BOSTON BIOMEDICAL
Dainippon Sumitomo Pharma Global Oncology

TITLE:	**A Phase III Randomized, Double-Blind, Placebo-Controlled Clinical Trial of BBI608 plus Weekly Paclitaxel vs. Placebo plus Weekly Paclitaxel in Adult Patients with Advanced, Previously Treated Gastric and Gastro-Esophageal Junction Adenocarcinoma**
PROTOCOL NUMBER:	**BBI608-336**
FDA IND Number	**100,887**
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STUDY DRUG:	**BBI608**
SPONSOR:	[redacted]
DATE OF PROTOCOL:	**March 28th, 2014**
DATE OF AMENDMENT:	**July 14th, 2017**
AMENDMENT:	**8**

This clinical study protocol is subject to critical review and has been approved by the Sponsor. The following personnel have approved this protocol:

Signed: _____ Date: _____

[redacted]

Confidentiality Statement

DOCUMENT REVISION HISTORY

Document	Version Date
Original protocol	28 March 2014
Amendment 1	15 May 2014 (Global)
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Amendment 4	05 August 2014 (Global)
Amendment 4.1	28 October 2014 (Local – United Kingdom)
Amendment 4.2	28 October 2014 (Local – Germany)
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Amendment 6	01 May 2015 (Global)
Amendment 7	24 March 2016 (Global)
Amendment 8	14 July 2017 (Global)

STUDY SYNOPSIS

Study Title:	**A Phase III Randomized, Double-Blind, Placebo-Controlled Clinical Trial of BBI608 plus Weekly Paclitaxel vs. Placebo plus Weekly Paclitaxel in Adult Patients with Advanced, Previously Treated Gastric and Gastro-Esophageal Junction Adenocarcinoma**
Study Number:	*BBI608-336*
Study Phase:	III
Study Drug:	BBI608 is a novel investigational orally administered small molecule anticancer drug that targets cancer stem cells (CSC). CSC are considered to be fundamentally responsible for malignant growth, relapse, metastasis, and resistance to conventional therapies. BBI608 blocks CSC self-renewal and induces cell death in CSC as well as non-stem cancer cells by inhibition of the STAT3, β-catenin and Nanog pathways. BBI608 has shown potent anti-tumor and anti-metastatic activities in pre-clinical gastric cancer models, and has shown highly synergistic effect in combination with paclitaxel. In a Phase Ib/II clinical trial, BBI608 in combination with weekly paclitaxel has been safely administered to more than 80 patients, with the Recommended Phase 2 Dose of BBI608 determined to be the full monotherapy dose. Adverse event (AE) profiles were similar to that of both agents in monotherapy, with no new or additive effects seen. BBI608 related AEs were generally gastrointestinal in nature, and most frequently CTCAE Grade 1 or Grade 2. Encouraging signs of activity were observed in patients with gastric/GEJ adenocarcinoma, with disease control in 6 of 7 patients, objective response in 3 of 7 patients (partial responses of 44%, 48%, and 100% respectively), and a median progression free survival of 23 weeks. Survival data is maturing.
Primary Objective:	To compare overall survival (OS) of patients with pre-treated, advanced gastric and gastro-esophageal junction (GEJ) adenocarcinoma treated with BBI608 plus weekly paclitaxel versus placebo plus weekly paclitaxel. OS is defined as the time from randomization until death from any cause.
Secondary Objective:	To evaluate the safety profile of BBI608 administered daily plus weekly paclitaxel in patients with pre-treated advanced gastric/GEJ adenocarcinoma, with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0.
Study Design:	This is a study which began as a randomized, double-blind, multi-center, phase III study of BBI608 plus weekly paclitaxel vs. placebo plus weekly paclitaxel for adult patients with advanced, pre-treated gastric or GEJ adenocarcinoma who have failed first line therapy containing a fluoropyrimidine and a platinum-based agent. At the time of this amendment, patients remaining on study treatment will be unblinded and the study will continue as a randomized, open-label, multi-center, phase III study of BBI608 plus weekly paclitaxel vs. weekly paclitaxel

	for adult patients with advanced, pre-treated gastric or GEJ adenocarcinoma. 700 patients will be randomized in a 1:1 ratio, stratified according to geographical region (Asia vs. North America, Australia and Europe vs. South America); time to progression on first line therapy (<6 months vs. ≥6 months); disease measurability (measurable disease present *vs* not present); and prior taxane therapy (yes vs. no). Until the time of this amendment, the study proceeded in 28-day (4-week) cycles. BBI608 or placebo was administered orally, twice daily, with doses separated by 12 hours. Paclitaxel 80 mg/m^2 IV was administered weekly, on day 1, 8, and 15 of each 28 day study cycle. BBI608 or placebo administration began 2 days prior to the first paclitaxel infusion. From the time of this amendment, and since unblinding of patients remaining on study treatment, patients will continue study treatment as prior to unblinding as long as it is felt to be in their best interest by the Investigator and with patient's informed consent. Placebo will no longer be administered. Tumor assessments will be performed every 8 weeks after randomization until objective disease progression.
Study Population:	This study will enroll patients with a cytological or histologically confirmed adenocarcinoma of the stomach or gastro-esophageal junction (GEJ) that is metastatic or locally advanced and unresectable. Patients will have failed treatment with one regimen containing at least a platinum/fluoropyrimidine doublet for unresectable or metastatic disease. Patients who have received prior taxane therapy may be enrolled, so long as the taxane was administered in the adjuvant or neoadjuvant setting and progression occurred more than 6 months following completion of therapy. Other inclusion criteria for all patients include: age ≥ 18 yrs.; ECOG performance status ≤ 1; and adequate hepatic, renal, and bone-marrow function.
Test Product, Dose, and Mode of Administration:	Until the time of this amendment, patients in this study received BBI608 or matched placebo orally, daily, at 480 mg bid (960 mg total daily dose). In each cycle BBI608 was taken daily for 4 weeks (28 days). BBI608 or placebo was 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. Patients received BBI608 or placebo in combination with paclitaxel, 80 mg/m^2 via 1-hour IV infusion on days 1, 8, and 15 of each 28 day cycle. Dose modification of BBI608/placebo and/or paclitaxel was allowed. From the time of this amendment, and since un-blinding of patients remaining on study treatment, patients will continue study treatment as prior to unblinding as long as it is felt to be in their best interest by the Investigator and with patient's informed consent. Placebo will no longer be administered.

Duration of Treatment:	Patients may continue to receive protocol therapy until September 15th 2017 and as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST criteria. If paclitaxel is discontinued due to toxicity, BBI608 may be continued as monotherapy until another discontinuation criterion is met. If BBI608 is discontinued due to toxicity, paclitaxel should be continued as monotherapy until another discontinuation criterion is met. The study is planned to close on September 15, 2017, at which time study medication will no longer be provided.
Statistical Methods:	The primary study endpoint is Overall Survival (OS). The study is designed to have a power of 90% and a two-sided alpha of 5% to detect a 24% reduction in the continuous risk of death (HR 0.76, which corresponds to an increase of median survival from 7.36 to 9.67 months) in the Intention to Treat (ITT) general study population. It is estimated that 566 events will be required to detect this reduction which would be observed by randomizing 700 patients over 24 months and following them for an additional 12 months (including up to 5% of yearly dropouts). There was one interim analysis in this study presented to the independent Data Safety and Monitoring Board (DSMB). Additionally, DSMB reviewed safety during conduct of the study. The role and responsibility of the DSMB was defined in a separate Charter. The interim analysis was performed on OS, the primary endpoint of this study, when at least 2/3rds of the required number of events (380) have been observed. This analysis, based on the stratified log-rank test adjusting for the stratification variables at randomization, tested the following: H_0: survival on BBI608 + paclitaxel ≤ survival on paclitaxel versus H_1: survival on BBI608+paclitaxel > survival on paclitaxel The comparison of the overall population was tested based on a generalization of the Lan-DeMets error spending function approach using an O'Brien-Fleming stopping boundary to reject H_0, controlling for a two-sided alpha of 5% at the end of the study. For example, if exactly 380 deaths (67% of the required events) were in the locked database for the interim analysis, the nominal critical point for rejecting H_0 would be 2.502, corresponding to a p-value of 0.012. Thus H_0 would be rejected, and superiority of BBI608 declared, early if the p-value from stratified log-rank test is $\leq$ 0.012.

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Boston Biomedical, Inc.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by Boston Biomedical, Inc. and/or the designated Contract Research Organization (CRO) to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Boston Biomedical, Inc. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Boston Biomedical, Inc. of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to Boston Biomedical Inc., and/or the designated CRO. The study may be terminated at any time by Boston Biomedical, Inc. with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Boston Biomedical, Inc. and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Principal Investigator
(printed name and signature)

Date

Protocol Number: BBI608-336

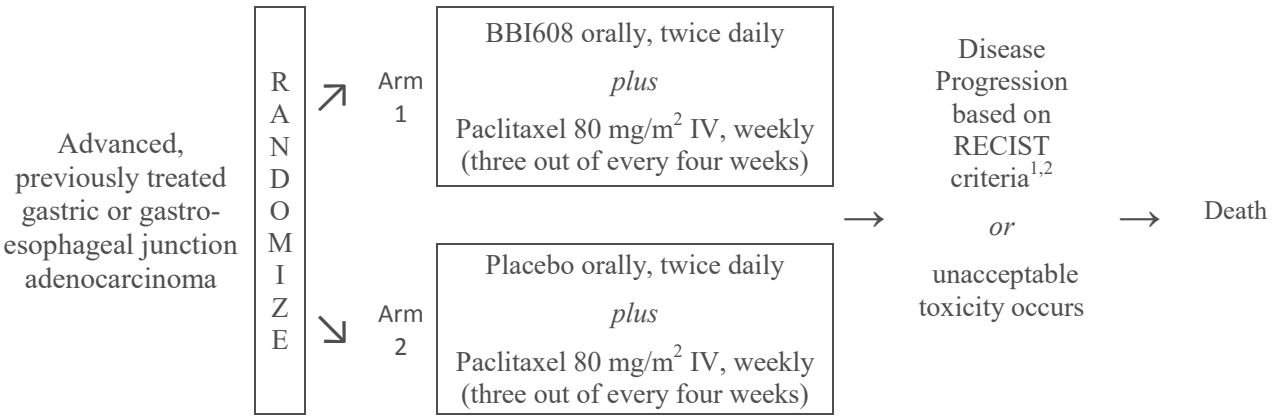
CENTER: _____

TREATMENT SCHEMA

This is an international multi-center, prospective, double-blind, randomized phase III trial of the cancer stem cell inhibitor BBI608 plus weekly paclitaxel *versus* matched placebo plus weekly paclitaxel in patients with advanced, previously treated gastric and gastro-esophageal junction (GEJ) adenocarcinoma.

Stratification:

- Geographical region (Asia *vs* North America, Europe, and Australia *vs* South America)
- Time to progression on first line therapy (<6 months vs. ≥6 months from start of first line therapy)
- Disease measurability by RECIST 1.1 (measurable disease present *vs* not present)
- Prior taxane therapy (yes *vs* no)



[1]If no other standard therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI608/Placebo may be continued in monotherapy as long as it is the opinion of the Investigator that the patient may continue to be deriving benefit.

Endpoints:

Primary

- Overall Survival in the general study population

Secondary

- Overall Survival in the predefined biomarker-positive sub-population[¥]
- Progression Free Survival in the general study population
- Progression Free Survival in the predefined biomarker-positive sub-population[¥]
- Objective Response Rate in the general study population
- Disease Control Rate in the general study population
- Safety Profile

[¥]This biomarker-positive sub-population is defined as those patients with nuclear β-catenin positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) archival tissue.

Sample Size:

Planned sample size is 700 patients (350 on Arm 1 and 350 on Arm 2).

Study Conduct Post-Unblinding:

Following the review of the interim analysis, per DSMB recommendations, patients remaining on study treatment were unblinded.

However, post-unblinding, the trial will continue with patients who have not yet met the primary study endpoint (death), and with patients currently on protocol therapy and who may receive BBI608 and paclitaxel on study based on the clinical judgement of the investigator that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also Sections 9.1.1 and 9.2.1). Patients will receive study treatment supply until any of the discontinuation criteria are met (see Section 11.1) or until September 15 2017, whichever occurs first. The protocol will continue to be followed for all endpoints.

1 *OBJECTIVES*

1.1 PRIMARY OBJECTIVE

- To compare Overall Survival (OS), defined as the time from randomization until death from any cause, in patients with pre-treated advanced gastric/GEJ adenocarcinoma treated with BBI608 plus weekly paclitaxel *versus* placebo plus weekly paclitaxel.

1.2 SECONDARY AND EXPLORATORY OBJECTIVES

- To evaluate the safety profile of BBI608 administered daily plus weekly paclitaxel in patients with pre-treated advanced gastric/GEJ adenocarcinoma, with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE version 4.0).
- To compare Progression-Free Survival (PFS), defined as the time from randomization until the first objective observation of disease progression or death from any cause, in patients with pre-treated advanced gastric/GEJ adenocarcinoma treated with BBI608 plus weekly paclitaxel *versus* placebo plus weekly paclitaxel.
- To compare the Objective Response Rate (OR), defined as the proportion of patients with a documented complete response or partial response (CR + PR) based on RECIST 1.1 criteria, in patients with pre-treated advanced gastric/GEJ adenocarcinoma treated with BBI608 plus weekly paclitaxel *versus* placebo plus weekly paclitaxel.
- To compare the Disease Control Rate (DCR), defined as the proportion of patients with a documented complete response, partial response and stable disease (CR + PR + SD) based on RECIST 1.1 criteria, in patients with pre-treated advanced gastric/GEJ adenocarcinoma treated with BBI608 plus weekly paclitaxel *versus* placebo plus weekly paclitaxel.
- To explore the exposure/response relationships of BBI608 and paclitaxel in patients with pre-treated advanced gastric/GEJ adenocarcinoma treated with BBI608 plus weekly paclitaxel *versus* placebo plus weekly paclitaxel using population pharmacokinetics with sparse PK sample collection.
- To explore an association between putative biomarkers as determined from paraffin-embedded tumor specimens and the potential for clinical benefit in terms of overall survival, progression-free survival, disease control rate, and objective response rate, from treatment with BBI608 plus weekly paclitaxel in patients with pre-treated advanced gastric/GEJ adenocarcinoma.
- To explore associations with baseline values and changes of putative biomarkers (see Section 14.6) in the blood and the potential for clinical benefit in terms of overall survival, progression-free survival, disease control rate, and objective response rate, from treatment with BBI608 plus weekly paclitaxel in patients with pre-treated advanced gastric/GEJ adenocarcinoma.
- To compare the Quality of Life (QoL), as measured using the EORTC QLQ-C30, in patients with pre-treated advanced gastric/GEJ adenocarcinoma treated with BBI608 plus weekly paclitaxel *versus* placebo plus weekly paclitaxel.

2 *BACKGROUND INFORMATION AND RATIONALE*

2.1 GASTRIC AND GASTROESOPHAGEAL JUNCTION (GEJ) CANCER

Gastric cancer and cancer of the gastro-esophageal junction (GEJ) are a significant cause of morbidity and mortality worldwide and have the second highest death rate of all cancers with 736,000 deaths recorded in 2008 *[WHO, 2013]*. Combined, they are the fourth most prevalent malignancy with nearly 1,000,000 new cases of gastric and GEJ cancer diagnosed annually worldwide *[Ferlay 2008]*. In the United States, 21,600 new cases of gastric and GEJ cancer are estimated for 2013 with 10,990 dying from the disease *[NCI 2013].* Surgery is considered the only potentially curative treatment, however, more than 70% of patients present with locally advanced or metastatic disease *[Sugano 2008]*. Out of the minority of presenting patients who qualify for curative surgery, most will develop disseminated advanced disease with a 5-year survival rate of only 20-25% *[Arak 1994; Cunningham 2006].*

Standard treatment for unresectable and metastatic disease currently includes first-line 5-fluorouracil (5-FU) and platinum chemotherapy based regimen (+/- human epidermal growth factor receptor 2 (HER-2) antibody) with patients ultimately progressing on first-line therapy or exhibiting primary refractory disease leading to a median survival between 9 and 14 months *[Cunningham 2008; Wagner 2006; Wagner 2010]*. A meta-analysis of 35 trials and 5726 patients suggested that the anthracycline compound, epirubicin, improves survival in combination with first-line 5-FU and platinum-based chemotherapy making the triple regimen of 5-FU, platinum and epirubicin a first-line treatment option for advanced gastric and GEJ cancer in the US and Europe *[Wagner 2010]*. A subsequent randomized phase 2 study, however, showed no benefit with the addition of an anthracycline to a 5-FU and platinum regimen *[Enzinger 2010]*.

