Statistical Analysis Plan

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

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STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
C_{max}	Maximum plasma drug concentration
CI	Confidence interval
CRF	Case report forms
CR	Complete Response
CV	Coefficient of variation
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GEJ	Gastro-Esophageal Junction
GLP	Good Laboratory Practice
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MET	Minimum Effective Treatment
MTD	Maximally Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PD	Progressive Disease
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal
WBC	White blood cell (count)
WHO-DD	WHO Drug Dictionary

AMENDMENT HISTORY

Version	Date	Brief description of change
V1.0	31 May 2017	
V2.0	14 February 2020	Amended to reflect the following (editorial updates are not listed): • Updated to cover patients with advanced malignancies besides Gastric/GEJ adenocarcinoma. • Updated determination of sample size for Phase II and sample size justification for Thymic Carcinoma Cohort. • Updated efficacy and safety analysis to be summarized by dose and diagnosis • Added analysis for prophylactic regimens. • Added Study Endpoint section • Deleted Minimum Effective Treatment Set, PFS/OS Analysis Set and Tumor Marker Analysis Set. • Combined PK Concentration Analysis Set and PK Parameter Analysis Set to PK Analysis Set. • Replaced duration of treatment with actual treatment duration. • Deleted the incidence of elevated liver function test results. • Added Physical Examination section. • Added safety and tolerability endpoints • Added PK data handling • Separated out the endpoints by phase • Added separate section for DLT • Moved ECOG/Karnofsky to safety section • Added missing dates handling for death dates and prior therapies • Deleted Biomarker Analysis Set • Added the sensitivity analysis of ORR/DCR based on Full Analysis Set • Added Study Drug Discontinuation due to AEs section.

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Boston Biomedical Protocol BBI608-201 for patients with advanced malignancies. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP has been developed using Protocol amendment 4 dated 10-May-2018[1] and the final eCRFs.

1.1 STUDY OBJECTIVES

The overall study objectives described in the clinical protocol are outlined below.

1.1.1 Primary Objective

Phase Ib:

The primary objective of the study was to determine the safety, tolerability and recommended Phase 2 dose (RP2D) of napabucasin when administered with paclitaxel in adult patients with advanced malignancies.

1.1.2 Secondary Objectives

The secondary objectives of the study include the following:

Phase Ib:

- To determine the pharmacokinetic profile of napabucasin and paclitaxel when administered in combination.
- To assess the preliminary anti-tumor activity of napabucasin when administered in combination with paclitaxel in patients with advanced malignancies.
- To determine the pharmacodynamics (e.g., biomarkers) of napabucasin.

Phase II:

To assess the objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), and overall survival (OS) of patients with selected tumor types treated with napabucasin in combination with paclitaxel.

1.2 STUDY ENDPOINTS

1.2.1 Primary Endpoint

Phase Ib:

Dose Limiting Toxicities (DLTs): For definition of DLT, see Section 4.6 of Protocol [1].

1.2.2 Secondary Endpoints

Phase Ib:

- PK parameters of napabucasin and paclitaxel when administered in combination.
- Objective tumor response, as assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.
- Objective response rate (ORR) of napabucasin administered in combination with paclitaxel is defined as the proportion of patients with a documented complete response (CR) or partial response (PR) based on RECIST 1.1 as determined by the investigator assessment collected in the CRFs (see Table 2 for Response Criteria).
- Pharmacodynamics parameters (e.g. biomarkers) of napabucasin administered in combination with paclitaxel.

Phase II:

- Disease control rate (DCR) of napabucasin administered in combination with paclitaxel is defined as the proportion of patients with documented CR, PR and stable disease (SD) based on RECIST 1.1.
- Progression free survival (PFS) of napabucasin administered in combination with paclitaxel is defined as the time from first dose of any study drug until the first objective observation of disease progression or death from any cause.
- Overall survival (OS) of patients administered napabucasin in combination with paclitaxel is defined as the time from first dose of any study drug until death from any cause.

1.2.3 Safety Endpoints

1.2.3.1 Adverse Events, Laboratory Test Results, and Other Safety Endpoints in Phase 1b and Phase II

- Adverse Events (AEs) as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.0), seriousness, and relationship to study therapy
- Laboratory test results as characterized by type, change from baseline, and severity (as graded by NCI CTCAE version 4.0)
- Other safety endpoints include physical examination, Karnofsky performance score, ECOG, electrocardiogram (ECG), and vital signs data.

1.2.4 Covariates

Demographic and baseline disease characteristics may be considered as covariates in population PK, PK/pharmacodynamic (biomarker), and anti-tumor efficacy exploratory analyses.

1.3 SUMMARY OF THE STUDY DESIGN

1.3.1 General Study Design and Plan

Phase Ib

Phase Ib is an open-label, multicenter study of oral napabucasin administered with paclitaxel to patients with advanced malignancies. The study is designed to explore the safety, tolerability and pharmacokinetics of napabucasin and paclitaxel and define a recommended Phase 2 dose (RP2D).

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

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

Dose escalation will be performed using three-patient cohorts as shown in the Table 1.

