performance status
- Vital signs (weight, pulse)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)

- Electrolytes (see Section 6.3)
- Urinalysis (see Section 6.3)
- Assess AEs
- Paclitaxel IV infusion over 1 hour begin 3 hours after first BBI608 dose
- The second dose of BBI608 will be taken approximately 12 hours after the first dose.
- Blood samples for pharmacokinetics [select study sites only], (Day 17 of Cycle 1 only [see Section 6.4])
- Dispense BBI608 (two week supply)

For patients enrolled at select study sites, blood samples for pharmacokinetics will be collected immediately prior to the first dose of BBI608 and will continue through 12 hours after administration of the first dose of BBI608. Specific details for the collection of blood samples for pharmacokinetics can be located in Sections 6.4 and Section 16.

5.3.2 Monthly Evaluations (Cycle 2 and beyond)

5.3.2.1 Week 1 (Day 3)

Patients will have the following assessments:

- Physical examination
- ECOG performance status
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- Urinalysis (see Section 6.3)
- Tumor markers, if applicable
- Assess adverse events (AE)
- Record concomitant medication
- Paclitaxel IV infusion over 1 hour begin 3 hours after first morning dose of BBI608
- Dispense BBI608 (28 day supply)

5.4 Tumor Evaluation Visits

Disease status and tumor response will be assessed in eight-week intervals up to one year after starting therapy (calculated from the first dose of BBI608) or as clinically indicated. Standard imaging studies should be performed according to institutional procedures. Tumor response for solid tumors will be evaluated using the guidelines for Response Evaluation Criteria in Solid Tumors (RECIST 1.1) outlined in Section 9.

Once progression of disease during therapy is documented, patients may receive any therapy as determined by their treating physician (see Section 5.6).

A protocol radiologic assessment consists of computed tomography (CT) imaging of the chest, abdomen, and pelvis with IV contrast. Non-contrast imaging is allowed in patients with an allergic reaction to IV contrast material despite appropriate use of premedication, provided the tumor lesions can be measured and followed reproducibly, according to the investigator. An alternate method for those with allergy to CT contrast material is an MRI of the abdomen and pelvis and a non-contrast CT of the chest.

Images should continue to be obtained every 8 weeks (56 days) from the first dose of BBI608 until radiologic disease progression is documented. A window of ± 7 days is allowed when scheduling scans.

A confirmatory scan should be performed 4 weeks following first observation of CR or PR. After the confirmatory scan, imaging will continue every 8 weeks (56 ± 7 days).

De-identified digital copies of radiologic images may be requested for the purposes of exploratory review.

5.5 End of Study Evaluation

All patients will be followed for a minimum of 30 days after the last dose of BBI608. If a patient is removed from the study due to drug-related adverse events, the patient will be followed until resolution of any drug-related AE occurring during the study or within 30 days of the last BBI608 dose, or for 30 days, whichever is longer. In the presence of toxic effects, follow-up visits will be required every four weeks until all study related toxicities have resolved to baseline (or < Common Terminology Criteria for Adverse Events [CTCAE] Grade 1), stabilized or are deemed irreversible.

The following assessments will be made during the end of study visit:

- Physical examination
- ECOG performance status
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Liver function tests (see Section 6.3)
- Electrolytes (see Section 6.3)
- Urinalysis (see Section 6.3)
- 12-lead ECG
- Tumor marker, if applicable
- Tumor measurement and staging if applicable for solid tumors and lymphoma
- Assess adverse events
- Record concomitant medications

5.6 Discontinuation from Study

Patients will be removed from the study at any time if they meet any of the following criteria:

- Documented radiologic* or clinical progression of disease
- Noncompliance with any part of the study, as evaluated by the Principal Investigator and Medical Monitor
- Withdrawal of consent
- Lost to Follow-up
- Death
- Clinically unacceptable toxicities despite optimal treatment or dose reduction.

*Since BBI608 targets cancer stem cells, patients may continue protocol therapy or BBI608 alone beyond radiologic progression provided there is no clinical deterioration.

Patients will be followed for Overall Survival after discontinuing protocol therapy. The follow-up schedule is quarterly for the first 18 months, and semi-annually thereafter. Follow-up will be performed by the clinical site, and may occur through review of the medical record, or through contact with the primary care doctor or primary oncologist for the patient.

6 STUDY PROCEDURES

6.1 Medical History

Medical history will include, but will not be limited to, the following:

- Demography: date of birth, sex, ethnic origin, height, and weight
- Clinically significant prior diagnoses, surgeries, and current medications
- Prior cancer history, current cancer diagnosis, tumor stage at time of diagnosis and screening, previous chemotherapy, including dates and duration of treatment, previous radiation therapy, including anatomic site, dose and date of treatment

6.2 Physical Examination

Complete physical examination including height, weight, blood pressure, heart rate, respiratory rate, temperature (oral, axillary or tympanic) and ECOG performance status (Section 15).

6.3 Clinical Laboratory Tests

Safety laboratory determinations will include hematology, blood chemistry, and urinalyses. All laboratory tests required during the study must be obtained at a primary laboratory designated by the Principal Investigator.

- Hematology: CBC including hemoglobin, hematocrit, white blood cell count with 5-part differential, red blood cell, platelet.
- Blood chemistry: HCO_2, calcium, phosphorus, magnesium, albumin, glucose, and serum creatinine
- Liver function tests: AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin, uric acid, total protein and blood urea nitrogen (BUN)
- Electrolytes: sodium, potassium, and chloride
- Routine urinalysis: dipstick and microscopy including protein, specific gravity, glucose and blood
- Serum pregnancy test for female patients of childbearing potential
- Plasma tumor markers, which may include exploratory markers, will be collected.

Cancer Type	Tumor Marker
Ovarian Cancer	CA-125
Gastric Cancer	CEA, CA 19-9
Pancreatic Cancer	CA 19-9
Hepatocellular Carcinoma	AFP
Prostate Cancer	PSA

6.4 Pharmacokinetic Assessments

Blood samples for the PK of BBI608 and paclitaxel will be collected from patients enrolled at selected study sites. Approximately 32 blood samples for PK will be collected for each patient. Collection, storage, and shipping of PK samples will be performed as described in Appendix D.

6.5 Pharmacodynamic Assessments

Pre-clinical studies conducted at BBI have identified several biomarkers in tumor tissues whose levels either increase or decrease upon exposure to BBI608. Tumor biopsies will be collected as described below provided the patient has accessible tumor and has signed the optional tumor biopsy consent. The goal of the proposed biomarker study is to examine the response of biomarkers in patients treated with BBI608. For tumor biopsies, tumor samples will be obtained before and after dosing in selected subjects. Subject tumor samples will be processed for determination of pharmacodynamic markers in malignant tissue by histopathology and flow cytometry.