Despite poor survival rates in gastric and GEJ cancer, the past decade has seen some progress in second-line therapy for this disease with approximately 20-50% of patients receiving second-line therapy world-wide *[Pozzo 2004; Bouche 2004; Chau 2004a; Lee 2007]*. Second-line therapy has shown a median survival of 5.6 months as compared to survival of approximately 2.5 months in patients not receiving treatment following progression on first-line therapy *[Chau 2004a]*. Three recent randomized phase III studies provide evidence to support the use of second-line therapy in advanced gastric and GEJ cancer, showing survival benefit of single agent docetaxel and irinotecan *[Kang 2012; Thuss-Patience 2011; Cook 2013]*. A meta-analysis of these three second-line gastric cancer trials (including a total of 410 patients) reported a significant reduction in the risk of death with a HR of 0.64 (CI 0.52-0.79 and P<0.0001) with administration of either docetaxel or irinotecan chemotherapy *[Kim 2013]*. A recently published study of paclitaxel compared with irinotecan shows that the two treatments have similar effects on overall survival, progression free survival and response rate. Additionally, paclitaxel was shown to have a superior safety profile to irinotecan with respect to gastrointestinal adverse events such as anorexia, nausea, vomiting, and diarrhea *[Hironaka 2013]*. In addition to improvements in survival, second-line therapy has also led to improvement in patient quality of life and significantly improved symptom scores for pain *[Cook 2013]*.

In 2013, ramucirumab, a monoclonal antibody VEGFR-2 antagonist, was reported to improve overall survival by 1.4 months as monotherapy in the second-line setting *[Fuchs 2013],* adding anti-angiogenic therapy to the gastric and GEJ cancer therapy armamentarium. Ramucirumab has also been studied in combination with weekly paclitaxel in the same patient population in the randomized phase III RAINBOW study which was recently announced to have met its primary endpoint of overall survival. The addition of ramucirumab to paclitaxel provided a 2.3 month

increase above the 7.36 month median overall survival of paclitaxel alone *[Wilke 2014]*. Ramucirumab received FDA approval in April 2014 for monotherapy treatment of gastric and GEJ adenocarcinoma following progression on fluoropyrimidine or platinum-based chemotherapy.

Currently, a patient with progressive disease on first-line therapy has limited treatment options. Given the morbidity associated with this disease, there is an urgent need to identify novel therapies to improve the outcome of patients with advanced chemo-refractory gastric and GEJ cancer. The poor survival rates seen with this disease may in part be related to a lack of standard recommendations for second-line therapy.

2.2 CANCER STEM CELLS (CSC) AND GASTRIC AND GEJ CANCER

CSCs or cancer cells with stemness phenotypes are a sub-population of cancer cells that have self-renewal capability, are highly malignant, and are considered to be fundamentally responsible for malignant growth, recurrence, drug-resistance and metastasis. Moreover, CSCs are highly resistant to traditional chemotherapies and current targeted agents. CSCs have been isolated from almost all major tumor types, including gastric cancer *[Takaishi 2007A]*. Targeting stem cells, therefore, holds great promise for fundamentally advancing cancer treatment.

Accumulating evidence indicates that CSCs play a key role in the pathogenesis of gastric cancer *[Takaishi 2008]*. Cancer stem cells have been isolated from human gastric cancer using cell surface markers such as Lgr5 and CD44 *[Barker 2010; Takaishi 2009]*. These CSCs isolated from gastric and GEJ cancer patients display tumour-initiating properties, as well as resistance to chemotherapeutic agents. These findings suggest that the development of cancer stem cell inhibitors represents a novel and compelling strategy for the treatment of gastric and GEJ cancer.

2.3 BBI 608

BBI608 is the most advanced agent developed by Boston Biomedical, Inc. (BBI) to target CSCs. BBI608 is a small molecule that blocks self-renewal of, and induces cell death in CSCs isolated from gastric and GEJ cancer as well as other types of cancer. BBI608 inhibits CSCs by binding to CSCP3, a proprietary CSC target discovered by scientists at Boston Biomedical. CSCP3 has been identified as STAT3. STAT3 is a known oncogene which is aberrantly activated in a wide variety of human cancers including all the major carcinomas as well as some hematologic tumors. Multiple animal models of gastric cancer support the role of STAT3 pathway activation in this disease. The $gp130^{F/F}$ mouse model for gastric cancer results in STAT3 hyper-activation, and these animals spontaneously develop gastritis and gastric tumors within 6-8 weeks *[Judd 2006; Ernst 2008]*. Another mouse model, the T3b-SOCS3 cKO mouse, develops STAT3-mediated gastritis and gastric tumors within 8 weeks *[Inagaki-Ohara 2012]*. In particular, approximately 20 to 50% of gastric and GEJ cancers feature dysregulation of STAT3 signaling *[Yu 2009; Tye 2012, Gong 2005; Yakata 2007]*. Moreover, activation of STAT3 pathway, as assessed in archival patient tumor samples, has been associated with reduced survival *[Kim 2009; Yakata 2007; Gong 2005; Lee 2009; Kanda 2004]*. These data provide strong rationale for the development of gastric and GEJ cancer therapies based on inhibition of STAT3 activity.

2.4 CLINICAL EXPERIENCE WITH BBI608 IN PATIENTS WITH GASTRIC AND GEJ CANCER

Based on compelling pre-clinical data, a Phase Ib/II study was initiated to evaluate the safety, recommended phase 2 dose (RP2D), and preliminary signs of activity of BBI608 administered in

combination with weekly paclitaxel in several solid tumors, including gastric/GEJ cancer. This study showed that BBI608 can be combined safely with weekly paclitaxel, with the RP2D of BBI608 in this combination determined to be the full monotherapy dose (480 mg, twice daily). The Adverse Event (AE) profile is similar to that of both agents in monotherapy, with no new or additive effects observed. AEs possibly related to BBI608 were generally mild, consisting primarily of Grade 1 and 2 diarrhea, nausea and vomiting.

To date, 7 subjects with advanced gastric/GEJ cancer have been enrolled in this study. All patients had been pre-treated, with most having received multiple lines of therapy in the metastatic setting, including prior taxanes. The Disease Control Rate (DCR) and Objective Response Rate (ORR) for BBI608 in combination with paclitaxel in the gastric/GEJ cancer patients was found to be 6 of 7 enrolled and 3 of 7 enrolled, respectively. Three patients had a partial response (PR) per RECIST 1.1 (100%, 45% and 48% regressions of target lesions), and the additional three patients had prolonged stable disease (SD)—one with 25% regression. Historically, a DCR of approximately 40-60% and an ORR of approximately 5-21% have been observed in this setting with taxane monotherapy *[Ford 2012; Graziano 2000; Kodera 2007; Hironaka 2013;Wilke 2014]*. Furthermore, for these patients, median Progression Free Survival (PFS) was approximately 23 weeks, which compares favorably with the median PFS (11.4 weeks) observed with weekly paclitaxel alone *[Wilke 2014]*. The phase II portion of the trial is ongoing, with enriched accrual of patients with previously treated gastric and GEJ cancer. Currently, BBI608 combined with weekly paclitaxel has been administered safely to more than 80 patients with various solid tumors.

The unmet clinical need, mechanism of action of BBI608, and encouraging pre-clinical and clinical data seen to date provide a strong rationale for further investigation of BBI608 in combination with weekly paclitaxel in patients with advanced gastric and GEJ cancer.

2.5 SUMMARY

BBI608-336 will primarily examine the effect of adding treatment with CSC inhibitor BBI608 to weekly paclitaxel on Overall Survival in patients with advanced Gastric and GEJ adenocarcinoma who have failed first line chemotherapy. Additional assessments will include Progression-Free Survival, Objective Response Rate, Disease Control Rate, Safety, Quality of life (QoL), Population Pharmacokinetics and putative predictive molecular markers.

3 *BACKGROUND THERAPEUTIC INFORMATION*

3.1 NAME AND CHEMICAL INFORMATION

BBI608

3.2 MECHANISM OF ACTION

BBI608 is a cancer stem cell (CSC) inhibitor. One of the hallmarks of CSCs is their ability to self-renew *[Al-Hajj 2004]*. A standard method of measuring self-renewal capacity is to assess the ability of CSCs to be cultured as spheres in the absence of serum or attachment *[Ponti 2005; Cho 2008]*. Treatment with BBI608 potently blocks *in vitro* sphere formation by gastric CSCs, as well as other types of CSCs. Moreover, BBI608 has also been shown to target CSCs *in vivo*. Treatment of nude mice bearing human tumor xenografts with BBI608 has been shown to reduce their CSC content by 4 to 5-fold after two weeks of treatment. This observation has been made in xenografted gastric cancer, as well as other cancer models. In contrast, treatment of xenograft-bearing mice with 5-FU and platinum-based agents led to an increased concentration of CSCs in the xenografts. Thus, BBI608 has been shown highly effective against CSCs *in vitro* and *in vivo*.

BBI608 targets CSCs by inhibiting STAT3, a proprietary target identified by Boston Biomedical. Scientists at Boston Biomedical have discovered that STAT3 is critical for the self-renewal and survival of cancer stem cells. Under normal conditions, STAT3 activation is transient and tightly regulated in normal adult cells and adult stem cells. While essential for embryonic development, STAT3 deficiency is well tolerated in adult mice *[Niwa 1998]*. Moreover, conditional knock-out of STAT3 in mice is associated with undetectable or mild phenotypes *[Akira 1999]*. Patients with Job's syndrome also survive well with STAT3 dominant negative mutations *[Holland 2007]*.

Increased levels of phospho-STAT3, the activated form of STAT3, are observed in both preclinical gastric cancer models as well as in human gastric cancer. Multiple animal models of gastric cancer support the role of STAT3 pathway activation in this disease. The $gp130^{F/F}$ mouse model for gastric cancer results in STAT3 hyperactivation and these animals spontaneously develop gastritis and gastric tumors within 6-8 weeks *[Judd 2006; Ernst 2008]*. In another mouse model, the T3b-SOCS3 cKO mouse, develops STAT3-mediated gastritis and gastric tumors within 8 weeks *[Inagaki-Ohara 2012]*. Approximately 20 to 50% of gastric and GEJ cancers feature dysregulation of STAT3 signaling *[Yu 2009; Tye 2012, Gong 2005; Yakata 2007]*. Moreover, activation of STAT3 pathway, as assessed in archival patient tumor samples, has been associated with lower patient survival *[Kim 2009; Yakata 2007; Gong 2005; Lee 2009; Kanda 2004]*. These data demonstrate that STAT3 is an important regulator of gastric and GEJ cancer proliferation and survival, as well as a key regulator of CSC-mediated invasion and metastasis. Moreover, they establish a powerful rationale for the development of gastric and GEJ cancer therapies based on inhibition of STAT3 activity.

STAT3 is closely linked to another important transcription factor oncogene, β-catenin, the effector of the Wnt signalling pathway. β-catenin contributes to tumorigenesis and metastasis in a wide range of cancers including gastric and GEJ cancer. It has been shown that constitutive activation of the β-catenin allele in mouse gastric epithelium leads to adenoma formation in the stomach antrum as well as adenomatous change in the more proximal stomach *[Radulescu 2013]* supporting the idea that Wnt pathway activation may play a role in the initiation of gastric and

GEJ cancer. Additionally, mouse models of gastric cancer show that induction of Wnt signalling synergistically cooperates with inflammatory signalling pathways to promote tumor development in gastric mucosa of the animals *[Oshima 2006]*. Moreover, Lgr5, a recognized gastric cancer stem cell marker, is a Wnt pathway target gene *[Van der Flier LG 2007]*, and increased Wnt signalling leads to accumulation of Lgr5 positive self-renewing, multi-potent stem cells responsible for long term renewal of the gastric epithelium *[Barker 2010]*.

In addition to the over-expression of β-catenin, its localization has important clinical implications. Membranous β-catenin is involved in maintaining cell-cell junctions and promoting a less-aggressive epithelial phenotype. By contrast, nuclear β-catenin is accumulated in human gastric cancer tumors *[Brabletz 2005, Clements 2002, Nakatsuru 1992, Park 1999]* and has been correlated with an invasive phenotype in intestinal-type gastric cancers *[Miyazawa 2000]*. Although nuclear β-catenin translocation (with or without demonstrated β-catenin mutations) has been reported in gastric cancer, the actual incidence has varied greatly among studies with approximately 30-50% of tumors showing nuclear accumulation of β-catenin *[Clements 2002, Park 1999, Ebert 2002]*.

A US based study evaluating 311 gastric cancers reported that approximately one third of all gastric tumors show β-catenin nuclear localization, with β-catenin mutations occurring equally among the diffuse and intestinal types of gastric and GEJ cancer *[Clements 2002]*. A Korean study looking at 598 gastric cancer samples reported nuclear β-catenin incidence of 20% in intestinal gastric cancer and 84% in diffuse type of gastric cancer, with 86% of more advanced stage gastric cancers of both histologic types exhibiting nuclear β-catenin staining. A separate study reported 24% of early stage gastric cancers and 80% of lymph node metastases of both histologic types of gastric cancer showing nuclear β-catenin translocation *[Kim 2009]*. A recent study from China looking at 144 gastric cancer samples reported a nuclear β-catenin frequency of 56% with presence of nuclear β-catenin denoting a worse prognosis for overall survival *[Liu 2012]*. A 1997 study evaluating 89 gastric carcinomas reported a statistically significant 3-5 fold survival advantage in patients retaining normal membranous β-catenin staining irrespective of histologic type, grade or stage of gastric cancer *[Jawhari 1997]*. Although the reported incidence of nuclear β-catenin staining varies in the literature, these studies demonstrate the presence of abnormally elevated levels of nuclear β-catenin in gastric and GEJ cancer and correlate nuclear β-catenin localization with more advanced disease as well as decreased survival. This provides a strong rationale for the development of gastric and GEJ cancer therapies with effects on β-catenin nuclear localization.

Studies conducted at Boston Biomedical have shown that BBI608 can directly inhibit phosphorylated STAT3, and also blocks the DNA-binding activity of STAT3 in cancer cells. Moreover, treatment of cancer cells with BBI608 inhibits STAT3 reporter gene activity in a dose-dependent manner. The ability of BBI608 to inhibit STAT3 nuclear translocation in heterogeneous cancer cells and CSCs has also been demonstrated by *in vivo* immunofluorescence studies. BBI608 treatment was also found to result in decreased STAT3-dependent gene expression in cancer cells, including β-catenin. Furthermore, BBI608 has been shown to decrease β-catenin levels in *in vivo* gastric cancer models (BBI's unpublished data).

3.3 EXPERIMENTAL ANTI-TUMOR ACTIVITY

BBI608 also exhibits strong effects against CSCs isolated from gastric cancer and various cancer types (IC_{50} ~100 to 500 nM) while sparing normal hematopoietic stem cells (IC_{50} not reached at 30 μM). These data suggest a wide (>50-fold) therapeutic window for BBI608. Additionally, since bulk cancer cell progeny retain dependency on STAT3 as CSCs, BBI608 has demonstrated inhibitory activities against a broad spectrum of heterogeneous cancer cells including those derived from pancreas, lung, cervix, breast, colon, head and neck, and prostate, as well as hematological malignancies including multiple myeloma, leukemia, and lymphoma (with IC_{50} values of ~100 nM to 500 nM).