Table 1 Dose escalation scheme for napabucasin

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

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

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

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

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

Phase II

In the phase II portion of the study, up to 570 patients with selected tumor types may be enrolled. This total includes patients previously enrolled under prior amendments, and enrollment of up to 15 total patients with thymic carcinoma.

1.3.2 Study Population

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

- Ovarian cancer
- Breast cancer
- Non Small-Cell Lung Cancer (NSCLC)
- Melanoma
- Gastric/GEJ/Esophageal Adenocarcinoma
- Thymic carcinoma

Inclusion of other tumor types may be permitted upon agreement between investigators and the sponsor. As of *February 2018,* the study is enrolling only patients with thymic carcinoma.

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

1.3.3 Determination of Sample Size

Phase Ib

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

Phase II

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

Sample Size Justification for Thymic Carcinoma Cohort:

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

2. ANALYSIS SETS

2.1 FULL ANALYSIS SET

The Full analysis set (FAS) will consist of all patients receiving at least one dose of either napabucasin or paclitaxel. This analysis set will be used for all safety related analyses such as AE, concomitant medication, laboratory tests, and vital signs and efficacy related analyses such as PFS, OS, ORR, DCR.

2.2 RESPONSE EVALUABLE ANALYSIS SET

The response evaluable analysis set will consist of patients who have received at least one cycle of study treatment and have had at least one disease assessment following the initiation of therapy. Initiation of therapy is defined as the date of the first dose of either napabucasin or paclitaxel. At least one cycle of study treatment is defined as at least 80% daily treatment compliance at the targeted dose level during a 28-day period prior to the first imaging assessment. This analysis set will be used for efficacy endpoints such as the BOR/ORR/ DCR analysis.

2.3 DLT ANALYSIS SET

The first 24 patients are considered as phase1b patients, evaluable for the determination of dose-limiting toxicity (DLT).

2.4 PK ANALYSIS SET

The napabucasin PK analysis set will consist of all patients receiving at least one dose of napabucasin and have at least one quantifiable concentration.

3. STUDY VARIABLES AND DEFINITON

3.1 EFFICACY VARIABLES

The tumor response includes Complete Response (CR), Partial Response (PR), Progressive Disease (PD), and Stable Disease (SD). The response criteria for solid tumors are described in

Table 2.

Table 2 Response Criteria

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

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

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

The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence and is determined as indicated in

Table 3. BOR is derived from the sequence of overall response. Assessments done after PD or after "new anti-cancer" treatment but prior to PD will not be considered evaluation of best overall response. In order to classify a BOR as SD, the assessment must be made a minimum of 8 weeks as allowed per protocol after first dose date of either napabucasin or paclitaxel. Otherwise the BOR will be not evaluable (NE). Confirmation of PR or CR is not required.

Table 3 Overall Response

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

Objective response rate (ORR) is defined as the proportion of patients with a documented complete response (CR) or partial response (PR) based on RECIST 1.1 as determined by the investigator assessment collected in the CRFs.

The DCR is the proportion of patients whose best overall response is CR, PR or SD based on RECIST 1.1.

Patients will be considered as non-responders until proven otherwise. Thus, the following patients are considered non-responders:

- Do not have CR or PR while on study; or
- Do not have a baseline or post-baseline tumor evaluation; or
- Do not have an adequate baseline tumor evaluation; or
- Receive anti-tumor treatment other than the study medication prior to reaching a CR or PR; or
- Die, progress, or drop out for any reason prior to reaching a CR or PR.

Progression free survival (PFS) is defined as the time from the date of the first dose of either napabucasin or paclitaxel to the date of PD, or death due to any cause, whichever comes first. If neither event has been observed, then the patient will be considered as censored. PFS (in months) will be calculated as (first event date – first dose date of either napabucasin or Paclitaxel + 1) / 30.4375.

Tumor assessments will be performed every 8 weeks. The censoring rules for the PFS analysis is summarized in Appendix B.

Overall survival (OS) is defined as the time from the date of the first dose of either napabucasin or paclitaxel to the date of death from any cause. Patients who are alive at the time of the final observation, or who have dropped out, will be censored at their last date known to be alive. OS in months is calculated as (date of death/last known to be alive date – first dose date of either napabucasin or paclitaxel +1) / 30.4375.

3.2 SAFETY VARIABLES

3.2.1 Safety and Tolerability

Safety and tolerability will be assessed using adverse events (AEs), physical examinations, electrocardiograms (ECGs), laboratory analyses, ECOG/Karnofsky and vital sign data.

3.3 PHARMACOKINETIC VARIABLES

The PK Analysis Set will be used to calculate the following PK parameters for BBI608 on Cycle 1 Days 3, 10, 16, and 17 and paclitaxel on Cycle 1 Days 3, 10, and 17, as data allow:

Table 4 Pharmacokinetic Parameters

Parameter	Definition
AUC_{last}	Area under the concentration - time curve from zero to the last quantifiable concentration
AUC_{tau}	Area under the concentration - time curve during a dosing interval at steady state
AUC_{0-t}	Area under the plasma concentration - time curve from zero to a definite time t
C_{max}	Maximum observed plasma concentration
T_{max}	Observed time to reach C_{max}
T_{last}	Time of last observed concentration

No PK parameters will be calculated from profiles with less than 4 quantifiable concentrations. Only Cycle 1 PK parameters will be summarized, PK parameters from other cycles will be listed.