6.5.1 Tumor Biopsy

Patients who are identified by the Principal Investigator as having a lesion, which could be biopsied with a minimally invasive procedure, will be asked to sign an additional consent. Tumor samples should be collected at baseline and approximately 4 h after administration of the BBI608 morning dose on Day 17. Collection, storage, and shipping of tissue samples will be performed as described in Appendix E.

7 TREATMENT

7.1 BBI608

BBI608 capsules will be supplied to the pharmacy at the clinical sites. BBI608 will be labeled as an investigational agent, limited by federal law. The pharmacist will dispense an appropriate number of each strength capsule to the Principal Investigator for in-clinic dosing. The appropriate quantity of capsules will be dispensed to the patient for three days of daily dosing on day 1, 1 week of daily dosing on day 3 and 10, and two weeks of daily dosing on day 17 during cycle 1, and for 1 month of daily dosing for cycle 2 and beyond at the prescribed dose, including two extra doses. These instructions must appear on the label for the container in which capsules are delivered to the patient.

Paclitaxel will be handled as described in the Product Label approved by US FDA or Health Canada (see **Appendix F**).

7.1.1 Investigational Product Accountability

BBI will provide all BBI608 required for completion of this study. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Until dispensed to the patients, the study drug will be stored at room temperature, in a secure locked area, accessible to authorized personnel only.

Accurate records of all BBI608 dispensed from and returned to the study site are to be maintained. The study site must supply a copy of their drug destruction policy to BBI before authorization for destruction will be granted. Product accountability will be monitored throughout the study. Upon completion or termination of the study, and after inventory by a BBI monitor or designated representative, all unopened drug is to be returned to BBI or designee in the original containers.

7.1.2 BBI608 Administration

- BBI608 will be administered daily for 28 consecutive days. BBI608 will be administered twice daily, one hour prior, or two hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours.

- Intra-patient dose escalation is permitted if the new dose level has been tolerated for at least one cycle in other patient(s).

- Intra-patient dose de-escalation is allowed provided that the new dose level is below MTD (maximum tolerated dose) and the new dose level is agreed by the Principal Investigator and the medical monitor of the sponsor.

7.1.3 Paclitaxel Administration

- Detailed instructions for the preparation, premedication, and administration of paclitaxel are provided in the Product Labels approved by Health Canada or US FDA (see **Appendix F**).

- Paclitaxel will be administered via IV at 80 mg/m^2 once weekly as a 1-hour infusion*, on Days 3, 10 and 17 of a 28 day cycle. Paclitaxel will be administered at 3 hours after the first daily dose of BBI608.

*In the case of an adverse or infusion reaction to paclitaxel, the rate of administration may be reduced according to institutional standards.

7.1.4 Body Surface Area Calculation

The calculation of the dose of paclitaxel will be based on the patient's body surface area (BSA)*. The BSA will be calculated before each cycle, based on the actual height and weight of the patient. The calculated dose will be adjusted downward to the nearest whole milligram.

*Mosteller method

7.2 Dose Modifications

Prior to the first dose of paclitaxel in a given cycle, the absolute neutrophil count (ANC) must be ≥1.5 $\times 10^9$/L and the platelet count must be ≥100 $\times 10^9$/L. If these parameters are not met, and in the opinion of the investigator the myelosuppression is most likely a result of paclitaxel therapy, the dose of paclitaxel should be reduced according to the following criteria:

- For ANC 0.5-1.49$\times 10^9$/L or platelet count 50-99.0$\times 10^9$/L, hold paclitaxel dose until recovery (ANC ≥1.5$\times 10^9$/L and platelet count ≥100 $\times 10^9$/L) then recommence on the same schedule and dose. Neupogen/G-CSF may be used at the discretion of the principal investigator.
- For ANC <0.499$\times 10^9$/L or platelet count <50.0 $\times 10^9$/L, hold paclitaxel dose until recovery (ANC ≥1.5 $\times 10^9$/L and platelet count ≥100$\times 10^9$/L) then recommence on the same schedule but reduce the dose level by 20%.

Prior to subsequent paclitaxel doses in a given cycle, the absolute neutrophil count (ANC) must be ≥1.0 $\times 10^9$/L and the platelet count must be ≥100 $\times 10^9$/L. If these parameters are not met, and in the opinion of the investigator the myelosuppression is most likely a result of paclitaxel therapy, the dose of paclitaxel should be reduced according to the following criteria:

- For ANC 0.5-0.99$\times 10^9$/L or platelet count 50-99.0$\times 10^9$/L, hold paclitaxel dose until recovery (ANC ≥1.0$\times 10^9$/L and platelet count ≥100 $\times 10^9$/L) then recommence on the same schedule and dose. Neupogen/G-CSF may be used at the discretion of the principal investigator.
- For ANC <0.499$\times 10^9$/L or platelet count <50.0 $\times 10^9$/L, hold paclitaxel dose until recovery (ANC ≥1.5 $\times 10^9$/L if the first of a cycle, otherwise ANC ≥ 1.0$\times 10^9$/L; and platelet count ≥100$\times 10^9$/L) then recommence on the same schedule but reduce the dose level by 20%.

If a dose of paclitaxel is held, it may be administered on an alternate week upon count recovery such that weekly administration of paclitaxel for 3 of every 4 weeks is maintained.

Patients who experience severe peripheral neuropathy and in the opinion of the investigator the peripheral neuropathy is most likely a result of paclitaxel therapy, the dose of paclitaxel should be reduced by 20% for subsequent doses of paclitaxel.

7.2.1 Additional Recommendations

The above are considered minimum guidelines. The paclitaxel dose may be adjusted by the clinical investigator for adverse events other than those specifically mentioned above.

In addition, if a toxicity has occurred for either BBI608 or paclitaxel, subsequent dosing may be delayed up to two weeks with the following conditions:

- If the toxicity resolves to ≤ grade 2 or to the baseline grade, dosing may resume at the current dose level.
- If criteria for treatment are still not met, the patient may be removed from the protocol.

Patients should continue to be treated using the same dosing regimen prescribed for the cohort in which they were originally enrolled. If breaks in treatment are required the following guidelines should be used:

- Patients experiencing an AE or potential DLT should resume treatment, if possible, using an alternative-dosing schedule (to be discussed with the Sponsor medical monitor). Patients who cannot tolerate their assigned dose after trying an alternative schedule should be replaced if they have not completed their first cycle (and are therefore not evaluable for determination of dose escalation).