BBI608 has demonstrated potent anti-tumor activity as a monotherapy *in vivo* in murine xenograft models of human gastric cancer. No treatment-related signs of toxicity were noted. BBI608 has also shown potent anti-tumor activity in a variety of other human cancer xenograft models including colorectal (including *k-Ras* mutant), pancreatic, head and neck, breast, prostate, and liver cancer.

Combined therapy with BBI608 and other anti-cancer agents has also been investigated *in vivo*. Significant synergy has been observed between BBI608 and chemotherapeutic agents, including paclitaxel, in a variety of murine xenograft models of human cancer including gastric, CRC, breast, non-small cell lung cancer, head/neck cancer, and ovarian cancer. These data suggest a significant potential for BBI608 in combination with chemotherapeutic agents for a wide variety of human cancers.

3.4 GLP TOXICOLOGY STUDIES (28-DAY & 90-DAY)

BBI608 was evaluated in 28-day repeat-dose GLP toxicology studies in both rats and dogs. Both species received BBI608 at dose levels of 10, 30 and 100 mg/kg/day for 28 days followed by a 14-day recovery period. In both species, adverse events were observed in the high dose (100 mg/kg) groups. Male rats in the 100 mg/kg group showed body weight loss, diarrhea, and decreased food consumption. Female rats in the 100 mg/kg group experienced weight loss only, which stabilized after the first week. In dogs in the 100 mg/kg group, weight loss, emesis, diarrhea, and soft/mucoid feces were observed in both males and females. Clinical pathology and histopathology findings in rats at high dose were consistent with dehydration and diarrhea. There were no related pathologic or histopathological findings in dogs at any dose level.

Under the conditions of the study, the 28-day oral NOAEL (no observed adverse effects level) in both rats and dogs was 30 mg/kg. From the rat NOAEL, conversion to a human equivalent dose (HED) yields 180 mg/m^2; and from the dog NOAEL, the HED is 600 mg/m^2. This dose corresponded to BBI608 plasma levels in both species above the *in vitro* IC_{50}, with exposure lasting beyond 10 hours.

Ninety-day repeat oral dose GLP toxicology studies of BBI608 were performed in both Sprague Dawley rats (at doses of 10, 20 or 40 mg/kg/day) and Beagle dogs (at doses of 10, 30 or 100 mg/kg/day) by oral gavage or capsule dosing, respectively, followed by a 28-day recovery period. Clinical observations, body weights, food consumption, and clinical pathology and histopathology were evaluated. There were no test article-related clinical observations in rats at any dose level. Test article-related effects included decreased body weight gain for male and female rats receiving 40 mg/kg/day. Test article-related organ weight changes at study day (SD) 91 were limited to increased relative (to body weight) mean spleen weight (21.7%), in male rats receiving 40 mg/kg/day. Clinical pathology changes included minimal decreases in total protein, albumin, and calcium in males and females given 40 mg/kg/day, and minimal to mild increases in total white blood cell counts and associated absolute neutrophil and absolute lymphocyte counts in males and females given 40 mg/kg/day. Treatment-related microscopic findings in rats given 40 mg/kg/day included: minimal to mild transitional epithelial hyperplasia and vacuolation in the urinary bladder; minimal to moderate epithelial hyperplasia, hyperkeratosis, inflammatory cell infiltrates and edema in the non-glandular stomach; minimal to mild erythropoiesis and pigmented macrophages in the spleen; and minimal to moderate medullary sinus mastocytosis, erythrocytosis and pigmented macrophages in mesenteric lymph nodes.

In dogs at all dose levels, there were no test article-related changes, including clinical observation, body weight, clinical pathology and histopathology. Treatment with BBI608 had no effect on ophthalmology, no treatment-related effects on any ECG parameters, and all ECGs were considered qualitatively and quantitatively normal for Beagle dogs.

Under the conditions of the study, the NOAEL level (based on clinical observation, laboratory tests, gross and histopathological changes) for rats administered BBI608 daily orally for 90 days was 20 mg/kg/day (human equivalent dose: 120 mg/m^2), and the NOAEL in dogs administered BBI608 daily orally for 90 days was 100 mg/kg/day (human equivalent dose: 2000 mg/m^2).

3.5 PHASE I TRIAL OF BBI608 MONOTHERAPY

The effects of BBI608 in humans have been evaluated in a phase I clinical trial, BBI608-101 (IND 100,887). The trial was a dose-escalation study designed to examine the safety, tolerability, and pharmacokinetics of BBI608 in patients with advanced malignancies of all types, whose cancer had progressed following standard therapy, or for whom no effective standard therapy was available. The preliminary anti-tumor activity of BBI608 was also examined.

In the dose escalation portion, 14 cohorts (N=41) were dosed from 20 mg to 2000 mg/day. Adverse events were generally mild, including grade 1-2 diarrhea, nausea, anorexia and fatigue with a total of 4 grade 3 events (diarrhea and fatigue). MTD was not reached. At 400 mg/day the plasma concentration of BBI608 was sustained at a concentration > 1.5 uM (several fold above the IC_{50}) for >8 hours. RP2D was determined to be 500 mg bid. Among those evaluable for tumor response (RECIST 1.1), disease control (disease stabilization and regression) was observed in 65% of patients. Prolonged time to progression was observed in 46% of evaluable patients, including patients with colorectal (CRC), head & neck, gastric, ovarian, melanoma, and breast cancer. Decreases in tumor markers (CEA and CA125) were also observed in colon cancer and ovarian cancer, respectively.

3.6 PHASE IB/II TRIAL OF BBI608 AND PACLITAXEL

A Phase Ib/II study was initiated to evaluate the safety, recommended phase 2 dose (RP2D), and preliminary signs of activity of BBI608 administered in combination with weekly paclitaxel in several solid tumors, including gastric/GEJ cancer. This study showed that BBI608 can be combined safely with weekly paclitaxel, with an RP2D of BBI608 in this combination determined to be the full monotherapy dose (480 mg, twice daily). The Adverse Event (AE) profile is similar to that of both agents in monotherapy, with no new or additive effects observed. AE attributed to BBI608 were generally mild, consisting primarily of Grade 1 and 2 diarrhea, nausea and vomiting.

The pharmacokinetics (PK) of BBI608 and paclitaxel were examined in the patients enrolled during the phase Ib portion of this study, at BBI608 doses from 400 to 1000 mg total daily dose. No significant difference in plasma exposures were noted with the addition of paclitaxel in comparison to PK data from the BBI608 monotherapy Phase I study.

To date, 7 subjects with advanced gastric/GEJ cancer have been enrolled in this study. All patients were pre-treated, with most having received multiple lines of therapy in the metastatic setting, including prior taxanes.

The Disease Control Rate (DCR) and Objective Response Rate (ORR) for BBI608 in combination with paclitaxel in the gastric/GEJ cancer patients was found to be 6 of 7 enrolled and 3 of 7 enrolled, respectively. Three patients had a partial response (PR) per RECIST 1.1 (100%, 45% and 48% regressions of target lesions), and the additional three patients had prolonged stable disease (SD)—one with 25% regression. The phase II portion of the trial is ongoing, with enriched accrual of patients with previously treated gastric and GEJ cancer. Currently, BBI608 combined with weekly paclitaxel has been administered safely to more than 80 patients.

3.7 EXPECTED POSSIBLE BBI608-RELATED ADVERSE EVENTS

In the BBI608-201 trial of BBI608 and weekly paclitaxel, the AE profile was similar to that of both BBI608 and paclitaxel in monotherapy, with no new, worsened or additive effects observed. As seen in Table 1 below, the most frequent AEs were gastrointestinally-related, most frequently Grade 1 or Grade 2 in severity. No subjects experienced Grade 4 symptoms. Other non-GI-related events included sequelae likely secondary to GI events, such fatigue and dehydration.

Table 1: Subjects with Adverse Events Possibly Related to BBI608 in Combination with Weekly Paclitaxel

		N =55					
System	***Event***	***Grade 1***		***Grade 2***		***Grade 3***	
		#	%	#	%	#	%
Gastrointestinal	Diarrhea	38	69.1%	12	21.8%	10	18.2%
	Nausea	16	29.1%	13	23.6%	1	1.8%
	Vomiting	12	21.8%	7	12.7%	2	3.6%
	Abdominal Pain	8	14.5%	3	5.5%	2	3.6%
	Flatulence	4	7.3%	2	3.6%	0	0.0%
	Fecal Incontinence	1	1.8%	0	0.0%	0	0.0%
	Blood in stool	1	1.8%	0	0.0%	0	0.0%
	Mucositis Oral	1	1.8%	0	0.0%	0	0.0%
	Burping	1	1.8%	0	0.0%	0	0.0%
	Bloating	1	1.8%	1	1.8%	0	0.0%
Constitutional	Fatigue	13	23.6%	11	20.0%	2	3.6%
	Chills	1	1.8%	0	0.0%	0	0.0%
	Weight Loss	1	1.8%	0	0.0%	0	0.0%
Metabolism and Nutrition	Anorexia	9	16.4%	5	9.1%	0	0.0%
	Hypokalemia	3	5.5%	1	1.8%	0	0.0%
	Hypomagnesemia	3	5.5%	1	1.8%	0	0.0%
	Dehydration	2	3.6%	3	5.5%	1	1.8%
Neuro-Psychiatric	Dysgusia	2	3.6%	0	0.0%	0	0.0%
	Confusion	1	1.8%	0	0.0%	0	0.0%
	Dizziness	1	1.8%	0	0.0%	0	0.0%
Renal and Urinary	Urine Discoloration	4	7.3%	1	1.8%	0	0.0%
Skin And Subcutaneous Tissue	Rash Maculo-Papular	1	1.8%	0	0.0%	0	0.0%

Diarrhea

The onset of diarrheal symptoms has been observed to occur predominantly during the first week of dosing. The diarrhea is non-bloody, non-inflammatory, and likely osmotic in etiology due to un-dissolved drug product in the gastrointestinal lumen. Symptoms can also be associated with abdominal cramping, though this is not the rule. As a result of the etiology of the diarrhea, oral fluids have been found to be helpful in preventing or alleviating these symptoms.

Aggressive up-front management with anti-diarrheal agents is effective and recommended, and combination therapy may be particularly useful. If needed, a brief dosing holiday of 1-2 days will promptly improve symptoms, often resolving them completely. Patients should then be re-challenged with BBI608. If symptoms happen to recur, a milder course can be expected.

Nausea, Vomiting, Anorexia, and Weight Loss
Nausea, vomiting, anorexia and weight loss have also been observed during treatment with BBI608. Symptoms often respond well to supportive management or are reversible upon 1 to 3 days of dosing holiday. Management with a $5HT_3$ receptor antagonist anti-emetic, or oral corticosteroids if needed, is effective. More traditional anti-histamine or dopamine antagonist anti-emetic can also be tried. Similar to observed diarrhea, these symptoms are also likely due to un-dissolved drug product in the gastrointestinal lumen. Oral fluids have been found to be helpful in preventing or alleviating these symptoms.

For detailed instructions on the management of treatment-associated diarrhea and other gastrointestinal symptoms, please refer to section 8.1.6.

3.8 PHARMACEUTICAL DATA

BBI608/Placebo

Supplied:

BBI608 is supplied in 80 mg strength capsules. Placebo is supplied in matching capsules.

Stability:
Initial product use dating is 24 months from the date of manufacture and can be extended to a maximum of 5 years from date of manufacture assuming acceptable results at re-assay time-point testing.

Storage:
BBI608 and Placebo capsules should be stored in a tightly closed container at a temperature between 15 to 25ºC (59 °F to 77 °F).

Route of Administration:
Oral: Patients should take BBI608 or Placebo twice daily, approximately one hour prior to or two hours after meals, with the first dose given in the morning and the second dose given approximately 12 hours later.

Paclitaxel

Please refer to the paclitaxel package insert for product description, stability information, storage instructions, and route of administration.

4 *TRIAL DESIGN*

This trial began as an international multi-center, prospective, double-blind, randomized phase III trial of the cancer stem cell inhibitor BBI608 plus weekly paclitaxel *versus* matched placebo plus weekly paclitaxel in patients previously treated for advanced (metastatic or locally advanced and unresectable), gastric or gastroesophageal junction (GEJ) adenocarcinoma.

At the time of this amendment and post-unblinding, the trial will continue in sites with patients who have not yet met the primary study endpoint (death), and with patients currently on protocol therapy who may receive BBI608 and paclitaxel on study based on the clinical judgement of the investigator that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also section 9.1.1 and 9.2.1). Patients will receive study treatment until any of the discontinuation criteria are met (see section 11.1) or until September 15 2017, whichever occurs first. Patients will be followed for serious adverse events.

4.1 STRATIFICATION

Patients will be stratified by:

1. Geographical region (Asia *vs* North America, Europe, and Australia *vs* South America)
2. Time to progression on first line therapy (<6 months vs. ≥6 months from start of first line therapy)
3. Disease measurability by RECIST 1.1 (measurable disease present *vs* not present)
4. Prior taxane therapy (yes *vs* no)

4.2 RANDOMIZATION

Patients will be randomized according to a 1:1 ratio using a permuted block randomization procedure to receive one of the following treatments: BBI608 plus weekly paclitaxel or placebo plus weekly paclitaxel to a planned sample size of 700 subjects.

Patients will be randomized to one of the following two arms:

Arm	Agent(s)	Dose and Route	Duration
1	BBI608	480 mg orally two times daily[1,2]	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST 1.1 criteria.[4,5]
	Paclitaxel	80 mg/m^2 IV, once weekly (for three of every four weeks[3])	
2	Placebo and Paclitaxel	Orally, two times daily[1,2] 80 mg/m^2 IV, once weekly (for three of every four weeks[3])	

[1] BBI608/Placebo should be taken one hour before or two hours after a meal, two times daily, with approximately 12 hours between doses. BBI608/Placebo administration will begin 2 days prior to the paclitaxel infusion on day 1 of cycle 1. These two days are referred to as *run-in day 1* and *run-in day 2*. Run-in day 1 should occur within 2 working days of patient randomization.

[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment, such as taking

BBI608/placebo with approximately 250 mL of fluid over the course of 30 minutes after the dose.

[3] Paclitaxel will be administered weekly via approximately a 1 hour infusion, at least 2 hours after the first daily dose of BBI608/Placebo, on Days 1, 8 and 15 of every 4 week study cycle.

[4] If paclitaxel is discontinued due to toxicity, BBI608/Placebo should be continued as monotherapy until another criterion for stopping treatment is met. If BBI608/Placebo is discontinued due to toxicity, paclitaxel should be continued as monotherapy until another discontinuation criterion is met.

[5] If no other standard therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI608/Placebo may be continued in monotherapy until September 15 2017 as long as it is the opinion of the Investigator that the patient may potentially continue to be deriving benefit

4.3 INCLUSION OF WOMEN AND MINORITIES

Patients enrolled in this study will be representative of the mix of genders, races and ethnicities seen in the general population of patients with gastric and GEJ adenocarcinoma. The effect of the intervention under investigation will be analyzed in gender, racial and ethnic subgroups, with recognition of the potentially limited statistical power of this analysis.

4.4 POTENTIAL CONTINUATION OF TREATMENT POST- UNBLINDING

Following unblinding, patients who have not yet met the primary study endpoint (death), and are currently on protocol therapy, may receive study treatment based on the clinical judgement of the investigator that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also Section 9.1.1 and 9.2.1). Patients will receive study treatment until any of the discontinuation criteria are met or until September 15 2017, whichever occurs first (see Section 11.1).

5 *STUDY POPULATION*

The trial population will consist of subjects with advanced (metastatic or locally advanced and unresectable) cytological or histologically confirmed gastric and GEJ adenocarcinoma. Subjects will have failed treatment with one regimen containing a fluoropyrimidine and a platinum-based agent in the metastatic setting.