4. ANALYSIS METHODS

4.1 GENERAL CONSIDERATIONS

The Phase Ib part of this study is an open-label, dose escalation study; therefore, no formal statistical analysis is planned. In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum for continuous variables, and number and percentage of patients in each category for categorical variables) will be provided.

The Phase II part of this study evaluated the tolerability, safety, and preliminary anti-cancer activity of napabucasin plus weekly paclitaxel in patients with selected tumor types. The analyses described herein are for those patients enrolled during Phase Ib and Phase II under prior

amendments and up to 15 total patients with thymic carcinoma.

The thymic cohort will be analyzed at a future time point since additional patients were added to this cohort later. More details of the analysis for the thymic cohort will be described in a SAP amendment.

All analyses will be based on observed data only, and missing observations will not be imputed. Measurements collected from unscheduled visits and from any repeated assessments will be included in the maximum change summary or figures as appropriate and will be included in the patient listings. Source data for the summary tables will be presented as patient data listings.

Baseline is defined as the last non-missing value prior to the first dose of napabucasin or paclitaxel, whichever is administered first.

Study day is calculated as assessment date – first dose date +1 if the assessment was performed on or after the first dose day. If the assessment was performed prior to the first dose date, study day is calculated as assessment date – first dose date.

Age will be calculated as (Date of Informed Consent – Date of birth + 1) / 365.25, and rounded down to the nearest integer. Any duration in weeks will be calculated using duration in days / 7; duration in months will be calculated using duration in days / 30.4375; duration in years will be calculated using duration in days / 365.25.

All tables will be summarized by napabucasin dose cohort and cancer type .

All analyses and descriptive summaries will be based on the observed data unless otherwise specified.

All summaries and statistical analyses will be generated using SAS® version 9.4.

4.2 STUDY PATIENTS

4.2.1 Disposition of Patients

Patient disposition will be summarized. The number of treated patients, ongoing patients and discontinued patients will be reported. Reason for discontinuation will also be summarized.

4.2.2 Eligibility

The reasons for inclusion criteria not met and exclusion criteria met will be summarized for the Full analysis set.

4.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The summaries for demographics and baseline characteristics will be presented for the Full analysis set by napabucasin dose cohort and cancer type and overall using the following information:

- Demographic:

- Sex: female, male
- Age (year): summary statistics
- Race: Caucasian, Hispanic, Black, Asian, Other
- Weight (kg): summary statistics
- Height (cm): summary statistics

- Baseline disease characteristics:
  - Stage of diagnosis
  - Eastern Cooperative Oncology Group (ECOG) status scale
  - Karnofsky performance status scale
  - Months from first pathological diagnosis to start date of administration: summary statistics (start date of administration – date of first pathological diagnosis +1)/ 30.4375
  - Prior treatment for primary cancer
    - Surgery: Yes, No
    - Radiotherapy: Yes, No
    - Hormone/biologics/chemotherapy/other: Yes, No

4.4 STUDY TREATMENT

4.4.1 Exposure

For an individual patient, treatment with napabucasin and paclitaxel will continue until unacceptable toxicity, disease progression (clinical or radiological) or another discontinuation criterion is met.

Napabucasin Treatment:

- Actual treatment duration (weeks) = (actual end of treatment date – date of first dose of study drug + 1) ÷ 7, where actual end of treatment date is the last dosing date.
- Cumulative dose, dose intensity, relative dose intensity:
  - Cumulative dose (mg) = Sum of all (total dose administered [mg])
  - Weekly dose intensity (mg/week) = (Cumulative dose) ÷ (Actual treatment duration)
  - Planned weekly dose intensity (mg/week) = starting assigned dose * 7 /week
  - Relative dose intensity (%) = (Weekly dose intensity) ÷ (Planned weekly dose Intensity) *100

The following exposure variables will be presented for Cycle 1 of napabucasin:

- Total Dose (overall)
- Treatment Duration (overall)
- Weekly dose intensity (overall)
- Relative dose intensity (overall)

Paclitaxel Treatment:

Exposure analyses will be based on body surface area (BSA, in m^2) for paclitaxel. The BSA to be used for calculating each dose of paclitaxel will be calculated using the Mosteller formula (see below) based on the last available weight and height prior to each infusion.

$$\text{BSA } [m^2] = \sqrt{\frac{\text{Weight [kg]} * \text{Height [cm]}}{3600}}$$

Calculated doses will be rounded to the nearest integer.

For patients who did not receive any amount of a study drug, the dose exposure parameters for that treatment (number of infusions, duration of treatment, cumulative dose, dose intensity, and relative dose intensity) will be set to 0. Cumulative dose, dose intensity and relative dose intensity will remain missing if they cannot be derived due to missing weight, height, or BSA.