For any BBI608-related intolerable grade 3 or intolerable grade 2 adverse event, persisting despite optimized medical management, a dose holiday of 1-3 days followed by dose modification is recommended. Dose modification may include reduction of the total daily dose and/or in the number of doses taken per day. Investigators should discuss dose modifications with the medical monitor for the sponsor. Patients may up-titrate dose to full dose as tolerated.

If a toxicity is thought by the Investigator to be related to both BBI608 and paclitaxel, then the dose modification rules for both agents should be followed.

7.2.2 Supportive Pharmacology

Pharmacologic agents that are commonly prescribed for the management of adverse events associated with anti-cancer therapy are listed in Table 1.

Table 1: Supportive Pharmacology*

Diarrhea & Abdominal Cramping	Nausea, Vomiting, or Anorexia[1]
Dicyclomine *(e.g., Bentyl)*: Recommended when the predominant issue is cramping or abdominal pain	**1st line:** 5HT3-inhibitors *(Ondansetron, Palonosetron, Granisetron)*
Diphenoxylate/atropine *(Lomotil)* **Loperamide** *(Imodium)* These agents may be particularly useful in combination	**2nd line:** Dexamethasone *(Decadron)*, ideally in combination with a 5HT3-inhibitor. Short term use can be very effective
Hyoscine *(Buscopan, Scopolamine, Levsin)*: Anti-spasmodic agents helpful for abdominal cramping	**Other agents**: NK antagonist (e.g. Aprepitant), atypical antipsychotic (e.g. olanzapine), benzodiazepines (e.g. lorazepam), phenothiazines (e.g. prochlorperazine), cannabinoids (e.g. dronabinol), and other agents such as metoclopramide or scopolamine.
Corticosteroid with limited systemic absorption[2]	

[1]Adapted from NCCN anti-emetic guideline 2017.
[2]Alimentary tract mucositis reflects mucosal injury across the continuum of oral and gastrointestinal mucosal. Expert opinion (2016 ESMO clinical practice guideline recommendations include systemic steroid treatment for the management of adverse event observed with the use of targeted agents.
*Decisions on ADR management are at the discretion of the investigator and must adhere with local regulatory guidelines.

Anti-diarrheal pre-medication administered 24 hours prior to the first dose of protocol therapy is recommended provided there is no medical contraindication.

Anti-emetic pre-medication is also recommended approximately one hour prior to the first dose of protocol therapy if the patient is not already on an anti-emetic regimen and provided there is no medical contraindication.

Recommendations for pre-medications are presented in Table 2 below.

Table 2: Pre-Medication Recommendations

Category	*Specific Measures*	*Start*	*End*
Anti-Diarrheal	Loperamide 4 mg BID or Diphenoxylate/Atropine 5 mg BID	24 hours prior to the first dose of BBI608 on Cycle 1, Day 1	Stop anti-diarrheal if there are no bowel movements by the morning of Cycle 1, Day 3. Can be continued and/or modified at the discretion of the treating investigator
Anti-Emetic	Ondansetron 8 mg once or Other anti-emetic (5HT3-antagonist preferred)	Approx. 1 hour prior to the first dose of BBI608 on Cycle 1, Day 1	May be continued and/or modified at discretion of treating investigator

7.3 Treatment Compliance

A patient is considered compliant with the study protocol when study medication is administered at a compliance level of greater than 80%.

BBI608 compliance will be calculated using the following equation:

(Number of capsules actually ingested /number of capsules that should have been ingested per dose level) x 100= % compliance

Paclitaxel compliance will be calculated using the following equation:

(Number of infusions performed /number of infusions that should have been performed per dose level) x 100= % compliance

7.4 Blinding

This is an open label study. Neither the patient nor the investigator and site staff will be blinded to the treatment administered.

7.5 Prior Treatment

Reasonable efforts will be made to determine all relevant prior treatments received by the patient within four weeks of the first BBI608 dose. All relevant information must be recorded on the appropriate patient's case report form (CRF). All surgical procedure history, prior chemotherapy and radiation therapy must be recorded on the appropriate CRF.

7.6 Concomitant Medication

7.6.1 Permitted Treatment

All information regarding concomitant treatments (medications or procedures) must be recorded on the patient's CRF (including the name of the medication or procedure and duration of treatment).

Palliative and supportive care for disease-related symptoms will be offered to all patients in this study. Patients may receive palliative radiation therapy.

In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions
- Epoetin alfa (Epogen®, Procrit®)
- Hematopoietic growth factors, including filgrastim (Neupogen®), or other granulocyte colony stimulating factors (G-CSF), are permitted following documented and clinically significant neutropenia after the patient has completed at least one cycle of treatment with BBI608
- Prophylactic antiemetics may be administered according to standard practice
- Megestrol acetate (Megace®)
- Dethamethasone
- Diphenhydramine
- Cimetidine
- Ranitidine

7.6.2 Prohibited Treatment

- Any concurrent chemotherapy, non-palliative radiotherapy, hormonal therapy, or immunotherapy
- Other investigational agents
- Immunosuppressive therapies, including systemic corticosteroids (except when used intermittently in an antiemetic regimen or when prescribed at a non-immunosuppressive dose for treatment of fatigue and low-appetite, or as a premedication for paclitaxel infusion)

7.6.3 Drug-Drug Interactions

No clinically apparent drug-drug interactions have been identified in patients administered BBI608, although a dedicated drug interaction study is currently ongoing in healthy human volunteers.

Napabucasin is primarily metabolized by the CYP P450 isoform 1A2. Therefore, caution should be exercised with drugs that are strong inhibitors or sensitive substrates of CYP1A2.

Examples of strong 1A2 inhibitors and sensitive inducers are presented below:

- Strong CYP 1A2 inhibitors: fluvoxamine, ciprofloxacin, enoxacin, zafirlukast
- Sensitive CYP1A2 substrates: alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine

Possible actions for investigators with patients taking medications as above include: discontinuing the medication entirely, continuing the medication and monitoring for adverse effects, and continuing the medication at a reduced dose and monitoring for adverse effects.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

8.1.1 Assessments

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study. All AEs considered to be related to BBI608 occurring after any administration of the study drug will be followed until the event resolves. AEs will be evaluated using the National Cancer Institute (NCI) CTCAE, Version 4.0, published 28 May 2009.

Investigators are required to document all AEs occurring during the clinical trial, commencing with the first dose of BBI608 and including the protocol-defined post-treatment follow-up period (21 Code of Federal Regulations [CFR] §312.64[b]) on designated CRF pages. AEs occurring following the signature of the informed consent, but prior to the first dose of study drug will not be reported as AEs. It is also important to record all AEs that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Serious adverse events (SAEs), as defined below, must be reported to Boston Biomedical Inc. or its representative within 24 hours of knowledge of their occurrence.