5.1 INCLUSION CRITERIA

Questions about eligibility criteria should be addressed prior to randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Written, signed consent for trial participation must be obtained from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study specific procedure.

5.1.2 Must have cytologically or histologically confirmed advanced gastric or GEJ adenocarcinoma that is metastatic or locally advanced and unresectable (with unresectability as defined by National Comprehensive Cancer Network Guidelines for Gastric Cancer [Version 2.2013] and Esophageal and Esophagogastric Junction Cancer [Version 2.2013]). GEJ cancers may include Siewert Class I, II or III types *[Siewert 1996]*.

5.1.3 Must have failed treatment with one regimen containing at least a platinum/fluoropyrimidine doublet for unresectable or metastatic disease. While not mandated, concomitant treatment with an anthracycline (epirubicin or doxorubicin) or anti-HER2 therapy (trastuzumab) in this setting is allowed. Patients who have progression of disease at any point during neoadjuvant or adjuvant treatment with a platinum/fluoropyrimidine doublet or < 6 months after the last dose of neoadjuvant or adjuvant treatment may be enrolled.

Treatment failure is defined as progression of disease (clinical or radiologic) during first line treatment for unresectable or metastatic disease or ≤ 6 months after last dose of first line treatment.

No additional prior lines of therapy in the metastatic setting will be allowed. A patient who has received neoadjuvant or adjuvant treatment, relapsed, and then received a platinum/fluoropyrimidine doublet as first-line treatment in the unresectable/metastatic setting would be allowed, however.

Patients who have received prior taxane therapy may be enrolled, so long as the taxane was administered in the adjuvant or neoadjuvant setting and progression occurred more than 6 months following completion of therapy. Patients who were intolerant to paclitaxel are not allowed, however.

5.1.4 Paclitaxel therapy is appropriate for the patient and is recommended by the Investigator.

5.1.5 Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease done within 21 days prior to randomization. Patients with either measurable disease OR non-measurable evaluable disease will be eligible.

5.1.6 Must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

5.1.7 Must be ≥ 18 years of age.

5.1.8 *For male or female patient of child producing potential:* Must agree to use contraception or take measures to avoid pregnancy during the study and for 6 months after the final dose of Paclitaxel or for 30 days for female patients and for 90 days for male patients, of the final BBI608/Placebo dose if Paclitaxel was not administered.

Adequate contraception is defined as follows:

1. Complete true abstinence: when this is in line with the preferred and usual lifestyle of the subject.
2. Consistent and correct use of one of the following methods of birth control:
   a. male partner who is sterile prior to the female subjects entry into the study and is the sole sexual partner for that female subject; or
   b. implants of levonorgesterol; or
   c. injectable progestagen; or
   d. any intrauterine device (IUD) with a documented failure rate of less than 1% per year; or
   e. oral contraceptive pill (either combined or progesterone only); or
   f. two barrier methods, for example diaphragm with spermicide plus condom with spermicide to be used by the patient and the partner.

5.1.9 Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 5 days prior to randomization. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhoea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL). Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be of child bearing potential.

5.1.10 Must have alanine transaminase (ALT) ≤ 3 × institutional upper limit of normal (ULN) [≤ 5 × ULN in presence of liver metastases] within 14 days prior to randomization.

5.1.11 Must have hemoglobin (Hgb) ≥ 9.0 g/dL within 14 days prior to randomization. Must not have required transfusion within 1 week of baseline Hgb assessment.

5.1.12 Must have total bilirubin ≤ 1.5 × institutional ULN [≤ 2.0 x ULN in presence of liver metastases] within 14 days prior to randomization.

5.1.13 Must have creatinine ≤ 1.5 × institutional ULN or Creatinine Clearance > 50 ml/min (as calculated by the Cockroft-Gault equation) within 14 days prior to randomization.

5.1.14 Must have absolute neutrophil count ≥ 1.5 x 10^9/L within 14 days prior to randomization.

5.1.15 Must have platelet count ≥ 100 x 10^9/L within 14 days prior to randomization. Must not have required transfusion within 1 week of baseline platelet assessment.

5.1.16 Other baseline laboratory evaluations, listed in Section 6.0, must be done within 14 days prior to randomization.

5.1.17 Patient must consent to provision of, and investigator(s) must confirm access to and agree to submit a representative formalin fixed paraffin block of tumor tissue in order that the specific correlative marker assays proscribed in Section 14.6 (Correlative Studies) of this protocol may be conducted. Submission of the tissue does not have to occur prior to randomization. Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 10-30 unstained slides of whole sections of representative tumor tissue are preferred. Where it is not possible to obtain two 2 mm cores of tumor from the block, 10-30 unstained slides of representative tumor tissue are also acceptable. Where no previously resected or biopsied tumor tissue exists or is available, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.

5.1.18 Patient must consent to provision of a sample of blood in order that the specific correlative marker assays proscribed in Section 14.6 (Correlative Studies) may be conducted.

5.1.19 Patients must be accessible for treatment and follow-up. Patients registered on this trial must receive protocol treatment and be followed at the participating center. This implies there must be reasonable geographical limits placed on patients being considered for this trial. Investigators must ensure that the patients randomized on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

5.1.20 Protocol treatment is to begin within 2 working days of patient randomization.

5.1.21 The patient is not receiving therapy in a concurrent clinical study and the patient agrees not to participate in other interventional clinical studies during their participation in this trial while on study treatment. Patients participating in surveys or observational studies are eligible to participate in this study.

5.2 EXCLUSION CRITERIA

Patients who fulfil any of the following criteria are not eligible for admission to the study:

5.2.1 Anti-cancer chemotherapy or biologic therapy if administered prior to the first planned dose of BBI608/placebo within period of time equivalent to the usual cycle length of the regimen. An exception is made for oral fluoropyrimidines (e.g. capecitabine, S-1), where a minimum of 10 days since last dose must be observed prior to the first planned dose of BBI608/placebo.

Radiotherapy, immunotherapy, or investigational agents within four weeks of first planned dose

of BBI608/placebo, with the exception of a single dose of radiation up to 8 Gray (equal to 800 RAD) with palliative intent for pain control up to 14 days before randomization.

5.2.2 Prior taxane therapy in the neoadjuvant or adjuvant setting with progression occurring within 6 months of completion of taxane therapy; or any taxane therapy in the metastatic setting.

5.2.3 More than one prior chemotherapy regimen administered in the metastatic setting.

5.2.4 Major surgery within 4 weeks prior to randomization.

5.2.5 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 randomization. Patients with known leptomeningeal metastases are excluded, even if treated.

5.2.6 Women who are pregnant or breastfeeding.

5.2.7 Gastrointestinal disorder(s) which, in the opinion of the Qualified/Principal Investigator, would significantly impede the absorption of an oral agent (e.g. active Crohn's disease, ulcerative colitis, extensive gastric and small intestine resection).

5.2.8 Severe hepatic impairment as per the Paclitaxel Summary of Product Characteristics.

5.2.9 History of severe hypersensitivity to paclitaxel or to any of the excipients, including macrogolglycerol ricinoleate.

5.2.10 Unable or unwilling to swallow BBI608/placebo capsules daily.

5.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure (> class II New York Heart Association (NYHA), unstable angina pectoris (including angina symptoms at rest, new onset angina begun $\leq$ 3 months prior, or myocardial infarction $\leq$ 6 months prior), clinically significant cardiac arrhythmia requiring anti-arrhythmic therapy, clinically significant valvular or pericardial disease, severe uncontrolled arterial hypertension, 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.

5.2.12 Peripheral neuropathy $\geq$ CTCAE Grade 2 at baseline

5.2.13 Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix and in-situ cancer of the urinary bladder, or other solid tumors curatively treated with no evidence of disease for $\geq$ 3 years.

5.2.14 Prior treatment with BBI608

5.2.15 Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy.

5.2.16 Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the

protocol.

6 *PRE-TREATMENT EVALUATION*

(See Appendix I)

Investigations		Timing prior to randomization[8]
History and Physical Exam including:	• Prior medical and therapeutic history[1] • Physical examination • Vital signs • Height, weight, ECOG performance status • Clinical tumor measurements • Concurrent medication list	≤ 14 days
Hematology	• CBC + differential • Platelet count	≤ 14 days[8]
Biochemistry	• Creatinine[2], Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	≤ 14 days[8]
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	≤ 14 days[8]
Cardiac Assessment	• ECG (12 lead)	≤ 28 days
Radiology & Imaging	• CT/MRI scan of chest/abdomen/pelvis with tumor measurement and evaluation by RECIST 1.1 criteria[3]	≤ 21 days
Correlative Studies	• Submission of representative block of diagnostic tumor tissue[4]	On request
	• Blood sample collection[5]	≤ 14 days
Other Investigations	• Serum or urine pregnancy test[6]	≤ 5days
Adverse Events[7]	• Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	≤ 14 days
Quality of Life	• EORTC QLQ-C30	≤ 14 days

1 Medical history must include date of diagnosis including histological documentation of malignancy, documentation of *Her2* status of tumor (if available), smoking history, prior anticancer therapy and prior date(s) of disease progression.

2 Baseline creatinine or creatinine clearance may be used to demonstrate eligibility as per section 5.1.

3 Standard tumor measurement procedures will be followed to assess response to therapy. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment.

4 Details for collection, processing, storing and shipping these samples will be provided in a separate laboratory procedure manual.

5 Details for collection, processing, storing and shipping these samples will be provided in a separate laboratory procedure manual.

6 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

7 Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III).

8 If required laboratory tests cannot be performed within indicated timelines due to technical reasons, lab retest and prolongation of the screening period for 3 working days is allowed.

7 *ENTRY/RANDOMIZATION PROCEDURES*

7.1 ENTRY PROCEDURES

All randomizations will be done through the BBI608-336 randomization and trial supply management (RTSM) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation.

All eligible patients enrolled on the study by the participating treatment center will be assigned a subject identification number which must be used on all documentation and correspondence.

The following information will be required:

- patient's date of birth (as allowed by local regulations) and age
- patient's initials (as allowed by local regulations)
- confirmation of the requirements listed in section 5.1 and 5.2
- stratification factors

7.2 STRATIFICATION

The permuted block randomization procedure will balance between treatment arms within each of the following stratification factors:

- Geographical region (Asia *vs* North America, Europe, and Australia *vs* South America)
- Time to progression on first line therapy (<6 months *vs* ≥6 months from start of first line therapy)
- Disease measurability by RECIST 1.1 (measurable disease present *vs* not present)
- Prior taxane therapy (yes *vs* no)

7.3 RANDOMIZATION

Patients will be randomized 1:1 between the two treatment arms and the randomization will be provided electronically (via RTSM).

Note: The validity of results of the trial depends on the authenticity of, and the follow-up of, all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients randomized to the trial will be followed by the coordinating center. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death or until sites are informed by the study sponsor that further follow-up is no longer required.

8 *TREATMENT PLAN*

Protocol treatment is to begin within 2 working days of patient randomization.

8.1 TREATMENT PLAN

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. Details of interventions (e.g. medications such as antibiotics, analgesics, antihistamines, steroids, G-CSF, erythropoietin), procedures (e.g. paracentesis, thoracentesis), or blood products (e.g. blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the case report forms.

8.1.1 BBI608 Adverse Event Prophylaxis

Gastrointestinal Prophylaxis

The major adverse events associated with the use of BBI608 are gastrointestinal events (nausea, diarrhea, and abdominal cramping) and fatigue. Fatigue is often secondary to gastrointestinal events. There is no hematologic toxicity associated with BBI608. We recommend that pre-exiting laxative bowel regimens, such as stool softeners, be held starting the day prior to first dose of study treatment and may be resumed in cases of no bowel movement during the first 2 days of protocol treatment. Fiber supplementation may be continued. Additionally, prophylactic anti-diarrheal medications, such as Loperamide and/or Diphenoxylate/Atropine, starting 1 day prior to start of BBI608 are strongly recommended for all patients. Details regarding the use of prophylactic medication for the management of common BBI608 related gastrointestinal adverse events are specified in the supplementary Adverse Event Management handout as well as in the Pharmacy Manual.

No hematologic toxicity related to BBI608 treatment has been observed.

Pre-Medication Recommendations for BBI608:

Category	*Specific Measures*	*Start*	*End*
Anti-Diarrheal	Loperamide 4 mg BID or Diphenoxylate/Atropine 5 mg BID	24 hour 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

8.1.2 Drug Administration

Treatment will progress in 4 week (28 day) study cycles, with BBI608/Placebo administered continuously, and paclitaxel administered once weekly, 3 out of 4 weeks. BBI608/Placebo administration will begin 2 days prior to the paclitaxel infusion on day 1 of cycle 1. These two days are referred to as *run-in day 1* and *run-in day 2*.

Arm	Agent(s)	Dose and Route	Duration
1	BBI608	480 mg orally two times daily[1,2]	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST 1.1 criteria. [4,5]
	Paclitaxel	80 mg/m^2 IV, once weekly (for three of every four weeks[3])	
2	Placebo and Paclitaxel	Orally, two times daily[1,2] 80 mg/m^2 IV, once weekly (for three of every four weeks[3])	

[1] BBI608/Placebo should be taken one hour before or two hours after a meal, two times daily, with approximately 12 hours between doses. BBI608/Placebo administration will begin 2 days prior to the paclitaxel infusion on day 1 of cycle 1. These two days are referred to as *run-in day 1* and *run-in day 2*. Run-in day 1 should occur within 2 working days of patient randomization.

[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment, such as taking BBI608/placebo with approximately 250 mL of fluid over the course of 30 minutes after the dose.

[3] Paclitaxel will be administered weekly via approximately a 1 hour infusion, at least 2 hours after the first daily dose of BBI608/Placebo, on Days 1, 8 and 15 of every 4 week study cycle.

[4] If paclitaxel is discontinued due to toxicity, BBI608/Placebo should be continued as monotherapy until another criterion for stopping treatment is met. If BBI608/Placebo is discontinued due to toxicity, paclitaxel should be continued as monotherapy until another criterion for stopping treatment is met.

[5] If no other standard therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI608/Placebo may be continued in monotherapy as long as it is the opinion of the Investigator that the patient may potentially continue to be deriving benefit

Patients will receive BBI608 or placebo two times daily, approximately one hour prior to or two hours after meals, with the first dose given in the morning and the second dose given approximately 12 hours later.

Paclitaxel will be administered via IV at 80 mg/m^2 once weekly as approximately a 1-hour infusion, on Days 1, 8 and 15 of each 28 day study cycle. Paclitaxel will be administered at least 2 hours after the first daily dose of BBI608/Placebo. Paclitaxel administration should proceed based on body surface area (BSA) according to the manufacturer's instructions and local standard practice (with respect to pre-treatment laboratory evaluation, clinical assessment, pre-medication, and monitoring during and after the infusion). The BSA of an individual can be calculated from the formula of Dubois [BSA (m^2) = Body weight (kg)$^{0.425}$ X Height (cm)$^{0.725}$ X 0.007184].

If paclitaxel is permanently discontinued due to toxicity, BBI608/Placebo should be continued as monotherapy until September 15 2017 or until another criterion for stopping treatment is met, whichever occurs first. If BBI608/Placebo is permanently discontinued due to toxicity, paclitaxel should be continued as monotherapy until September 15 2017 or until another criterion for stopping treatment is met.

As BBI608 targets cancer stem cells, it is possible that continued therapy after progressive disease per RECIST 1.1 may provide clinical benefit. If no other standard therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI608/Placebo may be continued in monotherapy as long as it is the opinion of the Investigator that the patient may be deriving benefit with continued therapy.

Handling instructions for BBI608/placebo will be provided to all sites. Investigators may refer to the Investigator Brochure for detailed instructions.