- Actual treatment duration (weeks; 14 days added to duration of treatment because last administration of each cycle is for 2 weeks [on day 3, 10, 17 of each 4-week cycle]) = [(actual end of treatment date – date of first dose of study drug) + 14] ÷ 7, where actual end of treatment date is the last dosing date.
- Cumulative dose, dose intensity, relative dose intensity:
  - Cumulative dose (mg/m^2) = Sum of all (total dose administered [mg] ÷ BSA using last available weight [m^2])
  - Weekly dose intensity (mg/m^2/week) = (Cumulative dose) ÷ (Actual treatment duration in weeks)
  - Planned weekly dose intensity (mg/m^2/week) = 3*80 mg/ m^2 / 4 weeks = 60 mg/ m^2/week
  - Relative dose intensity (%) = (Weekly dose intensity) ÷ (Planned weekly dose intensity) * 100

4.4.2 Treatment Compliance

<u>Napabucasin</u>

Treatment compliance for napabucasin is defined as follows,
(Cumulative total dose / total planned or intended dose) x 100= % compliance

Daily treatment compliance is defined as the ratio, expressed as a percentage, of the number of ***days*** a given patient received a defined total dose of napabucasin or higher out of total duration of treatment (days). Total duration of treatment in days = last dose date of napabucasin – first dose

date of napabucasin + 1. Daily compliance will be reported for each patient for the following dose-levels:

- The % of days the patient received a total dose of <starting assigned dose> mg napabucasin out of the actual treatment duration (days) of napabucasin.
- The % of days the patient received a non-zero dose of napabucasin out of the actual treatment duration (days) of napabucasin.

Paclitaxel

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.

Napabucasin and paclitaxel compliance will be summarized for the Full analysis set based on the following categories: < 60%, ≥ 60% - < 80%, ≥ 80% - < 90%, ≥ 90%.

4.5 CONCOMITANT MEDICATION AND TREATMENT

4.5.1 Prior and Concomitant Medications

Prior and concomitant medications will be coded to ATC (Anatomical Therapeutic Chemical) classification and Drug Class using WHO Drug Dictionary (WHO-DD) version March 2015.

Medications that start and stop prior to the date of first treatment administration (either napabucasin or paclitaxel, whichever is administrated first) will be classified as 'prior' medications. If a medication starts on or after the date of first treatment administration up to the last dose date of study medication (inclusive), then the medication will be classified as 'concomitant'. If a medication starts before the date of first treatment administration and stops on or after the date of first treatment administration, then the medication will be categorized as both a 'prior' and 'concomitant' medication.

Summaries of prior and concomitant medications will be provided by level 3 ATC classification and preferred name using frequencies and percentages for the full analysis set. A separate concomitant medications table using preferred base and level 4 ATC classification will also be provided using frequencies and percentages for the FAS.

4.5.2 Prior and Concomitant Treatment

Prior and concomitant treatment will be summarized by indication and dose cohort and listed for each patient in the full analysis set.

Prior cancer surgery will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA® 18.0) and summarized by MedDRA PT within MedDRA SOC. The number and percentage of patients in each type of prior cancer

surgery will also be reported by overall.

The total dose of prior cancer radiotherapy will be summarized.

Prior cancer therapies will be summarized by the number of unique agents per patients, the number and percentage of patients reporting each agent, time from start of first anticancer therapy to the first dose date of napabucasin, and time from the end of last anticancer therapy to the first dose date of napabucasin. Prior cancer therapies will be coded to Agent Received using WHO Drug Dictionary (WHO-DD) March 2015.

The reasons for the concomitant procedures will be summarized, and the procedures will be displayed alphabetically in the FAS.

4.6 MEDICAL HISTORY, CONCURRENT MEDICAL CONDITIONS AND EXTENT OF DISEASE

4.6.1 Medical History

Medical history will be coded by SOC and PT using MedDRA. Medical history will be summarized by SOC and PT using the number and percentage of patients for the full analysis set.

Concurrent Medical Conditions

Concurrent medical conditions will be summarized by SOC and PT and maximum grade using the number and percentage of patients for the FAS.

4.6.2 Extent of Disease

All target and non-target lesions at baseline will be analyzed for the full analysis set. Number of target lesions, the length of the largest target lesion, and sum of target lesions will be summarized.

4.7 PHARMACOKINETIC ANALYSES

Nuventra Pharma Sciences will compute PK parameters by noncompartmental analysis using Phoenix WinNonlin version 6.3 or higher (Certara, L.P., Princeton, NJ), and generate TLFs using a validated version of R version 3.3.1 [LL1] or later (R Foundation for Statistical Computing, Vienna, Austria).

Demographics for patients included in the PK Analysis Set will be summarized in the PK Report.

Per Sponsor request, the BBI608 and paclitaxel PK analyses were initiated prior to finalization of this analysis plan.