8.1.2 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical investigational patient administered a pharmaceutical product that does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Laboratory data are to be collected as stipulated in this protocol, and toxicity trends will be analyzed utilizing objective toxicity criteria. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for SAEs as defined below.

Patients should be instructed to report any AE that they experience to the investigator. Investigators should assess the patient for AEs at each visit. AEs occurring during the clinical trial and the follow-up period should be recorded on the appropriate AE CRF. To capture the most potentially relevant safety information during a clinical trial, it is important that investigators record accurate AE terms on CRFs.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

8.2 Serious Adverse Events

8.2.1 Definitions

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization, except for events that are clearly disease related
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events may be considered an SAE based upon appropriate medical judgment.

Under this protocol, scheduled hospitalizations or elective surgical procedures will not be considered SAEs. Prolongation of a scheduled hospitalization can be considered an SAE. Complications associated with scheduled procedures are considered an AE.

8.2.2 Reporting Serious Adverse Events

Any SAE, including death, due to any cause that occurs during this investigation, whether or not related to the administration of study drug, must be reported to the Sponsor immediately (not to exceed 24 hours) by telephone or facsimile. The reaction must be completely described on the CRF and SAE report form.

Primary Medical Monitor Contact information:
[redacted] Boston Biomedical, Inc 640 Memorial Drive Cambridge, MA 02139, USA Telephone [redacted] Fax: [redacted]
Emergency Number**:** [redacted]

9 ASSESSMENT OF ANTI-TUMOR ACTIVITY IN SOLID TUMORS

The following definitions and criteria (from Response Evaluation Criteria in Solid Tumors [RECIST 1.1, Eisenhauer et al. 2009][1]) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

Measurable disease - the presence of at least one measurable lesion.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥10 mm using conventional techniques or ≥10 mm with spiral CT scan. Malignant lymph nodes must be ≥15 mm in the shortest diameter.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <10 mm with conventional techniques, <10 mm with spiral CT scan or ≥10 mm to <15 mm in short axis), i.e., bone lesions, ascites, pleural/pericardial effusion, cystic lesions and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, and a measurement with a ruler to estimate the size of the lesion, is recommended.

9.1 Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.
- All imaging methods should be performed according to institutional standards with each patient having consistency of methods beginning from baseline through the course of the study.

9.2 Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of five lesions total with a maximum of 2 lesions per organ, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline*.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

**In most circumstances, a radiology report alone is not sufficient for the purposes of documenting target lesion measurements at baseline. The baseline images and images from each subsequent time point should be reviewed specifically according to RECIST 1.1 guidelines.*

9.3 Response Criteria

	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions Any pathological lymph nodes must have reduction in short axis of <10mm
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started. In addition to the increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions*

**Confirmation imaging a minimum of 4 weeks later is recommended in the case of equivocal new lesions or unequivocal progression of non-target lesions*

9.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and is determined as indicated in the table below:

Target lesions	**Non-Target lesions**	**Evaluation of New lesions**	**Overall response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

Because of the nature of this study, no formal statistical analysis is planned. Evaluation of the data will consist primarily of summary displays (i.e., descriptive statistics and graphs).

10.2 Determination of Sample Size

Phase Ib

The sample size for this study was determined by clinical rather than statistical considerations. With cohort sizes of three to six patients, if the true underlying rates of DLT are 0.1, 0.2, 0.3, 0.4, and 0.5, there will be 91%, 71%, 49%, 31%, and 17% chances, respectively, of escalating to the next full doses.

Phase II

There is no statistical hypothesis testing in the Phase II part and the planned sample size of Phase II (20 – 40 per cohort) is considered to be clinically adequate to assess tolerability, safety, and preliminary anti-cancer activity of study drugs of interest, and actual sample size depends on the actual enrollment in each arm.

Sample Size Justification for Thymic Carcinoma Cohort:

A total of 10 (minimum) to 15 (maximum) patients will be targeted to this cohort and a Bayesian posterior probability approach will be employed to monitor the enrollment based on the overall response rate (ORR) by Week 16. After the first 10 patients have response evaluation, or withdraw, or die by Week 16, the Bayesian posterior probability of the ORR being greater than a target value will be continuously evaluated. If the posterior probability is greater than 70% or less than 20%, then further enrollment may be stopped. Otherwise enrollment will continue until the enrollment cap of 15 is reached. The targeted ORR is set to be 0.45 for the thymic carcinoma cohort. The Bayesian approach incorporates the historical data into the decision process by employing a weakly informative beta prior on the ORR by Week 16 where the beta prior is chosen to have the mean equal to the historically observed ORR of 0.22 (Lemma 2011).

10.3 Analysis Populations

All patients receiving at least one dose of BBI608 will be considered evaluable for safety analysis. Adverse event incidence rates will be described by the frequency of adverse events, categorized by NCI CTCAE. Listings of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented.

Patients who have received at least one cycle of study treatment and have had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics.

For each tumor type, the following endpoints will be summarized: Objective response rate (ORR), defined as the proportion of patients with a documented complete response (CR) or partial response (PR) based on RECIST 1.1; Disease Control Rate (DCR), defined as the proportion of patients with documented CR, PR and stable disease (SD) based on RECIST 1.1; progression free survival (PFS), defined as the time from enrollment until the first objective observation of disease progression or death from any cause; and overall survival (OS), defined as the time from enrollment until death from any cause.

10.4 Demographics and Baseline Characteristics

Patient characteristics will include a complete summary of the following and will be recorded in the CRFs:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments

Other patient characteristics will be summarized as appropriate.

10.5 Statistical Analysis of Pharmacokinetic Variables

Timed blood sample collection for BBI608 and paclitaxel pharmacokinetic analysis will be performed on Days 16 and 17 of Cycle 1 for patients enrolled at select study sites in this study.

Bioanalytical analysis of patient samples will be conducted at a centralized laboratory using GLP-validated assays. Plasma concentrations will be summarized by descriptive statistics, including mean, standard deviation, coefficient of variation, minimum, maximum, and median**.**

Concentration profiles will be analyzed by noncompartmental and/or nonlinear least squares regression using WinNonLin. Pharmacokinetic parameters, including C_{max}, volume of distribution, distribution half-life, terminal half-life, and AUC will be evaluated.

10.6 Safety Analysis

Safety will be assessed by physical examination, and laboratory assessments. Adverse events will be graded according to the NCI CTCAE, version 4.0. The incidence of adverse events and DLTs will be evaluated for each dose level, and for all patients combined. Patients will be followed for adverse events for at least 30 days after the last dose of BBI608, or until recovered from all related BBI608 adverse events.