Drug Administration Post-Unblinding

Following this amendment and post-unblinding, the trial will continue in sites with patients who have not yet met the primary study endpoint (death), and with patients currently on protocol therapy and who may receive study treatment based on the clinical judgement of the investigator that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also Section 9.1.1 and 9.2.1). Patients will receive study supply BBI608 until any of the discontinuation criteria are met (see section 11.1) or until September 15 2017. Patients will be followed for serious adverse events.

Arm	Agent(s)	Dose and Route	Duration
1	BBI608	480 mg orally two times daily[1,2]	Patients may continue to receive protocol therapy until September 15 2017 as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST 1.1 criteria. [4,5,6]
	Paclitaxel	80 mg/m^2 IV, once weekly (for three of every four weeks[3])	
2	Paclitaxel	80 mg/m^2 IV, once weekly (for three of every four weeks[3])	

[1] BBI608 should be taken one hour before or two hours after a meal, two times daily, with approximately 12 hours between doses. BBI608 administration will begin 2 days prior to the paclitaxel infusion on day 1 of cycle 1. These two days are referred to as *run-in day 1* and *run-in day 2*. Run-in day 1 should occur within 2 working days of patient randomization.

[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment, such as taking BBI608 with approximately 250 mL of fluid over the course of 30 minutes after the dose.

[3] Paclitaxel will be administered weekly via approximately a 1 hour infusion, at least 2 hours after the first daily dose of BBI608, on Days 1, 8 and 15 of every 4 week study cycle.

[4] If paclitaxel is discontinued due to toxicity, BBI608 may be continued as monotherapy until September 15 2017 or until another criterion for stopping treatment is met, whichever occurs first. If BBI608 is discontinued due to toxicity, paclitaxel should be continued as monotherapy until September 15 2017 or until another criterion for stopping treatment is met, whichever occurs first.

[5] If no other standard therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI608 may be continued in monotherapy until September 15 2017 as long as it is the opinion of the Investigator that the patient may potentially continue to be deriving benefit.

[6] Study treatment with BBI608 with or without paclitaxel may be continued until September 15 2017 as long as the patient has not met any other study discontinuation criteria and as long as it is the opinion of the Investigator that the patient may continue to be deriving benefit.

8.1.3 Blinding/Unblinding

This trial was initiated as a double blind, placebo controlled study. Following the interim analysis, the study was amended to allow un-blinding of patients receiving study treatment. The Investigator may break the blind to determine study arm assignment of each individual patient remaining on study treatment in order to help inform the patient prior to determining if study

treatment should be continued or discontinued.

8.1.4 Patient Monitoring

For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit, and are to be instructed to call their physician to report any adverse events between visits.

8.1.5 BBI608/Placebo Dose Modification

The major adverse events associated with the use of BBI608 are gastrointestinal issues (nausea, diarrhea, and abdominal cramping) and fatigue. Fatigue is often secondary to gastrointestinal events. There is no hematologic toxicity associated with BBI608. We recommend that standing bowel regimens, such as stool softeners, be held at start of study and may be resumed in cases of no bowel movement during the first 2 days of protocol treatment. Fiber supplementation may be continued.

The guidelines which follow outline dosing modifications and recommended interventions should the above adverse events occur.

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (see Appendix III). If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

8.1.5.1 Hematologic Adverse Events

No hematologic toxicity related to BBI608 treatment has been observed. Should a study subject experience a Grade 1 or 2 hematologic adverse event, dosing may continue while an alternate explanation is sought and/or a therapeutic intervention is undertaken.

In the unlikely event of a Grade 3 or 4 hematologic adverse event related to BBI608/placebo, please contact the study Medical monitor, so that together with the study Investigator, the Medical Monitor can make recommendations on medical management. Since a Grade 3 or 4 hematologic event attributed to BBI608 has not been reported, a prompt evaluation for an alternate explanation is strongly recommended.

8.1.5.2 Non-Hematologic Adverse Events

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Appendix III).

BBI608/Placebo Dose Modification:

Suspected BBI608 -Related Adverse Event	Investigator Action
Grade 1 or tolerable Grade 2 Symptoms	Patient should remain at current dose. Attempt pharmacologic measures to minimize symptoms (see symptom specific treatment table below).
Intolerable Grade 2 Symptoms	If intolerable symptoms persist despite optimized medical management,

	dose reduction and sufficient oral hydration are recommended. A dose interruption of ½ to 3 days prior to reduction can also be considered. Dosing should be reduced to the next Modification Level on the *dose modification table*. Pharmacologic symptom support and/or prophylaxis should be maintained. After a dose reduction, AM and PM doses may be increased in 80 mg increments every 3-7 days as tolerated.*, **
Grade 3 or 4 Symptoms	A dose interruption of ½ to 3 days is recommended until symptoms are reduced to ≤ tolerable grade 2. Dosing should be reduced to the next Modification Level on the *dose modification table*. Pharmacologic symptom support and/or prophylaxis should be maintained. After a dose reduction, AM and PM doses may be increased in 80 mg increments every 3-7 days as tolerated.*, **
* If, during the course of re-escalation, a dosing regimen is not tolerated despite optimized medical management, dosing should return to the highest previously tolerated dosing regimen. ** Asymmetry between AM and PM dose is allowed during re-escalation (e.g. 320 mg AM/240 mg PM).	

BBI608/Placebo Dose Modification Table:

Dose Level	Dose
Full dose	480 mg twice daily (q12h)
Modification Level-1	240 mg twice daily (q12h), up titrate as tolerated**
Modification Level-2	80 mg twice daily (q12h), up-titrate as tolerated**
Modification Level-3	80 mg once daily*, up-titrate as tolerated**
* If 80 mg once daily is not tolerated, a dose interruption of 1-3 days followed by re-challenge at 80 mg once daily is recommended. ** Morning and evening doses can be increased in 80 mg increments every 3-7 days or slower as tolerated, up to 480 mg two times daily.	

Recommended symptom-specific supportive treatment for common BBI608-related adverse events is as follows (unless contraindicated):

Diarrhea & Abdominal Cramping	
Dicyclomine *(e.g., Bentyl)*: Recommended when the predominant issue is cramping or abdominal pain	
Diphenoxylate/atropine *(Lomotil)* **Loperamide** *(Imodium)*	These agents may be also be useful in combination
Systemic opioids (e.g. *Dilaudid, Codeine*): have been found effective in reducing abdominal pain and watery diarrhea	
Hyoscine *(Buscopan, Scopolamine, Levsin)*: Anti-spasmodic agents helpful for abdominal cramping	
Budesonide (Entocort EC): Corticosteroid with limited systemic absorption; 9 mg once daily for 8 to 12 weeks	

Nausea, Vomiting, or Anorexia
1st line: 5HT3-inhibitors *(Ondansetron, Palonosetron, Granisetron)*
2nd line: Dexamethasone *(Decadron)*, ideally in combination with a 5HT3-inhibitor. Short term use can be very effective
Other agents: anti-histamines, benzodiazepines, proton pump inhibitors/H2 antagonists, dopamine antagonists, and cannabinoids

Details regarding the use of supporting medication for the management of common BBI608-related adverse events are specified in the supplementary Adverse Event Management hand out as well as in the Pharmacy Manual.

8.1.5.3 *Other Situations*

Change in Urine Color and Odor:
Occasionally, subjects have reported an orange-brown color change to their urine. Rarely, subjects also report a new odor to their urine. All subjects should be made aware of the possibility of these effects. Patients can be reassured that these effects have no long term consequences, and that the effects are completely reversible. Dosing can be continued in the presence of these events.

8.1.6 Paclitaxel Dose Modification

Prior to each dose of paclitaxel, the absolute neutrophil count (ANC) and platelet count should be evaluated. If abnormalities are observed, and in the opinion of the investigator the myelosupression is most likely a result of paclitaxel therapy, dose modification should occur in the following manner:

Lab Value	Investigator Action
ANC ≥ 1.5 x 10^9/L **AND** platelets ≥ 100 x 10^9/L	Continue treatment at full (current) dose.
ANC 1.0-1.5 x 10^9/L **OR** platelets 75-100 x 10^9/L	Consider treatment at *next lower dose level or more (at discretion of Investigator)**. Paclitaxel does not need to be held.
ANC <1.0 x 10^9/L **OR** platelets < 75 x 10^9/L	Hold paclitaxel for that week. Recommence treatment at the *next lower dose level or more* at the next scheduled visit if ANC and platelet count have recovered (ANC ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L). **
*or maintain at full (current) dose ** Neupogen/G-CSF may be used at the discretion of the Investigator.	

The paclitaxel dose should be reduced by one or more dose levels if the dose is held more than once during a 4 week cycle.

For patients who experience a grade 3 non-hematologic adverse event (except alopecia), and in the opinion of the investigator the event is most likely a result of paclitaxel therapy, the dose of paclitaxel should be held until the adverse event has improved to grade 2, and then reduced by one or more dose levels for subsequent doses of paclitaxel.

Paclitaxel Dose Modification Table:

Dose Level*	Dose
Full dose	80 mg/m^2
Modification Level-1	70 mg/m^2
Modification Level-2	60 mg/m^2
Modification Level-3	40 mg/m^2**
* If the dose of paclitaxel is reduced because of potentially-related AEs, subsequent dose increases are not permitted. ** If paclitaxel dose is required to be reduced below 40 mg/m^2, or if any life-threatening paclitaxel-related events occur, paclitaxel should be permanently discontinued.	

When laboratory parameters indicate that the dose of paclitaxel should be delayed, the infusion of paclitaxel scheduled for that day is not given. The infusion is considered "missed", and is not made up at another time. The next paclitaxel infusion would be according to the protocol specified administration schedule. Laboratory parameters should be evaluated prior to the next scheduled dose of paclitaxel and actions taken according to the protocol parameters.

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

Paclitaxel has been shown to be a teratogen, embryotoxic and a mutagen. Therefore, female and male patients of reproductive age must take contraceptive measures during therapy and for 6 months after last dose of paclitaxel. Additionally, male patients are advised to seek advice on cryopreservation of sperm prior to treatment with paclitaxel due to the possibility of irreversible

infertility with paclitaxel therapy.

If paclitaxel is held or discontinued for toxicities solely related to paclitaxel, BBI/placebo therapy should be continued.

If BBI608/Placebo is permanently discontinued due to toxicity, paclitaxel therapy should be continued.

8.1.7 Concomitant Medications/Procedures

Permitted Treatments:
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).

As per the Summary of Product Characteristics for paclitaxel, although CYP2C8 inhibitors or inducers are permitted, caution should be exercised when co-administering these agents with paclitaxel. Similarly, caution should be exercised while co-administering CYP1A2 inhibitors and/or substrates of CYP enzymes 1A2, 2D6, 2C19 and 3A4 with BBI608.

Palliative and supportive care for disease-related symptoms will be offered to all patients.

All palliative and supportive care measures may be administered to patients in either study arm at the Investigator's discretion. Incident palliative radiotherapy is permitted in both study arms while on study, but requirement of radiation to the target lesion(s) will qualify the patient as having disease progression.

Although patients will have either metastatic or locally advanced but unresectable disease at randomization, it is possible that a patient's tumor may become operable over the course of treatment. Resection is allowed, and it is recommended that paclitaxel be held for 1 week prior to the surgery and 2 weeks after the surgery, or until post-surgical recovery, whichever is longer. BBI608 should be held 24 hours prior to the surgery to 1 week after the surgery as tolerated.

Non-Permitted Treatments:
Concurrent chemotherapy, hormonal therapy (except corticosteroids), immunotherapy, biologic therapy OR other experimental agents should not be given to study patients while on protocol treatment.

8.1.8 Duration of Therapy

Patients may continue to receive protocol therapy until September 15 2017 as long as they have not experienced any adverse events requiring permanent discontinuation of protocol treatment and have not demonstrated disease progression based on RECIST 1.1 criteria. For details concerning toxicity, please consult section 8.1.4 and 8.1.5. For a complete list of general criteria for stopping study treatment, please see section 12.0.

8.1.9 Patient Compliance

Treatment compliance for BBI608/Placebo is defined as the ratio, expressed as a percentage, of the number of capsules (BBI608 or placebo) taken by a patient over the course of a time interval

to the number of capsules intended to be taken over that same time interval as per the dose prescribed by the Investigator.

Treatment compliance for paclitaxel is defined as the ratio, expressed as a percentage, of the amount of paclitaxel administered to a patient (milligrams/m^2) over the course of a time interval to amount of paclitaxel intended to be administered over that same time interval as per the dose prescribed by the Investigator.

Treatment compliance in both arms will be monitored by drug accountability, as well as the monitoring of patient-reported compliance.

9 *EVALUATION DURING AND AFTER PROTOCOL TREATMENT*

Evaluations will be performed at different intervals throughout the study. If dose delays occur for any reason on the study, other study assessments, including assessment by physician and Quality of Life questionnaires, will not be delayed, but should continue at the time indicated from randomization.

9.1 EVALUATION DURING PROTOCOL TREATMENT

Investigations		Timing
Physical Examination	• Physical examination • Vital signs • ECOG Performance status • Concurrent medication list	Day 1 of every 28 day study cycle, starting with Cycle 2[1] (+/-3 days)
Weight	• Weight	Day 1 of every 28 day study cycle[1] AND On each additional paclitaxel infusion day (hematology investigations should be performed within 72 hours prior to Day 1 of each study cycle, and within 72 hours prior to each paclitaxel infusion)
Hematology	• CBC + differential, Platelet count	
Biochemistry	• Creatinine, Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	Day 1 of every 28 day study cycle, starting with Cycle 2[1] (laboratory investigations should be performed within72 hours prior to Day 1 of each study cycle)
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	
Other Investigations	• Serum or urine pregnancy test [2]	
Adverse Events [3]	• Adverse Event evaluation must be done at each study visit[3]	Day 1 of every 28 day study cycle AND On each additional paclitaxel infusion day
	• Adverse Event evaluation by phone[3]	On *run-in day 2*
Cardiology Assessment	• ECG	Within 2 hours of completion of paclitaxel infusion on first day of paclitaxel treatment and as clinically indicated thereafter

Serious Adverse Events [4]	Serious Adverse Event evaluation will be done from the time of informed consent and for 30 days following the last dose of protocol therapy.	
Radiology & Imaging	• CT/MRI scan as per baseline assessment with tumor measurement and evaluation by RECIST 1.1 criteria[5]	Every 8 weeks (every 56 days) after randomization[5] (+/-5 days)
Correlative Studies	• Submission of blood samples[6]	At 4 weeks after randomization (+/-3 days)
Sparse PK Collection	• Submission of blood plasma samples to central lab[6]	At Day 8 and 15 of Cycle 1 and Day 1 of Cycle 2 (corresponding to the 2nd, 3rd and 4th paclitaxel infusion days)
Quality of Life	• EORTC QLQ-C30 [7]	At 4, 8, 12, 16 and 24 weeks after randomization (+/- 3 days)
Paclitaxel Administration	• IV paclitaxel infusion	Days 1, 8 and 15 of every 4 week (28 day) study cycle (+/-3 days)

1 Patients are to be assessed every 4 weeks (28 days) while on study medication and until September 15 2017 or until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days, whichever occurs first.
2 In women of childbearing potential only a negative pregnancy test must be demonstrated every 4 weeks until 4 weeks after the administration of the final dose of protocol therapy. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
3 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III).
4 Serious adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III).
5 The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until September 15 2017 or until progressive disease is documented (as described in section 10), whichever occurs first. For patients who remain on protocol therapy after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumor measurements and assessment must be reported until September 15 2017.
6 Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.
7 To be completed in clinic. Questionnaires should be completed prior to any interactions with clinical team to avoid any influence.

9.1.1 Patient Evaluation After Unblinding and Continued Protocol Treatment

Please refer and follow section 9.1 until permanent discontinuation of protocol treatment or until September 15 2017, whichever occurs first.