4.7.1 Concentrations

Plasma concentrations for each analyte will be listed and summarized by nominal timepoint using descriptive statistics, including N, arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum, maximum, and median. Concentrations will be summarized by dose, dose frequency, dose interval, formulation, and nominal time post-dose by day within Cycle 1. Actual elapsed time from dosing will be included in individual subject listings.

Figures of individual patient drug concentrations vs actual elapsed time will be presented on linear and semi logarithmic scales by treatment, as appropriate. Figures illustrating the mean drug concentration vs nominal time will be overlaid and presented for relevant comparisons on linear and semi logarithmic scales, as appropriate. The relevant comparisons include:

- Dose, separated by dose frequency, dose interval, formulation and day
- Day, separated by dose, dose frequency, dose interval and formulation
- Formulation, separated by day, dose, dose frequency and dose interval

4.7.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be listed and summarized by treatment using descriptive statistics, including N, mean, SD, CV, geometric mean, geometric CV, minimum, maximum, and median. For Tmax, N, minimum, maximum and median will be reported. Parameters will be summarized by day within Cycle 1, dose, dose interval, dose frequency, and formulation.

All PK parameters will be estimated using actual elapsed time from dosing. Imputation of concentration data below the lower limit of quantification (BLQ) is described in Section 4.7.3.

Scatter plots and box and whisker plots of C_{max} and AUC will be generated to evaluate napabucasin exposure over the dose range tested by formulation, as data permit. Dose proportionality will be assessed for C_{max} and AUC over the evaluated dosing range using the following power model:

where ‘μ’ is the intercept and ‘β’ is the slope.

The estimate (SE) of the slope and associated 90% CI will be reported.

The effect of co-administration of paclitaxel on napabucasin PK will be assessed, as data permit, using data collected on Day 16 (without paclitaxel) and Day 17 (with paclitaxel). A mixed effects model will be used to analyze the natural log-transformed PK parameters (AUC and C_{max}) of napabucasin between treatments. The model will include treatment as a fixed factor and subject as a random factor. The geometric mean ratios for each AUC and C_{max}, along with their two sided 90% CIs will be derived from the least-squares mean difference. Matchstick plots and box and whisker plots of C_{max} and AUC will also be generated to evaluate BBI608 exposure with and without paclitaxel.

4.8 PHARMACODYNAMIC/BIOMARKER ANALYSIS

The correlations between the biomarker results, pharmacokinetic parameters, and measures of anti-tumor/anti-cancer efficacy signals or safety signals will be explored if data allow and it is deemed appropriate.

4.9 Analysis for Primary Endpoint

4.9.1 DLT (Phase 1b)

Dose Limiting Toxicity (DLT) is the primary endpoint of the dose escalation component of the study. A DLT summary table and a listing of the DLTs will be provided for the DLT analysis set.

4.10 Efficacy Analyses

All efficacy analyses will be summarized by napabucasin dose cohort and cancer type based on the Full analysis set and the Response evaluable analysis set as appropriate.

4.10.1 Objective Tumor Response

The objective response rate (ORR) and the disease control rate (DCR) will be calculated based on the Response evaluable analysis set. Exact 2-sided 95% confidence interval (CI) using a method based on the F distribution (i.e., the Clopper-Pearson method) will be used to calculate the confidence interval for each proportion.

A sensitivity analysis for ORR and DCR will be performed based on the Full analysis set.

4.10.2 Progression Free Survival

PFS will be summarized based on the Full analysis set. Median progression free survival time will be estimated using Kaplan-Meier method, and their 95% confidence intervals will be calculated based on the Brookmeyer R and Crowley JJ method. Survival probability at 6 months, 1 year, and 18 months will be summarized using the Kaplan-Meier method and a 2-sided CI will be calculated using the normal approximation to the log transformed cumulative hazard rate. Survival data will be summarized only when the number of events in that dose and diagnosis is at least 5.

4.10.3 Overall Survival

OS will be summarized based on the Full analysis set. The analysis of OS will be the same as the analysis of PFS. Median overall survival time will be estimated using Kaplan-Meier method and their 95% confidence intervals will be calculated based on the Brookmeyer R and Crowley JJ method. Survival probability at 6 months, 1 year, and 18 months will be summarized using the Kaplan-Meier method and a 2-sided CI will be calculated using the normal approximation to the log transformed cumulative hazard rate. Survival data will be summarized only when the number of events in that dose and diagnosis is at least 5.

4.11 Safety analyses

All safety analyses will be summarized by napabucasin dose cohort and cancer type based on the Full analysis set.

4.11.1 Overall Summary of AEs

An AE will be regarded as **treatment-emergent**, if

- its onset date occurs any time on or after the first dose date of either napabucasin or paclitaxel up to 30 days after the last dose of study treatment; or
- it occurs prior to first dose date of either napabucasin or paclitaxel and worsens in severity on therapy or up to 30 days after the last dose of study treatment

The date of the last dose of study treatment will be determined from either drug administration data or the end of study CRF, whichever date is later.

Adverse events will be coded by SOC and PT using the MedDRA v18.0. The severity of AEs will be graded by the investigator using NCI CTCAE Version 4.0.