11 QUALITY CONTROL AND ASSURANCE

The study will be initiated and conducted under the Sponsorship of BBI. The clinical supplies of BBI608, and CRFs will be supplied by BBI or its representative. Representatives of BBI will monitor the study to verify study data, medical records, and CRFs in accordance with current ICH GCPs and other applicable regulations and guidelines.

11.1 Compliance with the Protocol

The Investigator will notify the Sponsor of any deviations from the protocol. Such contact with the Sponsor will be made as soon as possible to permit a decision as to whether or not the subject (for whom the deviation from the protocol was affected) is to continue in the study. The case records will describe the deviation from the protocol and state the grounds for it.

11.2 Registration and Enrollment

This is an open-label, non-randomized study. Boston Biomedical should be notified as soon as a subject qualifies for entry in the protocol. Subjects will be registered by faxing Boston Biomedical or their designee, within 7 days prior to the 1st drug administration. At that time the dose level will be assigned. The subject will be enrolled into the study when the subject receives the 1st dose of study drug. Registration and enrollment forms and faxing instructions will be provided with the case report forms (CRFs). The site should maintain a log of all subjects who are screened but do not qualify for the study or who do not receive study drug. The reason for disqualification should be noted in the log.

11.3 Removal, Replacement, or Early Withdrawals of Subjects

If a subject exits the study prior to receiving four weeks of BBI608 or does not receive four weeks of BBI608 for a reason other than DLT, an additional subject may be recruited to replace the subject.

12 COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS AND INFORMED CONSENT

12.1 Institutional Review Board

The protocol, any protocol modifications, informed consent form that will be used, and, if applicable, the permission to use private health information must be approved by the Investigator's IRB or Independent Ethics committee (IEC) (compliant with federal regulations 21 CFR 56) before the study is initiated. Documentation of this approval (i.e., a copy of the document showing IRB/IEC approval including the chairperson's signature and the date of approval) must be provided to Boston Biomedical or its designee, and made available during an inspection by the FDA, Health Canada or other regulatory agency inspectors. The Investigator will submit to Boston Biomedical:

- A list of the names, occupations, and affiliations of the members of the IRB
- Documentation that the IRB is duly constituted or a General Assurance Number
- No supplies will be shipped until the IRB has given written approval of the protocol and informed consent and Boston Biomedical has received copies of the approvals

It is the responsibility of the Investigator to:

- Submit to the IRB/IEC for review any advertisements that will be used to recruit subjects
- During the conduct of the study, submit progress reports to the IRB, if required, and request review of the study
- Report, in writing, to the IRB all SAEs that occurred during the study or SAEs reported in other studies using study drug, per local IRB regulations
- Inform the IRB of any changes in the protocol and obtain documented IRB approval of the changes
- Maintain a file of study-related information, including all correspondence with the IRB/IEC
- Within 3 months of study completion, provide the IRB with a final report on the study

12.2 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with IRB/IEC informed consent regulation and the ICH GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants.

This study will be conducted according to the current revision of the Declaration of Helsinki (Revised Edinburgh, Scotland, 2000) and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Before initiating a trial, the Investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol/amendment(s), written informed consent form, patient recruitment procedures (e.g., advertisements) and written information to be provided to patients.
Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

12.3 Informed Consent and Permission to Use Private Health Information

The Investigator, or designee, is responsible for the content of the informed consent form, but the content must be submitted and approved by Boston Biomedical prior to submission to the IRB. Before the start of required study procedures, the Principal Investigator or associate must obtain informed consent from each study participant (or the subject's parent/guardian) in accordance with the US federal regulations (21 CFR Part 50) and ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. It should also include any additional information required by local laws relating to institutional review.

Informed consent must be obtained from the subject before any screening activity, washout of medication, or treatment (that is not part of routine care) is undertaken. Informed consent will be obtained by discussing with the subject the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the subjects.

The subject or his/her legal representative will document their informed consent by signing the current version of the written, IRB-approved, informed consent form in the presence of a witness.

The person, who conducted the informed consent discussion with the subject and/or guardian, must also sign the informed consent form. The subject should be given a copy of the informed consent form with all of the appropriate signatures.

The Principal Investigator will ensure that a copy of the signed consent is kept with the Clinical Trial Master File.

The Investigator or designee must explain to the patient subject that for evaluation of study results, that subject's private health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and ECs/IRBs, before enrolling that subject into the study. It is the Investigator's (or designee's) responsibility to obtain permission to use private health information per HIPAA from each subject, or if appropriate, the subject's parent or legal guardian.

13 STUDY MANAGEMENT

13.1 Amendments to the Protocol

Once the protocol has been approved by the IRB, the Investigator will not modify it without obtaining the prior concurrence of Boston Biomedical. In turn, Boston Biomedical will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any informed consent modifications to the IRB, and approval must be obtained before the modifications are implemented. Boston Biomedical will submit protocol modifications the FDA, and to Health Canada.

13.2 Investigator Brochure and Information Materials

Before the study begins, the Investigator will receive an Investigator's Brochure describing all known contraindications, warnings, precautions, and adverse reactions associated with the administration of the study drug. If such information is revised while the study is in progress, the brochure will be amended or revised, and Boston Biomedical will provide the most current version to the Investigator.

13.3 Pre-investigational Documents

Prior to the shipment of the study drug(s), the Investigator will supply Boston Biomedical with the following:

- A signed Investigator Clinical Research Agreement
- A completed Form FDA 1572 signed by the Investigator
- Current curricula vitae and copy of current medical license for the Principal Investigator and Sub-Investigators listed on Form FDA 1572
- A completed financial disclosure form for all personnel listed on Form FDA 1572
- Signed and dated protocol signature page by the Principal Investigator
- A copy of the approval for this protocol from the IRB listed on Form FDA 1572
- A copy of the approval for the informed consent from the IRB listed on Form FDA 1572
- A copy of the IRB-approved informed consent
- Evidence of laboratory certification and a list of laboratory normal ranges for all laboratories listed on Form FDA 1572
- A list of the IRB members (listed on Form FDA 1572) and the member occupations and affiliations; written verification that the IRB is duly constituted or the General Assurance Number

13.4 Drug Inventory Record

The Investigator, or a responsible party (research pharmacist or other) designated by the Investigator, must maintain an inventory record of drug received and dispensed. Boston Biomedical will provide forms to facilitate the inventory control. These forms must be used unless the Investigator has previously established a system that complies with FDA and/or Health Canada regulations and is approved by Boston Biomedical. The study drug must be dispensed only to the institutions(s) specified on form FDA 1572.