9.2 EVALUATION AFTER PROTOCOL TREATMENT DISCONTINUATION

Investigations		Timing
Physical Examination	• Physical examination • Vital signs • Weight + ECOG Performance status • Subsequent cancer treatments[1] • Concurrent medication list	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days. (+/- 3 days)
Adverse Events [2]	• Adverse Event evaluation must be done at each study visit[2]	
Serious Adverse Events [3]	Serious Adverse Event evaluation will be done from the time of informed consent and for 30 days following the last dose of protocol therapy.	
Overall Survival	• Assess for survival of patient [4]	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days, and every 8 weeks (56 days) thereafter. (+/- 3 days)
Other Investigations	• Serum or urine pregnancy test [5]	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Hematology	• CBC + differential, Platelet count	
Biochemistry	• Creatinine, Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	
Urinalysis	• Dipstick(including protein, specific gravity, glucose and blood)	
Cardiology Assessment	• ECG	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Radiology & Imaging	• CT/MRI scan as per baseline assessment with tumor measurement and evaluation by RECIST 1.1 criteria [6]	Every 8 weeks (56 days) after randomization until objective disease progression is documented.[6] (+/- 5 days)
Correlative Studies	• Submission of blood samples[7]	At first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Quality of Life	• EORTC QLQ-C30[8]	At first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)

1	After protocol treatment discontinuation Physical examination, Vital signs, ECOG status and subsequent cancer treatment will be recorded at the regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days). Subsequent cancer treatment will be captured until end of study.
2	Adverse events related to protocol treatment will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III). Adverse events relevant to cancer or to subsequent cancer treatments will not be captured. Attribution of adverse events will continue to be recorded following treatment discontinuation.
3	Serious adverse events related to protocol treatment will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III).
4	In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.
5	In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
6	The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until progressive disease is documented (as described in section 10). If a patient discontinues protocol treatment for a reason other than objective progression, every effort should be made to obtain this assessment on the same schedule until progression is observed.
7	Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual. The sample will be collected only if the patient discontinues protocol treatment prior to 4 weeks of therapy.
8	To be completed in clinic. Questionnaires should be completed prior to any interactions with clinical team to avoid any influence. Questionnaire will be collected in the post-treatment discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.

9.2.1 Patient evaluation After Permanent Discontinuation of Protocol Therapy, Post-Unblinding

Sites should complete the evaluations for the current reporting period as per section 9.2. Subsequently, evaluations can switch as follows:

Investigations		Timing
Physical Examination	• Physical examination • Vital signs • Weight + ECOG Performance status • Subsequent cancer treatments[1] • Concurrent medication list	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days. (+/- 3 days)
Adverse Events [2]	• Adverse Event evaluation must be done at each study visit[2]	
Serious Adverse Events [3]	Serious Adverse Event evaluation will be done from the time of informed consent and for 30 days following the last dose of protocol therapy.	
Overall Survival	• Assess for survival of patient [4]	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days, and every 8 weeks (56 days) thereafter. (+/- 3 days)
Other Investigations	• Serum or urine pregnancy test [5]	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Hematology	• CBC + differential, Platelet count	
Biochemistry	• Creatinine, Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	
Urinalysis	• Dipstick(including protein, specific gravity, glucose and blood)	

Cardiology Assessment	• ECG	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Radiology & Imaging	• CT/MRI scan as per baseline assessment with tumor measurement and evaluation by RECIST 1.1 criteria [6]	Every 8 weeks (56 days) after randomization until objective disease progression is documented.[6] (+/- 5 days)
Correlative Studies	• Submission of blood samples[7]	At first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Quality of Life	• EORTC QLQ-C30[8]	At first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)

1 After protocol treatment discontinuation Physical examination, Vital signs, ECOG status and subsequent cancer treatment will be recorded at the regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days) or until September 15 2017, whichever occurs first. Subsequent cancer treatment will be captured until end of study (September 15 2017).

2 Adverse events related to protocol treatment will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III). Adverse events relevant to cancer or to subsequent cancer treatments will not be captured. Attribution of adverse events will continue to be recorded following treatment discontinuation.

3 Serious adverse events related to protocol treatment will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III).

4 In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact until study closure.

5 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

6 The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until September 15 2017 or until progressive disease is documented (as described in section 10), whichever occurs first. If a patient discontinues protocol treatment for a reason other than objective progression, every effort should be made to obtain this assessment on the same schedule until progression is observed or until September 15 2017, whichever occurs first.

7 Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual. The sample will be collected only if the patient discontinues protocol treatment prior to 4 weeks of therapy.

8 To be completed in clinic. Questionnaires should be completed prior to any interactions with clinical team to avoid any influence. Questionnaire will be collected in the post-treatment discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.

10 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 DEFINITIONS

10.1.1 *Evaluable for Adverse Events:* All patients who have received at least one dose of BBI608/placebo will be evaluable for adverse events from the time of their first dose of BBI608/placebo.

10.1.2 *Evaluable for Overall Survival (OS):* All randomized patients will be included in the analysis of OS, which is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis, or who have become lost to follow-up will be censored at their last date known to be alive.

10.1.3 *Evaluable for Progression Free Survival (PFS):* All randomized patients will be included in the analysis of PFS, which is defined as the time interval between the date of randomization and the date of objective disease progression or death, whichever comes first. If neither event has been observed, then the patient will be censored at the date of the last tumor assessment.

Disease progression is defined as objective progression per RECIST 1.1 *[Eisenhauer 2009]*. It is required to perform, whenever possible, a radiological confirmation of the clinical suspicion of tumor progression. In the situation where there is clinical suspicion of progression but objective progression cannot be determined per RECIST 1.1, disease is defined as clinical deterioration without objective evidence of progression.

The date of disease progression is defined as the date when the criteria for objective progression are first met.

10.1.4 *Evaluable for Objective Response Rate (ORR):* Patients with measurable disease by RECIST 1.1 at randomization will be included in the analysis of ORR which is defined as a composite of Partial Response and Complete Response as classified according to the definitions set out below *[Eisenhauer 2009].* For patients who discontinue protocol therapy prior to their first objective assessment of response, it is imperative that an objective response assessment be undertaken as close to the protocol specified schedule as possible.

10.1.5 *Evaluable for Disease Control Rate (DCR):* Patients who have measurable disease by RECIST 1.1 at randomization will be included in the analysis of DCR which is defined as a composite of Stable Disease, Partial Response and Complete Response as classified according to the definitions set out below [Eisenhauer 2009]. For patients who discontinue protocol therapy prior to their first objective assessment of response, it is imperative that an objective response assessment be undertaken as close to the protocol specified schedule as possible.

10.1.6 *Evaluable for Quality of Life Assessment:* All patients who have completed the baseline quality of life questionnaire and at least one other QoL questionnaire are evaluable.

10.2 RESPONSE AND EVALUATION ENDPOINTS

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee.

10.2.1 *Measurable Disease:* Measurable *tumor lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan, or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

10.2.2 *Non-measurable Disease:* All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

10.2.3 *Target Lesions:* When more than one measurable tumor lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

10.2.4 *Non-target Lesions:* All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

10.2.5 *Response:* All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target*. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Eisenhauer 2009]*) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for

tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.

Stable Disease (SD): neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of $\geq$ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	tumor nodes < 10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once $\geq$ 6 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	tumor nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without radiological progression having been observed at that time should be reported as "symptomatic deterioration". This is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

10.3 RESPONSE DURATION

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

10.4 STABLE DISEASE DURATION

Stable disease duration will be measured from the time of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.5 METHODS OF MEASUREMENT

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. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

Additionally, for optimal tumor assessment scanning options are listed below in the decreasing order of preference:

Order of Preference	Scanning Option
1	Chest-Abdomen-Pelvis CT with oral and I.V. contrast
2	Chest CT without I.V. contrast PLUS MRI Abdomen-Pelvis with oral and I.V. contrast[1]
3	Chest-Abdomen-Pelvis CT with oral contrast[2]

[1]If Iodine contrast media is medically contraindicated.
[2]If Iodine contrast media is medically contraindicated and MRI cannot be performed.

10.5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

10.5.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions $\geq$ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

10.5.3 *CT/MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case *[Eisenhauer 2009]*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

10.5.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

10.5.5 *Endoscopy/Laparoscopy*. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

10.5.6 *Cytology/Histology.* These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11 *SERIOUS ADVERSE EVENT REPORTING*

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) and Serious Adverse Event (SAE) reporting (version can be found in Appendix III).

All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting to the Sponsor. The term 'reportable SAE' is used in the definitions which follow to describe those SAE's which are subject to expedited reporting to the Sponsor.

11.1 *SERIOUS ADVERSE EVENT REPORTING ON STUDY POST-UNBLINDING*

Serious adverse events that are considered related (i.e. possibly, probably or definitely) to protocol therapy must continue to be reported in an expedited manner (see Section 10) for patients receiving BBI608 or paclitaxel on study after unblinding.

11.2 DEFINITION OF A PROTOCOL REPORTABLE SERIOUS ADVERSE EVENT

- **All serious** adverse events must be reported in an expedited manner (see section 11.2 for reporting instructions). These include events occurring from the time the patient signs consent until 30 days after last protocol treatment administration. Determination of relationship between the event and study drug should be made by a qualified physician Investigator.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death;
  - is life-threatening;
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care);
  - results in persistent or significant disability or incapacity;
  - is a congenital anomaly/birth defect.
- NOTE: Serious adverse events which are unequivocally related to the underlying malignancy or disease progression do **NOT** require expedited reporting. These include such adverse events as admission for pain control, palliative care or paracentesis of malignant effusions.
- In addition, the following events will **NOT** be recorded as AEs (or SAEs):
  - lack of efficacy/disease progression (will be recorded separately on CRF);
  - elective hospitalization for medical, radiological or surgical procedures for treatment of disease or to simplify treatment for study procedures (will be recorded separately on CRF);
  - hospitalization for palliative care or pain control.

Note: clinically significant test results should be recorded on the AE CRF using the appropriate CTCAE description and grading scale.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization and which are NOT definitively related to the underlying malignancy or disease progression but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.3 SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

SAE reporting will commence following the signature of the informed consent and continue for 30 days following the last dose of BBI608/Placebo.

All protocol specified (section 11.1) reportable serious adverse events must be reported using the SAE Report Form for this trial.

Within 24 hours:	Submit Initial Serious Adverse Event Report
Within 7 days:	Submit Follow-up Serious Adverse Event Report updated with as much detail as possible.

Detailed instructions for the submission of SAE Reports will be provided separately.

11.4 PROCEDURES IN CASE OF AN OVERDOSE

Use of BBI608/Placebo in doses in excess of that specified in the protocol should be reported in the following manner:

If an adverse event(s) is associated with ("results from") the overdose of BBI608/Placebo, the overdose and adverse event are reported on the SAE Report Form, even if no other criteria for serious are met. The SAE Report Form should be submitted within 24 hours. The overdose should also be recorded on the relevant AE form in the eCRF using the term "accidental or intentional overdose with adverse effect."

If the overdose of BBI608/Placebo is not associated with an adverse event, the overdose is reported as a non-serious AE, on the relevant AE form in the eCRF within 24 hours, using the event term "accidental or intentional overdose without adverse effect." The Clinical Research Associate responsible for the investigational center should also be notified of the event within 24 hours.

Investigators/site personnel are to consult the local, approved paclitaxel product label for guidance on the definition of an overdose of this agent as well as for guidance on reporting of any AE or SAE associated with paclitaxel overdose.

11.5 OTHER PROTOCOL REPORTABLE EVENTS – PREGNANCY/EXPOSURE REPORTING

Women of childbearing potential (WOCBP) may be enrolled in this clinical trial. WOCBP are defined as women who have had a menstrual period during the last year and have not had a hysterectomy. Precautions are required to be taken to prevent pregnancy during the clinical trial

when the research population includes WOCBP. This includes pregnancy testing, use of effective methods of birth control, and pregnancy as an exclusion factor. The trial sample informed consent form includes *the potential for unidentified risks to the embryo/fetus.* It also includes general information on pregnancy prevention and the required minimum period during which birth control must be utilized.

11.4.1 *Pregnancy Prevention*

WOCBP and males who are enrolled in the trial must be informed of the requirement to use contraception as outlined in the eligibility criteria (Section 5.1). Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

A highly effective method of birth control is defined as those which result in a failure rate of <1% per year when used consistently and correctly.

11.4.2 Pregnancy Occurring in WOCBP Exposed to Study Agent

Any female participant who becomes pregnant during the course of the trial should be instructed to stop taking study medication immediately.

The investigator should provide counselling and discuss the risks and possible side effects to the embryo/fetus from BBI608 and paclitaxel. Monitoring should continue until conclusion of the pregnancy. The same should occur for female partners of a male participant, or any female exposed to BBI608 when appropriate and compliant with local policy.

11.4.3 Pregnancy/Exposure Reporting

The investigator is required to report to the sponsor any pregnancy where the embryo/fetus could have been exposed to BBI608. This means pregnancies occurring in female participants, female partners of male participants, or females exposed through direct contact with the agent during their pregnancy (for example, environmental exposure involving direct contact with the agent). Pregnancies occurring until 30 days in female patients and until 90 days in partners of male patients, after the completion of BBI608 as well as until 6 months following last paclitaxel infusion must also be reported.

The investigator is required to inform the Sponsor within 24 hours of learning of the pregnancy using the SAE reporting form appropriate for the trial as indicated above. In the Adverse Event column please enter the following: “pregnancy, puerperium and perinatal conditions – other, specify” (fetal exposure). Please note that the patient identification number must correspond to the participant in the main trial. Specifically, in the case of pregnancy in the female partner of a male participant, the male participant’s patient identification number should be used for reporting purposes.

The SAE form must be updated to reflect the outcome of the pregnancy. For example:

- “pregnancy, puerperium and perinatal conditions – other, specify” (normal live birth),
- “pregnancy, puerperium and perinatal conditions – other, specify” (therapeutic abortion), or
- another term under "pregnancy, puerperium and perinatal conditions" as applicable.

Information on the medical history of the parents that may relate to assessing any potential fetal

outcomes is requested, *as is information on the health of the newborn*. The narrative section of the SAE form should be used to communicate all relevant information pertaining to the pregnancy.

11.6 RESPONSIBILITY FOR REPORTING SERIOUS ADVERSE EVENTS TO REGULATORY AGENCIES

Boston Biomedical, or the delegated CRO, will provide expedited reports of SAEs to FDA and other applicable regulatory authorities, for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are related to protocol treatment:

- **Unexpected** adverse events are those which are not consistent in either nature or severity with information contained in the Investigator's Brochure
- Adverse events considered **related to protocol treatment** are those events which lack a plausible alternate explanation.

Boston Biomedical will determine which SAEs meet the criteria for regulatory reporting.

11.7 REPORTING SAFETY REPORTS TO INVESTIGATORS

Boston Biomedical, or the delegated CRO, will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment.

12 *PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING*

12.1 CRITERIA FOR DISCONTINUING PROTOCOL TREATMENT

Patients should stop protocol treatment in the following instances:

- Progressive Disease (see section 10.2.5).
- Pregnancy
- Intercurrent illness which would, in the judgement of the Investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy
- Unacceptable toxicity
- Request by the patient
- Post-unblinding, the trial will continue at sites with patients who have not yet met the primary study endpoint (death), and with patients currently on protocol therapy who may receive BBI608 on study based on the clinical judgement of the investigator that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also section 9.1.1 and 9.2.1). Patients will receive study treatment until any of the discontinuation criteria are met or until September 15 2017, whichever occurs first.

If a patient discontinues protocol treatment for a reason other than objective progression, every effort should be made to obtain tumor evaluations on the same schedule until September 15 2017 or until progression is observed, whichever occurs first.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 DURATION OF PROTOCOL TREATMENT

Patients may continue to receive protocol therapy until September 15 2017 as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST criteria.

As BBI608 targets cancer stem cells, it is possible that continued therapy after progressive disease per RECIST 1.1 may provide clinical benefit. If no other standard therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI608 may be continued in monotherapy until September 15 2017 as long as it is the opinion of the Investigator that the patient may potentially be deriving benefit.