An overview of treatment-emergent adverse events (TEAEs) will be provided. The number and percentage of patients with the following will be summarized for:

- Patients with at least one TEAE
- Patients with TEAE of CTCAE grade 3 or higher
- Patients with serious TEAE
- Patients with serious TEAEs related to napabucasin
- Patients with serious TEAEs related to paclitaxel
- Patients with serious TEAEs related to study drug (napabucasin or paclitaxel)
- Patients with napabucasin related TEAE
- Patients with napabucasin related TEAE of CTCAE grade 3 or higher
- Patients with paclitaxel related TEAE
- Patients with paclitaxel related TEAE of CTCAE grade 3 or higher
- Patients with TEAEs leading to napabucasin being held
- Patients with TEAE leading to dose reduction of napabucasin
- Patients with TEAE leading to paclitaxel being held,
- Patients with TEAE leading to dose reduction of paclitaxel

4.11.2 Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term

The number and percentage of patients with AEs by SOC and PT and maximum CTCAE grade will be summarized. A summary of TEAEs of CTCAE grade 3 or higher (Grade 3, 4, 5) will be presented by SOC and PT and maximum CTCAE grade. A summary of TEAEs by PT and maximum grade will be presented in descending order of frequency counts for all grades. The most commonly reported TEAEs using different cutoffs (e.g., 2%, 5% or 10% or more of patients in either arm) may also be summarized by PT as needed for various reporting purposes. Adverse events associated with dose held/dose reduction of either napabucasin and/or paclitaxel will also be summarized by SOC and PT and maximum CTCAE grade.

4.11.3 Treatment-Related Treatment-emergent Adverse Events

TEAEs reported with a relationship to a treatment (napabucasin or paclitaxel) considered by the investigator to be "possible", "probable" or "definite" will be considered "Related" to study treatment or paclitaxel, respectively. Missing relationship will be considered as "Related". Similar summaries of all causality TEAEs will be provided along with TEAEs leading to dose modification, reduction, or discontinuation.

4.11.4 Serious Treatment-emergent Adverse Events and Death

Treatment-emergent SAEs and treatment-related TESAEs will be summarized by MedDRA SOC and PT and maximum CTCAE grade.

Patients who experienced an SAE during the AE reporting period will be listed for all safety patients. The number and percentage of patients who experienced any treatment-emergent SAE will be summarized by SOC, PT, and maximum CTCAE grade. A similar summary for treatment-related TESAEs will also be provided.

Deaths that occur on or after the first dose of study treatment and within 30 days of the last dose of any study treatment will be summarized. The number and percentage of patients who died during the study treatment and within 30 days after the last dose will be presented.

TEAEs and treatment-emergent SAEs leading to death will also be summarized by MedDRA SOC, PT, and maximum CTCAE grade.

A listing of death data will also be provided and will include all deaths that occurred during the reporting period for deaths, which started from signing the informed consent to the end of the follow-up period. The listing will include date of death, and the number of days relative to the administration of first and last dose of study drug.

4.11.5 Adverse Events of Clinical Relevance (AECRs)

Selected AEs are specified for additional focus due to the potential clinical significance of the event and/or the potential association with the investigational product. These events include those in the standard MedDRA query (SMQ) terms (narrow or broad, as follows in Table 5):

Table 5 Adverse Events of Clinical Relevance (AECRs)

MedDRA v18.0 Term	SMQ class
Ventricular fibrillation	NA (individual PT)
Ventricular tachycardia	NA (individual PT)
Non-infectious diarrhea	Broad
Gastrointestinal haemorrhage	Narrow
Gastrointestinal obstruction	Narrow

Acute kidney injury	Narrow (acute renal failure)

Tables summarizing the incidence and maximum severity of these events in the full analysis set will be generated.

4.11.6 Prophylactic Regimens by Adverse Events and CTCAE Grade

There are three prophylactic regimens started before the first dose of napabucasin. A summary of prophylactic regimen by selected adverse events including Nausea, Diarrhea or Vomiting and CTCAE grade will be provided.

4.11.7 Study Drug Discontinuation due to AEs

The number and percentage of patients with TEAEs leading to end of treatment for napabucasin by SOC and PT and maximum CTCAE grade will be summarized. These TEAEs will be obtained from the End of Study CRF, as AEs leading to napabucasin treatment discontinuation were not collected in the AE CRF.

4.11.8 Clinical Laboratory Evaluation

4.11.8.1 Summary of Hematology and Biochemistry

Hematology and biochemistry will be summarized based on the Full analysis set.

For all laboratory parameters collected in the CRF, summary statistics for baseline values and maximum change from baseline will be presented for overall based on the Full analysis set. Figures of maximum post-baseline values versus baseline will be plotted for key lab parameters, including but not limited to ANC, platelets, and liver function tests (ALT/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin) as well as E-DISH scatter plots.

All the lab tests collected in CRF will be listed.

4.11.8.2 Summary of CTCAE Grade

The results of laboratory parameters will be graded according to NCI CTCAE v4.0 and summarized at baseline and post baseline by maximum CTC grade. The CTCAE grading will be performed based only on observed values, without considering any clinical symptoms or findings. Shift tables summarizing the baseline grades to the maximum CTCAE grades post baseline will be provided. The CTCAE terms to be graded are listed in Table 6.