13.5 Disposition of Used and Unused Study Drug

Upon completion or termination of the study and after inventory by a Boston Biomedical monitor or designated representative, all unopened drug is to be returned to Boston Biomedical

in the original containers. All used vials will be retained until released for destruction by the Boston Biomedical monitor. Unopened returned drug, with completed Boston Biomedical forms for return shipment, should be shipped as instructed by the Sponsor.

13.6 Study Records

Boston Biomedical will provide the Investigator with drug shipment records, CRFs designed to collect the data specified for each individual, and other forms as necessary.

The Investigator and/or institution is required to prepare and maintain these forms in accordance with federal regulations (set forth in the Statement of Investigator Form FDA-1572) and to sign, date, and return them to the Sponsor.

Upon the request of authorized Boston Biomedical or appropriate regulatory agency personnel, the Investigator will make available for inspection subject source documents, e.g., records of each subject who participates in this study. This information will be treated as confidential.

13.7 Record Retention

Records must be maintained for 25 years:

If the Investigator leaves the institution where the study was conducted, he/she agrees that the records will be retained and will not be destroyed without prior notification of Boston Biomedical.

Boston Biomedical will notify the Investigator when records are no longer required.

13.8 Subject Confidentiality

Every effort will be made to keep all subject identities confidential. All reports and communications submitted to the Sponsor will be identified only by the subject's initials and subject number. The identity of an individual subject may not be disclosed in any publication relating to this study.

In connection with this study, representatives of Health Canada, or other regulatory bodies outside of Canada, such as the United States Food and Drug Administration representatives of the local IRB may, in certain circumstances, review study source documentation including subject medical records.

13.9 Monitoring

In accordance with good clinical practices, the study will be monitored by Sponsor representatives. These representatives will have access to and will review source documents relating to this study, including subject medical records.

The status of drug storage, dispensing, and accountability will also be assessed during periodic visits.

At any time, each site may be audited either by Boston Biomedical personnel, or by a contractor acting on behalf of Boston Biomedical, or by a regulatory agency such as the FDA or Health Canada.

13.10 Case Report Form (CRF) Completion

A set of CRFs will be provided for each study subject. All forms must be filled out in non-erasable ink or typed*. The Investigator will sign and date each CRF as indicated. Correction of data on a CRF will be made by crossing out the incorrect data in a manner that leaves the previous entry legible and writing the correct information next to the crossed out entry. "White-out" and erasures are not permitted. Each correction must be initialed and dated by the individual making the correction. After the CRFs have been collected by Boston Biomedical, all corrections will be made via a query resolution form, and no further corrections should be made on the site's copy of the CRF.

*electronic CRFs (eCRFs) may also be provided that are 21 CFR part 11 compliant. Completion guidelines for eCRFs will be available.

13.11 Final Site Report

The Principal Investigator or associate must notify the IRB when the study is closed and provide a final report to the IRB within 90 days of the last subject's completion of the study. A copy of this final report must also be provided to Boston Biomedical.

13.12 Final Study Report

At the conclusion of the study, after the data are analyzed, Boston Biomedical will prepare a final study report. A copy of this report will be provided to the Principal Investigator at each center.

The preparation of the final study report may be delegated to a contract research organization.

13.13 Use of Information

All personal information pertaining to subjects in this study and in any subsequent reports will be kept confidential. Subjects will be identified only by their initials and by a subject number. It is the responsibility of the Investigator to keep a subject listing for cross-referencing.

The Investigator understands that the information developed in the clinical study will be used by Boston Biomedical in connection with the development of the study drug. This information may be disclosed to other clinical investigators, the FDA, Health Canada and other government agencies.

All information disclosed to the Investigator(s) by Boston Biomedical for the purpose of having the Investigator(s) conduct the clinical trial described in this protocol or generated by the Investigator(s) as results in the clinical trial shall be treated by the Investigator(s) as strictly confidential. The Investigator(s) shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is to colleagues and/or employees who reasonably require the information to assist in carrying out the clinical trial and who are bound by like obligations of confidentiality. Notwithstanding, the Investigator(s) may use or disclose to others any information which: (i) was known to the Investigator(s) prior to the date of its disclosure, (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the Investigator(s) on a non-confidential basis by a third party who is not obligated to Boston Biomedical or any other party to retain such information in confidence.

13.14 Publication

Boston Biomedical acknowledges that the Investigator(s) have certain professional responsibilities to report to the scientific community on findings in clinical investigations they conduct. The Principal Investigator shall have the right to publish the results of research performed under this protocol, provided such publication does not disclose any Confidential Information or trade secrets of Boston Biomedical (other than the Clinical Data). If the Study is conducted as part of a multi-center protocol, Principal Investigator agrees not to independently publish their findings except as part of an overall multi-center publication, unless specifically approved in writing by Boston Biomedical. The Principal Investigator agrees to, prior to submitting a manuscript, abstract, or any other written or oral presentation describing the Data for publication or presentation, forward to Boston Biomedical a copy of the item to be submitted for publication or presentation. Upon reasonable request by Boston Biomedical within 30 days of receipt, the Principal Investigator agrees to withhold such publication an additional 60 days to permit the preparation and filing of related patent applications. In addition, Boston Biomedical shall have the right to require the Principal Investigator to delete from any publication or presentation any Confidential Information (other than the Clinical Data) of Boston Biomedical's and to require that any publication or presentation concerning the Study acknowledge the Sponsor's support.

13.15 Research Outside the Terms of this Protocol

Boston Biomedical has a legal responsibility to report fully to the regulatory authorities all the results of administration of its investigational drugs.

No investigative procedures other than those described in this protocol shall be undertaken on subjects enrolled in this study (unless required for the care of the subject), without the agreement of the IRB/Ethics Committee and Boston Biomedical. The nature and results of any such procedures must be recorded and reported by a method agreed between Boston Biomedical and the Investigator. The consent of the subjects must be obtained before any such procedures are undertaken.

The investigative drug provided to the Investigator for use under this protocol may not be used for any other purpose, including another study, compassionate use, or personal use.