12.3 THERAPY AFTER PROTOCOL TREATMENT IS STOPPED

Treatment after all protocol therapy has been discontinued is at the discretion of the Investigator. Information on post-study anti-cancer treatment will be collected in this study until September 15 2017.

12.4 FOLLOW-UP OFF PROTOCOL TREATMENT

Follow-up will continue after treatment completion according to the plan described in the protocol (see section 9.2). Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.5 UNBLINDING

All patients receiving protocol treatment at the time of this amendment must be unblinded. The process of unblinding patient treatment is contained in Appendix V.

13 *CENTRAL REVIEW PROCEDURES, TISSUE COLLECTION, AND CORRELATIVE STUDIES*

13.1 CENTRAL RADIOLOGY REVIEW

There will be no central radiology review for this study.

13.2 CENTRAL PATHOLOGY REVIEW

There will be no central pathology review for this study.

13.3 TISSUE COLLECTION

Protocol-Mandated Correlative Studies:
The submission of a representative diagnostic tumor tissue and of a blood sample for correlative studies defined in Section 14.6 (Correlative Studies) is mandatory for participation in this trial (although submission of the tissue does not have to occur prior to randomization). Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 10-30 unstained slides of representative tumor tissue are requested. Where it is not possible to obtain two 2 mm cores of tumor from the block, 10-30 unstained slides of representative tumor tissue are requested. Where no previously resected or biopsied tumor tissue exists, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.

After patient consent, blood sample and paraffin tumor blocks will be the preferred tissue material to collect. If tumor blocks are unavailable, then two 2 mm cores of tumor from the block and 10-30 specimen slides are preferred. Where it is not possible to obtain two 2 mm cores of tumor from the block, 10-30 unstained slides of representative tumor tissue are also acceptable. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial and the surgical/ histology number. Material issued to researchers will be anonymous and only identified by a coded number.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

All patients on whom a blood sample and/or diagnostic tumor block is collected will be aware of this retrieval and will have given their consent.

13.4 SPARSE PHARMACOKINETIC PLASMA SAMPLE COLLECTION

Plasma samples for sparse pharmacokinetics (PK) analysis will be obtained from all patients at the study visits occurring on Day 8 and 15 of Cycle 1 and Day 1 of Cycle 2 (corresponding to paclitaxel infusion days).

Day 8 (Cycle 1) Study Visit:
The Day 8 (Cycle 1) visit should be scheduled prior to 10 AM. On the day of this visit, patients should be instructed to wait to take their first daily dose of BBI608/Placebo until they arrive in

clinic. After arrival in the clinic, but within approximately 5 minutes prior to administration of the first daily dose of BBI608/Placebo, a plasma sample will be obtained. Paclitaxel infusion will be started approximately 2 hours after BBI608/Placebo administration. A second plasma sample will be obtained within approximately 30 minutes after the end of the 1 hour paclitaxel infusion.

Day 15 (Cycle 1) Study Visit:
On Day 15 (Cycle 1) visit, patients will be instructed to take BBI608/Placebo as normal. Paclitaxel infusion will be given in clinic at least 2 hours after the BBI608/Placebo administration. A single plasma sample will be obtained between 2 and 4 hours after the completion of the paclitaxel infusion.

Day 1 (Cycle 2) Study Visit:
On Day 1 (Cycle 2) visit, patients will be instructed to take BBI608/Placebo as normal. Paclitaxel infusion will be given in clinic at least 2 hours after the BBI608/Placebo administration. A single plasma sample will be obtained between 5 and 7 hours after the completion of the paclitaxel infusion.

For all days during which a plasma sample is obtained for PK analysis, the precise time of all doses of BBI608/Placebo (on the day of sampling and the day prior), the precise time of the initiation of paclitaxel administration, and the precise time of all PK sampling must be captured.

Samples will be processed, stored and shipped according to the instructions provided in the separate Sparse PK sampling laboratory manual for this study.

14 *STATISTICAL CONSIDERATIONS*

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

14.1 OBJECTIVES AND DESIGN

The primary objective of this study is to assess the effect of orally administered BBI608 plus weekly paclitaxel, in comparison to placebo plus weekly paclitaxel on the Overall Survival in patients with pre-treated advanced gastric/GEJ adenocarcinoma.

Secondary objectives include comparisons of Overall Survival in the predefined biomarker-positive population, Progression Free Survival, and Adverse Events between the two treatment arms.

This study began as a multi-center, prospective, double blind, placebo controlled, randomized phase III trial. Patients will be randomized to receive either BBI608 plus weekly paclitaxel, or placebo plus weekly paclitaxel in a 1:1 ratio and will be stratified by geographical region (Asia *versus* North America, Europe, and Australia *versus* South America), time to progression on first line therapy (<6 months *versus* ≥6 months from start of first line therapy), disease measurability by RECIST 1.1 (measurable disease present vs not present), and prior taxane therapy (yes *versus* no).

At the time of this amendment, patients remaining on study treatment will be unblinded and the study will continue as a randomized, open-label, multi-center, phase III study of BBI608 plus weekly paclitaxel vs. weekly paclitaxel for adult patients with advanced, pre-treated gastric or GEJ adenocarcinoma.

14.2 STUDY ENDPOINTS AND ANALYSIS

Primary Endpoint:

Overall Survival in the General Study Population

Overall Survival in the general study population, the primary endpoint of this study, is defined as the time from randomization to death from any cause. Patients who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive. Patients will be analyzed in the arm to which they are randomized regardless of the treatment they received (intent-to-treat analysis). The survival experience of patients in both treatment groups will be summarized by the Kaplan-Meier method and compared primarily by a stratified log-rank test adjusting for stratification variables at randomization.

Sensitivity analyses based on stratified Cox proportional hazards model will also be performed. These sensitivity analyses are not included in the hierarchical testing for secondary outcomes detailed below and, as such, do not control for type I error. Geographical region (Asia *versus*

North America, Europe, and Australia *versus* South America), time to progression on first line therapy (<6 months *versus* ≥6 months from start of first line therapy), disease measurability by RECIST 1.1 (measurable disease present *vs* not present), and prior taxane therapy (yes *versus* no) will be the stratification factors to define the stratified Cox proportional hazards model. Besides the treatment factor (BBI608+paclitaxel *versus* placebo+paclitaxel), the following factors at patient entry will be included in the stratified Cox proportional hazards model:

- Number of previous chemotherapy drug classes [platinum, fluropyrimidine, taxane, anthracyclines], including during adjuvant or neoadjuvant therapy (< 3 *versus* ≥ 3)
- Age (< 65 *versus* ≥ 65)
- Sex (male *versus* female)
- Prior trastuzumab-containing therapy (yes *versus* no)
- Location of primary tumor (gastric *versus* GEJ)
- Prior radiotherapy (yes *versus* no)
- Presence of peritoneal metastases (yes *versus* no)
- Histologic type (diffuse, intestinal, mixed, other)
- Received post protocol anticancer treatment [i.e. 3rd line regimen] (yes *versus* no)
- Number of organ sites involved at baseline (≥2 *versus* <2)
- Presence of primary tumor (present *versus* absent)

A subset analysis for the primary endpoint (OS) as sensitivity analyses will be conducted to address the benefit of BBI608 between the groups defined by the above factors and the following:

- Geographical region (Asia *vs* North America, Europe, and Australia *vs* South America)
- Time to progression on first line therapy (<6 months *versus* ≥6 months from start of first line therapy)
- Disease measurability by RECIST 1.1 (measurable disease present *vs* not present)
- Prior taxane therapy (yes *versus* no)
- Race (white, black, Asian, other)

Again, these sensitivity analyses are not included in the hierarchical testing for secondary outcomes detailed below and, as such, do not control for type I error.

Secondary Endpoints

The following secondary outcomes will be inferentially assessed using a hierarchical analysis method (eg, inferential analysis will stop and not continue to subsequent secondary outcomes after obtaining a probability greater than 0.05). The order of endpoint presentation below reflects the hierarchy of inferential testing. Inferential assessment of secondary outcomes will take place only if the primary outcome (OS) is found to differ significantly between treatments when analyzed via the primary analysis method detailed above.

Overall Survival in the Predefined Biomarker-positive Population

Overall Survival (OS) in the biomarker-positive population [those patients with nuclear β-catenin positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) archival tissue] is defined as the time from randomization to death due to any cause. All analyses

for OS in the general study population will also be performed for OS in the biomarker-positive population, using similar methodology.

Progression-Free Survival in the General Study Population

Progression-Free Survival (PFS) in the general study population is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last tumor assessment. This includes patients who are lost to follow-up or have withdrawn consent. All analyses for OS in the general study population will also be performed for PFS in the general study population, using similar methodology.

Progression-Free Survival in the Predefined Biomarker-positive Population

PFS in the biomarker-positive population [those patients with nuclear β-catenin positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) archival tissue] is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause. All analyses for OS in the general study population will also be performed for PFS in the biomarker-positive population, using similar methodology.

Objective Response Rate in the General Study Population

Objective Response (ORR) is defined as the proportion of patients with a documented complete response or partial response (CR + PR) based on RECIST 1.1. The primary estimate of ORR will be based on patients with measurable disease by RECIST 1.1 at randomization.

Disease Control Rate in the General Study Population

Disease Control Rate (DCR) is defined as the proportion of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1. The primary estimate of DCR will be based on patients with measurable disease by RECIST 1.1 at randomization.

Safety Analysis

All patients who have received at least one dose of study treatment (either BBI608/Placebo or paclitaxel) will be included in the safety analysis. The incidence of adverse events will be summarized by type of adverse event and severity using the NCI Common Terminology Criteria for Adverse Events Version 4.0. A Fisher's exact test will be used to compare adverse events between the two arms if required.

14.3 SAMPLE SIZE AND DURATION OF STUDY

The primary study endpoint is Overall Survival (OS). The study is designed to have a power of 90% and a two-sided alpha of 5% to detect a 24% reduction in the continuous risk of death (HR 0.76, which corresponds to an increase of median survival from 7.36 to 9.67 months) in the Intention to Treat (ITT) general study population. It is estimated that 566 events will be required to detect this reduction which would be observed by randomizing 700 patients over 24 months and following them for an additional 12 months (including up to 5% of yearly dropouts).

Assuming that 40% of deaths occur in patients who are biomarker-positive, the study will have 90% power to detect a 31% reduction in the risk of death (HR 0.69) at two-sided 0.05 alpha level in the secondary analysis of the biomarker-positive population.

When the required number of events for the primary endpoint has been reached, all randomized patients still alive will have continued study follow up through to their deaths.

14.4 SAFETY MONITORING

Adverse events will be monitored on an on-going basis by central review.

14.5 INTERIM AND FINAL ANALYSES

There will be one interim analysis in this study to be presented to the independent Data Safety and Monitoring Board (DSMB). Additionally, DSMB will review safety during conduct of the study. The role and responsibility of the DSMB will be defined in a separate Charter.

The interim analysis will be performed on OS, the primary endpoint of this study, when at least $2/3^{rd}$ of the required number of events (380) have been observed. This analysis, based on the stratified log-rank test adjusting for the stratification variables at randomization, will test the following:

H_0: survival on BBI608 + paclitaxel ≤ survival on placebo + paclitaxel

versus

H_1: survival on BBI608+paclitaxel > survival on placebo + paclitaxel

The comparison of the overall population will be tested based on a generalization of the Lan-DeMets error spending function approach using an O'Brien-Fleming stopping boundary to reject H_0, controlling for a two-sided alpha of 5% at the end of the study. For example, if exactly 380 deaths (67% of the required events) were in the locked database for the interim analysis, the nominal critical point for rejecting H_0 would be 2.502corresponding to a p-value of 0.012. Thus H_0 would be rejected, and superiority of BBI608 declared, early if the p-value from stratified log-rank test is ≤ 0.012.

This trial was activated on October 2, 2014 and a total of 714 patients were randomized. The 714th patient was randomized on December 13, 2016. The cleaning of the data which are required for the first interim analysis were completed on May 19, 2017 with the cut off for safety portion of analysis being April 15 2017 and the cut off for the efficacy portion of the analysis being December 20 2016. Safety data and primary analysis based on the first 380 events were presented to DSMB on June 14, 2017. Additionally, the DSMB were presented with uncleaned and unlocked efficacy data for additional 142 deaths occurring by the cut-off date of May 25 2017. After reviewing the results on June 21 2017, the DSMB recommended unblinding of patients remaining on study treatment to allow patients to make an informed decision regarding continuing or discontinuing study treatment. On June 24th, 2017 notification was sent to sites, and investigators were instructed to inform patients of the *first interim analysis* findings and of their treatment arm allocation. All patients were directed to decide together with their investigator if continuing study therapy is in their best interest. Given that no safety concerns were identified by the DSMB, in cases in which a patient appears to be deriving benefit from BBI608 and is tolerating treatment well, open-label continuation of study treatment was permitted with patient consent.

Due to study unblinding the analysis plan is amended as follows: analysis will be conducted for primary endpoint of OS as outlined in Section 13.3. Patients will continue to receive treatment, if felt to be potentially beneficial by their Investigator, until a discontinuation criterion is met or until September 15 2017, whichever occurs first. Additionally, all secondary and exploratory analyses will be performed as outlined in the protocol.

14.6 CORRELATIVE STUDIES

The correlative science component of the BBI608-336 trial will include tumor and blood based assays to identify biomarkers of benefit from BBI608 therapy, as well as biomarkers of BBI608 resistance. The purpose of these studies is to explore the relationship between biomarkers and disease response. The research aims to validate molecular markers such as genes (DNA) and gene products (mRNA or proteins), with measurements of their sequence, post translation modifications or degree of expression, that can guide the use of appropriate therapeutic treatment regimens. The ultimate goal of identifying molecular markers is to improve subject responses and other measures of clinical benefit by matching an individual subject's tumor diagnostic profile with an anticancer agent that has demonstrated a therapeutic advantage in subjects with a similar diagnostic profile.

Using data from this and other trials, the relationship between a number of molecular markers associated with the STAT3, β-catenin and other related pathways, and the clinical outcomes with BBI608 therapy will be explored. Multiple molecular markers in a paraffin-embedded tumor tissue sample can be determined by analyzing RNA and protein in the tissue sample.

In addition to analysis of potential biomarkers of benefit from BBI608 therapy, an analysis of markers of resistance to BBI608 will be conducted using blood samples drawn at baseline as well at 4 weeks post initiation of therapy. This analysis may involve SNPs, CYPS, and metabolomics.

Paraffin-embedded tumor specimens, or cores (two 2 mm cores of tumor from the block) and 10-30 unstained slides obtained from paraffin embedded specimens will be required. Where it is not possible to obtain two 2 mm cores of tumor from the block, 10-30 unstained slides of representative tumor tissue are also acceptable. Patients who do not have available archival tissue may enroll on the study with permission of the Sponsor/CRO.

Blood samples will be collected prior to dosing with BBI608 and then at week 4 while on BBI608/Placebo.

The following analysis will be performed to investigate the relationship between endpoints and biomarker levels (e.g. STAT3, phospho-STAT3, β-catenin, etc):

For each biomarker, Cox Proportional Hazards model will be used to model the relationship between Overall Survival, Progression-Free Survival and duration of response with baseline value of the biomarker. The model will also include assigned treatment, interaction between treatment and biomarker, and will be stratified by baseline ECOG performance status.

For biomarkers with post-baseline measurements, similar analysis will be done with change from baseline of a biomarker as a covariate, for both time points. An additional model that includes prognostic factors may be investigated.

The relationship between the endpoint and binary biomarkers (e.g. baseline phospho-STAT3 status, β-catenin, etc) will be also examined using the log-rank test, stratified by treatment and baseline ECOG performance status. Subgroup analysis by the status of the binary biomarker may also be performed. The Kaplan-Meier method will be used to describe overall survival, progression-free survival and duration of response by the status of the biomarker (e.g. phospho-STAT3-high vs. phospho-STAT3-low) and by treatment group.