Table 6 CTCAE Grading for Laboratory Parameters

Hematology	**Biochemistry**
White blood cell decreased	Creatinine increased
Leukocytosis	Blood bilirubin increased
Anemia	Alanine aminotransferase increased
	Aspartate aminotransferase increased

Hemoglobin increased	Alkaline phosphatase increased
Platelet count decreased	Hypoalbuminemia
Neutrophil count decreased	Hyperkalemia
Lymphocyte count decreased	Hypokalemia
Lymphocyte count increased	Hypermagnesemia
	Hypomagnesemia
	Hypophosphatemia
	Hyponatremia

A listing of all laboratory parameters including hematology, biochemistry, and urinalysis will be provided, including the test results, units, normal range (H and L), change from baseline, and CTCAE grades if graded. Patients who developed toxicities of Grade >= 3 will also be listed.

4.11.9 Vital Signs

For weight, heart rate, systolic blood pressure, and diastolic blood pressure, summary statistics for baseline values and maximum change from baseline will be summarized based on the Full analysis set.

Summaries of markedly abnormal vital signs parameters, including blood pressure (BP) and pulse, will be presented.

Values for vital signs for all patients will be presented in a listing, and patients with markedly abnormal values will be flagged.

Markedly abnormal ranges for vital signs parameters are given in Table 7.

Table 7 Vital Sign Threshold of Interest

Vital Sign Parameter	Markedly Abnormal (Low)	Markedly Abnormal (High)
Systolic BP	Absolute value ≤ 90 mmHg, or a decrease from baseline ≥20 mmHg	Absolute value ≥ 180 mmHg, or an increase from baseline ≥20 mmHg
Diastolic BP	Absolute value ≤ 50 mmHg, or a decrease from baseline ≥15 mmHg	Absolute value ≥ 105 mmHg, or an increase from baseline ≥ 15 mmHg
Pulse	Absolute value ≤ 50 bpm, or a decrease from baseline ≥ 15 bpm	Absolute value ≥ 120 bpm, or an increase from baseline ≥ 15 bpm
BMI	Absolute value ≤ 18 kg/m^2	Absolute value ≥ 25 kg/m^2

4.11.10 12-lead ECG Evaluation

12-lead ECG with categorical results (normal, abnormal [not clinically significant], abnormal [clinically significant]) will be summarized based on the Full analysis set.

The shift from baseline to worst post baseline values will be summarized. A patient listing will be provided.

4.11.11 Physical Examination

Physical examination abnormalities will be summarized for baseline and worst values any time post baseline by dose cohort and cancer type.

A patient listing will be provided.

4.11.12 ECOG Performance Status

ECOG will be summarized in a shift table from baseline to worst post baseline.

4.11.13 Karnofsky Performance Status

Karnofsky performance status for all patients will be summarized in a shift table from baseline to the worst post baseline and presented in a listing.

5. INTERIM ANALYSIS

No formal interim analyses are planned for this study.

6. DATA HANDLING

6.1 METHODS FOR HANDLING MISSING DATES

For the patient data listings, no imputation of incomplete dates will be applied. The listings will present the incomplete dates without any change.

Missing or Partial Death Dates

Completely missing death dates will be imputed as the day after the date of last contact.

A death date missing month and day will be imputed as Jan 1st of the year or the date after the date of last contact, whichever comes last.

A death date missing day will be imputed as the 1st of the month or the day after the date of last contact, whichever comes last.

Date of Last Dose of Study Drug

No imputation will be done for first dose date. No imputation will be done for the date of last dose for patients off study. Date of last dose will be imputed by the analysis cutoff date for ongoing patients.

Date of Start of New Anti-Cancer Therapy

Incomplete dates for start date of new anti-cancer therapy will be imputed as follows and will be used for determining censoring dates for efficacy analyses:

- Completely missing start date will be imputed as the day after study treatment failure/relapse/PD, or the end date of new anti-cancer therapy if available, whichever comes first
- Start date missing both month and day will be imputed as Dec 31st of the year, or the end date of new anti-cancer therapy if available, whichever comes first
- Start date missing day will be imputed as the last date of the month, or the end date of new anti-cancer therapy if available, whichever comes first

Missing Dates in Adverse Events/Concomitant Therapies

Every effort will be made to avoid missing/partial dates in on-study data. Start dates of adverse events/concomitant therapies will be imputed as follows:

- Completely missing start date will not be imputed.
- Start date missing both month and day will be imputed as:
  - the date of first dose if the year of the start date is the same as the date of first dose;
  - otherwise, Jan 1st of the year of the start date will be used.
- Start date missing day will be imputed as:
  - the date of first dose if the year and month of the start date are the same as the date of first dose;
  - otherwise, the 1st of the month of the start date will be used.