14 APPENDIX A: SCHEDULE OF ASSESSMENTS

Tests & Procedures	Pre-Study Evaluation	Study Evaluations[1]										End of Study Visit	Follow-up
		Cycle 1						Cycle 2 & Beyond					
Week	0	1		2	3		4	1	2	3	4		
Day	0	1	3	10	16	17		3	10	17		≥ 30 days from last BBI608 dose	≥ 60 days from off-study date
Window	-10 to 0 days	± 1 day						± 1 day				± 7 days	
Medical history	X												
Physical examination	X							X				X	
Serum pregnancy test[3]	X												
ECOG performance status	X		X	X		X		X				X	
Vital signs, Weight	X		X	X		X		X				X	
Hematology[2]	X		X	X		X		X				X	
Blood chemistry[2]	X		X	X		X		X				X	
Liver function tests[2]	X		X	X		X		X				X	
Electrolytes[2]	X		X	X		X		X				X	
Urinalysis[2]	X		X			X		X				X	
12-Lead electrocardiogram	X	X										X	
Tumor markers[3]	X							X				X	
Tumor biopsy[3]	X					X						X	
Pharmacokinetics*					X	X							
Tumor measurement & staging[4,5]	X[6]	Scans will be performed at 8-week (56 day) intervals from Cycle 1, Day 1										X[7]	
Concomitant medications	X		X	X		X		X				X	
Adverse events[8]			X	X		X		X				X	
Dispense BBI608		X	X	X		X		X					
Paclitaxel infusion			X	X		X		X	X	X			
Disease progression													X[9]
Overall survival													X[10]

* At selected study sites

1. Calculated from the date of first BBI608 dose.
2. Refer to Section 6.3 for description of laboratory assessments.
3. If applicable
4. Including tumor measurements, following RECIST 1.1. The End of Study scan is not required to coincide with the End of Study visit.
5. Prior to cycle 3 and every other cycle thereafter, assessments must be made utilizing the same imaging method as baseline.
6. Unless CT/MRI has been performed within last three weeks.
7. Unless CT/MRI has been performed within last four weeks.
8. Patients will be followed until resolution of any drug-related AE or SAE occurring during the study or within 30 days of last BBI608 administration.
9. Patients will be followed quarterly after the date of the last BBI608-201 dose, until the date of RECIST categorization of progressive disease (if known).
10. Patients will be followed quarterly until the date of death.

15 APPENDIX C: PERFORMANCE STATUS

ECOG Performance status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

16 APPENDIX D: PHARMACOKINETIC STUDIES

Instructions for Collecting and Processing Samples

Sampling to define the plasma pharmacokinetics of BBI608 and paclitaxel will be performed for patients enrolled at selected study sites. Samples are taken on Day 16 and Day 17 of cycle 1. The sampling schedule and summary of procedures that are to be used to establish times, collect samples, and process specimens for storage prior to analysis, to insure the acquisition of accurate pharmacokinetic data, are described below. The sampling schedule has been devised to accommodate treatment on an outpatient basis. Dosing of the first dose of drug must be started before 10 a.m. on a Tuesday, Wednesday, or Thursday to facilitate the collection of the pharmacokinetic samples at the scheduled times during the regular operating hours of the outpatient clinics.

Before starting the BBI608 administration, place a large gauge peripheral catheter (e.g., 19 or 20 gauge angiocath straight set with T-connector, or similar IV access device) within a vein in the arm of the subject for the collection of pharmacokinetic blood samples. Patency of the sampling catheter should be maintained between blood draws using either a heparin lock (e.g., 10 U/mL in normal saline) or a slow drip of Normal Saline for Injection, USP (e.g., 10 mL/hr). Extraordinary caution should be taken to prevent hemolysis in the blood sample. Blood may be obtained directly by venipuncture on days when only a single pharmacokinetic blood specimen is scheduled for collection. When sampling through the peripheral catheter, begin to clear the catheter approximately 1 min before the specified sample time by withdrawing the lock solution and approximately 0.5 mL of blood into a syringe. Remove and properly dispose the syringe used to clear the catheter.

A battery-powered digital timer/stopwatch programmed to operate continuously as a 24-hr clock will be used to accurately monitor drug administration and sample collection times. The same timer must be allowed to run without interruption until the last blood specimen has been obtained from the subject during the first cycle of therapy. Timer readings will be noted at the precise time that the administration is started as well as at the beginning and ending times of the blood sample collection intervals. Readings of the digital timer must be directly recorded on a copy of the appropriate Pharmacokinetic Dosing and Blood Collection Time Form.

Please note that blood and plasma must be protected from direct exposure to light and all sample processing procedures are to be performed in a room with indirect lighting. The volume of blood collected for each pharmacokinetic sample will be 3 mL. This volume has shown to be adequate for the pharmacokinetic assay. Samples are to be collected in plastic Vacutainer plasma collection tubes. Immediately wrap the tube with aluminum foil to protect it from exposure to light. Promptly mix the plasma collection tube by gently inverting 6-times, then place it on wet ice, and centrifuge (1,100-1,300 x g, 10 min, 4°C) within 5-10 min after collection. Separate the plasma from the blood cells using a pipette and transfer approximately equal volumes into three 2 mL self-standing opaque amber polypropylene microcentrifuge cryogenic tubes with external threads. Affix a pre-printed label (protocol number, subject initials, subject number, sample collection date and time) to the cryotube, oriented lengthwise

toward the upper part of the tube. Hand-written information on sample tube labels is absolutely prohibited. Completely cover the label with protective cryogenic freezer tape. Place the tube on crushed dry-ice until stored in a freezer maintained at ≤ -70°C. Any deviation from the sample collection time needs to be documented in the study subjects' case report forms and in their study binder.

The total volume of blood collected for pharmacokinetic studies, 100-120 mL, represents < 5% of the total blood volume for a 60 kg subject, during a 28-day treatment cycle. As pharmacokinetic data becomes available during the course of the trial, it may be necessary to modify the number of samples or the times at which they are collected to more accurately define the plasma concentration-time profile of the drug. However, the cumulative volume of blood collected for pharmacokinetic sampling will not exceed 240 mL, or approximately 5% of the total volume of a 60 kg subject during the first 4 weeks of study treatment.

*Computer files for dose administration and sample collection time forms and specimen tube labels will be placed in a subdirectory located on a secure network server. All members of the clinical, laboratory, and administrative staff involved with phase Ib studies will be given read-only access to this subdirectory. The files are placed under the following subdirectories: PK_Time_Forms; PK_Tube_Labels. Files for the PK time forms are printed directly from the file stored on the network server for each subject study. Since changes may be periodically made to these forms, they cannot be copied onto user personal computers and staff members are instructed not to make photocopies of blank forms. The PK_Tube_Label files are templates, and the files are copied to user computers and the limited information pertaining to each subject studied, typically the subject entry no., is added by editing the computer file, then printed onto adhesive-backed labels. Hand-written information on sample tube labels is absolutely prohibited. There are separate sets of labels for blood collection vials and sample storage tubes. Blood collection vials are prelabeled.