The relationships between the binary response variable (e.g. objective response, DCR) with baseline values of biomarkers as well as with their change from baseline and at week 4 time point will be investigated using logistic regression that includes assigned treatment and biomarker value and treatment-by-biomarker interaction, stratified by baseline ECOG performance status. An additional model that includes prognostic factors may be investigated. The relationship between response and binary biomarkers (e.g. baseline phospho-STAT3 status or STAT3 status) will also be examined using the CMH test, stratified by treatment and baseline ECOG performance status. Subgroup analysis by the status of the binary biomarker may also be performed.

Exploratory analyses, in addition to those described in this section, such as alternative modeling approaches and analyses of other biomarkers are expected and may be performed. All analyses described in this section are based on availability of data.

14.7 EXPLORATORY ANALYSES

Objective Response Rate in the Predefined Biomarker-positive Population
Objective Response (ORR) in the biomarker-positive population [those patients with nuclear β-catenin positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) archival tissue] is defined as the proportion of patients with a documented complete response or partial response (CR + PR) based on RECIST 1.1. The primary estimate of ORR will be based on patients with measurable disease by RECIST 1.1 at randomization.

Disease Control Rate in the Predefined Biomarker-positive Population
Disease Control Rate (DCR) in the biomarker-positive population [those patients with nuclear β-catenin positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) archival tissue] is defined as the proportion of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1. The primary estimate of DCR will be based on patients with measurable disease by RECIST 1.1 at randomization.

Sparse Pharmacokinetic Analysis
Exploratory analyses will be performed on the bioanalytic data obtained from sparse plasma sampling in order to characterize the population pharmacokinetics of BBI608. Demographic and pathophysiologic factors that affect plasma concentration of BBI608 and paclitaxel in this population of patients with pre-treated advanced gastric/GEJ adenocarcinoma will be examined. The exposure-response relationship between clinical and safety endpoints and BBI608/paclitaxel exposure will also be examined.

Quality of Life Analysis
The Quality of Life (QoL) of patients will be assessed using EORTC QLQ-30 while the patient remains on BBI608/Placebo as per Section 9.1. The EORTC QLQ-30 is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functional domains, a global quality of life domain, three symptom domains, and six single items. Scoring of the EORTC QLQ-30 data will be completed following the procedures recommended by the EORTC Study Group on Quality of Life. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100. The quality of life data will be analyzed to look for statistically

and clinically significant differences between the BBI608 *versus* placebo groups. Questionnaire compliance rates will be ascertained for each group at each measurement time point. Mean baseline scores for each subscale and summary scores will be calculated.

The endpoints in QoL analysis are the mean EORTC QLQ-C30 QoL change scores from baseline at time 2 (~8 weeks) and time 4 (~16 weeks) for the physical function and global health status/quality of life subscale scores. Wilcoxon tests will be used to compare the difference at each of these two time points between two treatment arms for each of these two subscales. The Hochberg method *[Hochberg 1988]* will be used to adjust for four comparisons in the primary analyses. The proportion of patients in either arm with at least a minimum of 10 unit(s) deterioration in change scores at both 8 and 16 weeks will be compared by means of Fisher's exact test.

15 *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. A 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. No other publication is allowed before the primary peer-reviewed scientific publication

The primary author 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 no less than forty-five (45) days prior to their submission. Upon reasonable request by Boston Biomedical, the primary author agrees to withhold such publication an additional 30 days to permit the preparation and filing of related patent applications. In addition, Boston Biomedical shall have the right to require the primary author 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.

15.1 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.

16 *ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES*

16.1 REGULATORY CONSIDERATIONS

All institutions must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

The conduct of this trial must comply with local laws and national regulations [e.g. in the United States of America with applicable US FDA Regulations; in Canada with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act)] relevant to the use of new therapeutic agents in the country of conduct.

16.2 INCLUSIVITY IN RESEARCH

Individuals must not be excluded from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and Institutional Review Board (IRB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and IRB should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centers are expected to ensure compliance with local IRB or institutional policy regarding participation of vulnerable persons/groups. It is the center's responsibility to ensure compliance with all local SOPs.

Persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited to this study. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local IRB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. The Sponsor will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 OBTAINING INFORMED CONSENT

Informed consent will be obtained for each participant/potential participant in this trial, in accordance with ICH-GCP section 4.8. The center is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, the Sponsor may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study at which time participants remaining on study treatment will be re-consented.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. The Sponsor recognizes that in many centers other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Principal Investigator to delegate the responsibility for conducting the consent discussion.

The Sponsor requires that each participant sign a consent form prior to their enrolment in the study to document his/her willingness to take part. The Sponsor may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study and participants remaining on study treatment will be re-consented. In conjunction with GCP 4.8.2, the communication of this information should be documented.

The Sponsor allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local center. Centers should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read, then informed consent may be obtained by having the consent form read and explained to the subject. This process must be thoroughly documented.

16.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the pregnant female is not a participant in the main trial, consent should be obtained via use of the *exposure/*pregnancy follow-up consent form.

In the case of information collected about a newborn, consent should be provided by the legal guardian. In cases where the legal guardian is the participant in the main trial, consent is obtained via the main consent. If the legal guardian is not the trial participant, consent should be obtained via the exposure/pregnancy follow-up consent.

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy*/exposure*. Similarly, male participants

will not be withdrawn from the main study should their partner refuse/withdraw permission.

16.4 DISCONTINUATION OF THE TRIAL

The trial is scheduled to discontinue on September 15 2017, at which time the Sponsor will cease provision of study treatment. If this trial is discontinued prior to September 15 2017 for any reason by the Sponsor, all centers will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the Sponsor will provide this information to centers as well.

If this trial is discontinued at any time by the center (prior to closure of the trial by the Sponsor), it is the responsibility of the Principal Investigator to notify the Sponsor of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the Sponsor or locally by the center, it is the responsibility of the Principal Investigator to notify the local Institutional Review Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 RETENTION OF PATIENT RECORDS AND STUDY FILES

All essential documents must be maintained in accordance with ICH-GCP.

The Principal Investigator must ensure compliance with GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the center (25 years post final analysis, last data collected, or closure notification to IRB, whichever is later), or until notified by the Sponsor that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, IRB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

The Sponsor will inform the Investigator/Institution as to when the essential documents no longer need to be retained.

16.6 ON-SITE MONITORING/AUDITING

In addition to the routine review of case report forms and supporting documents sent to the central office, site monitoring will be conducted at participating centers in the course of the study as part of the overall quality assurance programme. The monitors/auditors will require access to patient medical records to verify the data, as well as pharmacy, essential document binders, standard operating procedures (including electronic information) and ethics documentation.

At any time, your site may be subject to an inspection by a regulatory agency such as the Health Canada Inspectorate or the FDA. Your site may also be subject to an audit by the Sponsor.

16.7 CASE REPORT FORMS

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. Details for accessing the EDC system and completing the on-line Case Report Forms will be provided separately.

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Tests & Procedures	Pre-Treatment	During Protocol Treatment (+/-3 days)								After Protocol Treatment Discontinuation (+/- 3 days)	
		run-in[1]		Cycle 1			Additional Cycles				
Day		day 1	day 2	1	8	15	1	8	15		
Timing	≤14 days prior to randomization									4 weeks post protocol treatment	Every 8 weeks thereafter[15]
History[2] and Physical Exam	X						X			X	
ECOG PS	X						X			X	
Weight	X						X			X	
Height	X										
Vital signs	X						X			X	
Paclitaxel Infusion[3]				X	X	X	X	X	X		
Begin BBI608/Placebo administration		X									
Hematology[4,5]	X			X	X	X	X	X	X	X	
Biochemistry[5]	X						X			X	
Urinalysis[5]	X						X			X	
ECG (12-lead)	X			X						X	
Radiology and Imaging[6]	X	Every 8 weeks until progressive disease is documented									
Submission of representative block of diagnostic tumor tissue	upon request after randomization										
Blood collection for correlative studies[7,8]	X						X				
Blood collection for sparse PK analysis					X	X	X				
Pregnancy test, serum or urine (if applicable)[9,10]	X						X			X	
Adverse Event assessment[11,12]	X	X	X[12]	X	X	X	X	X	X	X	X[15]
Quality of Life assessment (EORTC QLQ-C30)[13]	X						X			X[14]	
Assessment for survival of patient										X[16]	X[16]

1 BBI608/Placebo administration will begin 2 days prior to the paclitaxel infusion on day 1 of cycle 1. These two days are referred to as *run-in day 1* and *run-in day 2*. *Run-in day 1* should occur within 2 working days of patient randomization.

2 Medical history must include date of diagnosis including histological documentation of malignancy, documentation of *Her2* status of tumor (if available), prior anticancer therapy and prior date(s) of disease progression.

3. Paclitaxel administration should proceed according to institutional standard practice (with respect to pre-treatment laboratory evaluation, clinical assessment, pre-medication, and monitoring during and after infusion).

4 Hematology should be done within 72 hours prior to paclitaxel administration.

5 Laboratory investigations should be performed within72 hours prior to Day 1 of each Cycle of protocol treatment

6 Tumor measurement and evaluation by RECIST 1.1 criteria. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until progressive disease is documented (as described in section 10) or until September 15 2017, whichever occurs first. For patients who remain on protocol therapy

after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumor measurements and assessment must be reported until September 15 2017. Tumor assessments should be obtained within +/- 5 days of protocol specified schedule.

7 Sample collection should be performed at baseline and at 4 weeks after randomization.

8 A sample will be collected following protocol treatment discontinuation if discontinuation occurs prior to 4 weeks of therapy.

9 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. Baseline pregnancy test should be done within 5 days of randomization.

10 In women of childbearing potential only a negative pregnancy test must be demonstrated every 4 weeks until 4 weeks after the administration of the final dose of protocol therapy.

11 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix III).

12 Adverse event assessment by phone should be performed on *run-in day 2*.

13 To be completed in clinic. Questionnaires should be completed at baseline and At 4, 8, 12, 16 and 24 weeks after randomization for as long as patient remains on Protocol therapy or until deterioration to ECOG PS 4 or hospitalization for end of life care or until September 15 2017.

14 EORTIC QLQ-C30 questionnaire will be collected in the post-protocol discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care and until September 15 2017.

15 After the first visit at which the patient has been off protocol treatment for 4 weeks, patients will be assessed every 8 weeks for survival and any protocol treatment related adverse events until September 15 2017. Medical history at post-progression follow up must include post-protocol treatment cancer therapies.

16 In the event that the patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact

Evaluation Post-Unblinding & Permanent Treatment Discontinuation

Following unblinding, patients who have not yet met the primary study endpoint (death), and are currently on protocol therapy may receive study treatment until September 15 2017 based on the clinical judgement of the investigator that this is in the patients' best interest, providing the patient is fully informed and provides consent. Please refer to Sections 9.1.1 and 9.2.1.

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	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.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare 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.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

APPENDIX IV - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

Study staff should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, for as long as the patient continues on Protocol therapy, as required by the schedule at approximately:

- 4, 8, 12, 16 and 24 weeks or until deterioration to ECOG PS 4 or hospitalization for end of life care
- the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days) if study therapy discontinuation occurred prior to 24 weeks and until deterioration to ECOG PS 4 or hospitalization for end of life care

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

   Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

   If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

   If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

   If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

   Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

   Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

Quality of Life Questionnaire – ENGLISH

This **page** to be completed by the Clinical Research Coordinator

Patient Information

Study ID#: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

OR

During chemotherapy (timing from randomization):

☐ Week 4 ☐ Week 8 ☐ Week 12 ☐ Week 16 ☐ Week 24

OR

After chemotherapy has stopped (timing from randomization):

☐ First regularly scheduled 4 week assessment following Protocol therapy discontinuation

Were ALL questions answered? ☐ Yes ☐ No → If no, reason: _____

Was assistance required? ☐ Yes ☐ No →If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another center

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

This box to be completed by the clinical research coordinator: Study ID #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research coordinator: Study ID #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research coordinator: Study ID #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX V - UNBLINDING

All patients remaining on study treatment at the time of this amendment must be unblinded. The process for unbinding is outlined in Appendix VI.

Patients who discontinued study treatment prior to the time of this amendment must remain blinded. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's or subject's partner urgent management, the blind for that subject may be broken by the treating physician. Before breaking the blind of an individual subject's blinded treatment (for the subjects who discontinued study treatment prior to the time of this amendment), the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's or subject's partner immediate management. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject was receiving active product without the need for unblinding.

For any treatment code unblinding, including patients who on study treatment at the time of this amendment as well as those who discontinued study treatment prior to this amendment, the reason and parties involved must be documented in the patient's medical record. Treatment identification information for patients who discontinued study treatment prior this amendment should be kept confidential. Further, for the patients who discontinued study treatment prior to this amendment, the Sponsor/CRO must be made aware of the break of the blind prior to the event taking place except in cases where an immediate need for unblinding exists for reasons of patient safety at which time the investigator can unblind the patient prior to notifying the Sponsor. However, the investigator will have the final decision and unilateral right for unblinding in matters involving the safety of study subjects.

APPENDIX VI: UNBLINDING PROCEDURE

PLEASE FOLLOW THESE STEPS:

- Call the Perceptive Support Help telephone number for your country. Refer to the table on page 2 to find the contact number for your country.

- Inform the Perceptive Support Help agent that you wish to unblind a patient receiving study treatment at the time of unblinding.

- Provide the Perceptive Support Help agent with the following information:
  - The study name and number – **The BRIGHTER Trial – BBI608-336**
  - Your name
  - Your site number
  - Your email address
  - The Patient ID, Year of Birth and Gender of the subject you wish to unblind
  - The reason for unblinding (e.g. patient is receiving study treatment at the time of this amendment or information is critical to urgent medical management for a patient who discontinued trial treatment prior to the time of this amendment)

- PLEASE NOTE: When you reach Perceptive Support Help, the agent will speak to you in English. You may request a translator to assist if necessary.

Upon receipt of the required information the Perceptive Support Help agent will immediately unblind the patient treatment assignment and forward the patient treatment assignment to you at the email address you provided.

IMPORTANT REMINDERS

- Treatment assignments will only be provided to the Principal Investigator
- Requests to unblind a subject who discontinued study treatment prior to this amendment should only be made when the safety and urgent medical management of the subject require knowledge of the study treatment.
- Unblinding must be performed for all patients remaining on study treatment at the time of this amendment.
- For any treatment code unblinding, the reason and parties involved must be documented in the subject's medical record.
- Treatment assignment information must be kept confidential for patient who discontinued study treatment prior to the time of this amendment.
- The Sponsor/CRO request that **whenever possible** they be **notified** of the intent to break the blind prior to contacting Perceptive Support Help (except for patients on study treatment at the time of this amendment). Please send notifications to BRIGHTER_MM@parexel.com. Please ensure you also copy your CRA.
- In cases where an **immediate** need for unblinding exists for patients remaining on active study treatment at the time of this amendment or for reasons of subject safety for the patients who discontinued study treatment prior to the time of this amendment, the Principal Investigator may unblind the subject prior to notifying the Sponsor.

Country	Perceptive Support Help Toll Free Number	Country	Perceptive Support Help Toll Free Number
Australia	1 800 504340	Italy	800 783294
Belgium	0800 74226	Japan	0120 984 280
Brazil	0800 891 7744	Korea	00308 132 311
Bulgaria	08001104403	Lithuania	880030003
Canada	1 877 798 5016	Poland	00800 441 1385
Czech Republic	800 142091	Romania	08008 94401
Estonia	800 0044161	Russia - Moscow	(8) 495 580 9515
France	0800 900578	Russia – Other Areas	8~10 800 110 1011 + 866 893 1621
Germany	0800 182 2394	Spain	900 9977160
Hungary	06800 18058	United Kingdom	08003890918
Israel	1809 431402	United States	1 877 819 6025

You may also use this link to find the Perceptive Support Help telephone number for your country
support.perceptive.com/support/home.aspx/phones