Stop dates of adverse events/concomitant therapies will be imputed as follows:

- Completely missing stop date will not be imputed.
- Stop date missing both month and day will be imputed as Dec 31st of the year of stop date.
- Stop date missing day will be imputed as the last date of the month of the stop date.

After imputation, the imputed date will be compared against the date of death, if available. If the planned imputed date is later than the date of death, the date of death will be used as the imputed date instead. In any cases above, if the imputed start date is after the end date, then set the start date the same as the end date.

Missing Dates in Prior Therapies

Start dates of prior therapies will be imputed as follows:

- Completely missing start date will not be imputed.
- A prior therapy date missing month and day will be imputed as July 1st of the year or the date of informed consent, whichever is earlier.
- A prior therapy date missing day will be imputed as the 15th of the month or the date of informed consent, whichever is earlier.

6.2 PARTIAL DATE FOR PATHOLOGICAL DIAGNOSIS

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to calculate the months from the first pathological diagnosis.

- The missing day of the first pathological diagnosis will be set to the first day of the month that the diagnosis occurred.

- If the date of the first pathological diagnosis is missing both the day and month, the diagnosis date will be set to January 1 of the year of diagnosis.

6.3 PARTIAL DATE FOR BIRTH DATE

Birth dates missing the day will be imputed as the 15th of month. If both the day and month are missing, birth date will be imputed as July 1 of the birth year.

6.4 PHARMACOKINETICS

For individual concentration-time plots and the calculation of PK parameters using noncompartmental analysis, individual BLQ values will be converted using the following rules:

- If a BLQ value occurs in a profile before the first quantifiable concentration, it will be assigned a value of zero.

- If a BLQ value occurs after a quantifiable concentration in a profile and is immediately followed by a value above the LLQ, then the BLQ value should be treated as missing.

- If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration) it will be treated as missing.

- If two BLQ values occur in succession after Cmax, the profile will be deemed to have terminated at the first BLQ value and any subsequent quantifiable concentrations will be omitted from PK calculations by treating them as missing.

When imputing BLQ concentrations for the generation of summary statistics at a given time point, all BLQ values will be set to zero except when an individual BLQ falls between two quantifiable values, in which case it will be treated as missing. These same imputations apply to imputation of BLQ concentrations used for generation of concentration-time profiles based on summary statistics.

7. REFERENCES

[1] A Phase Ib/II Clinical Study of BBI608 Administered with Paclitaxel in Adult Patients with Advanced Malignancies, Amendment 4, Dated May 10, 2018

[2] Brookmeyer R, Crowley JJ. A confidence interval for the median survival time. Biometrics. 38:29-41, 1982.

[3] Eisenhauer EA, Therasse P, et al. (2009) "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer.45 (2):228-47.

8. APPENDIX A: SCHEDULE OF ASSESSMENTS

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

*At selected study sites

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

9. APPENDIX B: EVENT OR CENSOR TIME FOR PFS

Censoring Hierarchy	Situation	Date of Event or Censor	Primary Analysis
1	**No baseline** radiological tumor assessment available	Date of first dose	Censored
2	**New anticancer treatment** started before tumor progression or death	Date of previous adequate radiological assessment immediately prior to start of new therapy or Date of first dose, whichever comes later	Censored
3	**Tumor progression** (per RECIST 1.1) documented or death after 2 scan intervals following previous adequate radiological tumor assessment, no new anticancer treatment started	Date of previous adequate radiological assessment or Date of first dose, whichever comes later	Censored
4, 5	**No tumor progression** (per RECIST 1.1), no death reported and subject lost to follow-up or withdrawal of consent, no new anticancer treatment started	Date of last adequate radiological assessment or date of first dose, whichever comes later	Censored
6	**No tumor progression** (per RECIST 1.1) and no death reported within 2 scan intervals following last adequate radiological tumor assessment or date of first dose (if no post baseline tumor assessment available), no new anticancer treatment started	Date of last adequate radiological tumor assessment or date of first dose, whichever comes later	Censored

7	**No tumor progression** (per RECIST 1.1) and no death reported and none of the conditions in the prior hierarchy are met	Date of last adequate radiological tumor assessment or date of first dose, whichever comes later	Censored
	No tumor progression (per RECIST 1.1) but death reported within 2 scan intervals following last adequate radiological tumor assessment or date of first dose (if no post baseline tumor assessment available)	Date of death	Event
	Tumor progression (per RECIST 1.1) documented within 2 scan intervals following previous adequate radiological tumor assessment	Earliest of the target, non-target and new tumor assessment dates	Event

Notes: (1) Symptomatic deteriorations (i.e. symptomatic progressions, which are not radiographically confirmed) will not be considered as progressions.
(2) If target, non-target and new lesion assessments have different dates within a visit, then the earliest of those dates will be considered as the date of the tumor assessment if the assessment for that visit is progressive disease (PD); otherwise the latest date will be used.
(3) Adequate radiographical tumor assessment refers to an assessment with overall response of CR, PR, SD or PD.
(4) Comparing date of last tumor assessment to date of first dose is necessary if the last tumor assessment is baseline assessment

10. APPENDIX C: PERFORMANCE STATUS

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