Time points will be determined as the difference between the midpoint of the blood collection interval and starting time of dose administration. Concentration-time profiles of BBI608 and paclitaxel will be analyzed by noncompartmental methods and/or nonlinear least squares regression using WinNonlin (Scientific Consulting, Inc.). Pharmacokinetic parameters and variables will be calculated according to standard equations.

*These instructions may require modification based on updates to best practices

Pharmacokinetic Sample Collection: on Day 16 in CYCLE 1 ONLY

Cycle No.	Procedure	Sample No.	Desired Time
1	Draw blood sample	PK-01	-5 min
	Start BBI608 administration		0 min
	Draw blood sample	PK-02	30 min
	Draw blood sample	PK-03	60 min
	Draw blood sample	PK-04	120 min
	Draw blood sample	PK-05	175 min
	Draw blood sample	PK-06	210 min
	Draw blood sample	PK-07	235 min
	Draw blood sample	PK-08	250 min
	Draw blood sample	PK-09	270 min
	Draw blood sample	PK-10	300 min
	Draw blood sample	PK-11	360 min
	Draw blood sample	PK-12	420 min
	Draw blood sample	PK-13	475 min
	Draw blood sample	PK-14	510 min
	Draw blood sample	PK-15	540 min
	Draw blood sample	PK-16	600 min
	Draw blood sample	PK-17	660 min
	Draw blood sample(pre-dose)	PK-18	720 min
	Start BBI608 administration		720 min

Pharmacokinetic Sample Collection: on Day 17 in CYCLE 1 ONLY

Cycle No.	Procedure	Sample No.	Desired Time
1	Draw blood sample	PK-01	-5 min
	Start BBI608 administration		0 min
	Draw blood sample	PK-02	30 min
	Draw blood sample	PK-03	60 min
	Draw blood sample	PK-04	120 min
	Draw blood sample	PK-05	175 min
	Start Paclitaxel infusion		180 min
	Draw blood sample	PK-06	210 min
	Draw blood sample	PK-07	235 min
	Draw blood sample	PK-08	250 min
	Draw blood sample	PK-09	270 min
	Draw blood sample	PK-10	300 min
	Draw blood sample	PK-11	360 min
	Draw blood sample	PK-12	420 min
	Draw blood sample	PK-13	475 min

	Draw blood sample	PK-14	510 min
	Draw blood sample	PK-15	540 min
	Draw blood sample	PK-16	600 min
	Draw blood sample	PK-17	660 min
	Draw blood sample(pre-dose)	PK-18	720 min
	Start BBI608 administration		720 min

17 APPENDIX E: TUMOR BIOPSIES

Instructions for Collecting, Processing and Shipping Samples

Archival tissues:

Archival tissue samples should be collected from all patients enrolled in the clinical trial if they are available. Submission of paraffin embedded tissue blocks to Boston Biomedical is preferred; however, if tumor blocks are not available, 20 positively charged, unstained tissue slides at 5 micron thickness should be sent to Boston Biomedical. Archive tissue labels should be coded with the protocol number, study site number, the patient's initials and the patient number. Paraffin embedded tissue blocks or prepared tissue slides should be shipped by courier to Boston Biomedical at the address listed below.

Fresh Tumor Biopsies:

Patients who are identified by the principal investigator as having a lesion, which could be biopsied with a minimally invasive technique, will be asked to sign an additional consent. Tumor biopsy samples should be collected at baseline and 4 hours after administration of BBI608 on Day 17 of cycle 1. Tumor biopsies will be collected for immunohistochemistry-based analysis of the target and its downstream genes and for the analysis of the effect of BBI608 on cancer stem cells. These samples will be used for research purposes only. Tumor biopsies for analysis should be collected by core biopsy or minimally invasive procedures. Tumor specimen samples should be processed sterilely into three parts: fixed, frozen, and fresh.

Fixed Tumor Biopsies for Immunohistochemistry

The sample should be processed to yield paraffin embedded tissues by the hospital pathology department using their standard operating procedures. The samples should be labeled and coded with the protocol number, study site number, the patient's initials, the patient number and the sample collection date and time. The paraffin embedded tissue blocks should be shipped to Boston Biomedical at the address listed below.

Fresh and Frozen Tumor Biopsy for cancer stem cell assays

Tumor biopsies for the analysis of the effect of BBI608 on cancer stem cells should be collected by core biopsy or similar minimally invasive procedures. Once the biopsy tissue is obtained, half of the biopsy tissue should be immediately and sterilely placed into CSC transport media provided by Boston Biomedical, stored and shipped at 4ºC. Overnight shipment should be arranged on the same day as the biopsy is performed. A label should be affixed to all sample tubes containing with the protocol number, study site number, the patient's initials, the patient number and the sample collection date and time. The other half should be immediately snap-frozen in liquid nitrogen, and then transferred to a polypropylene microcentrifuge cryogenic tube. The tissue sample should then be stored at ≤ -70ºC until being shipped to Boston Biomedical on dry ice to the address listed below.

Shipping information:

Please ship all tumor samples to the following address:

[redacted]
Discovery Research Group
Boston Biomedical, Inc.
640 Memorial Drive
Cambridge, MA, 02139 USA
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

On the day that specimens are sent to Boston Biomedical, please contact Boston Biomedical by phone, fax or email to notify what is being sent and when the shipment is expected to arrive.

18 APPENDIX F: PACLITAXEL PRODUCT LABEL

Please refer to the package insert.

19 SPONSOR SIGNATURE

Study Title: A Phase Ib/II Clinical Study of BBI608 Administered with Paclitaxel in Adult Patients with Advanced Malignancies

Study Number: BBI608-201

This clinical study protocol is subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: _____

[redacted]

Boston Biomedical, Inc.

20 INVESTIGATOR'S SIGNATURE

Study Title: A Phase Ib/II Clinical Study of BBI608 Administered with Paclitaxel in Adult Patients with Advanced Malignancies

Study Number: BBI608-201

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Printed Name:_____

Signature: _____Date: _____

21 REFERENCES

[Please find a list of updated reviews on cancer stem cells in all major cancer types in the **June 10 special issue of Journal of Clinical Oncology on cancer stem cells** (J Clin Oncol. 2008 Jun 10;26(17)).]

Boman BM, and Wicha MS. (2008). “Cancer Stem Cells: A Step Toward the Cure.” J Clin Oncol 26(17):2795-2799.

Lobo N, Shimono Y, et al. (2007). "The Biology of Cancer Stem Cells." Annu Rev Cell Dev Biol 23: 675-699.

Chandesris MO, et al. (2012). “Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey.” Medicine 91(4):e1-19.

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