Footnotes to Table 11 Screening through –Treatment Period

a. Written IRB-approved informed consent must be obtained prior to any screening assessments being performed.

b. Documented medical history to include concurrent baseline conditions (using NCI-CTCAE V4. Appendix 2), prior cancer treatment and surgeries. Any events occurring from consent to first dose of study medication will be recorded as medical history.

c. Complete physical exam including height and weight at screening, directed physical exam for day 1, on days 8, 15 of each cycle (if clinically indicated) and at the EOT, if deemed necessary. Measurement of weight (kg) and BSA calculation prior to dosing (After Cycle 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Cycle 1 /Day 1.

d. Vital signs to include: Blood pressure, pulse, respiratory rate, and temperature.

e. ECOG Performance Status must be 0 or 1 to be eligible for entry to the study.

f. Refer to Table 12 for details of required labs to be included. Adequate organ function must be demonstrated in accordance with protocol criteria within 10 days of start of study medication as defined in Table 4.

g. Plasma ascorbic acid to be collected within 60 minutes prior to start of AA infusion, 5-10 minutes prior to end of infusion (+/- 5 min) and 60 minutes (+/- 5 min) post end of ascorbic acid infusion.

h. Negative serum pregnancy test is required for women of child-bearing potential within 72 hours of start of study medication; adequate contraception (both males and females) as defined by the protocol should be used throughout the study through one month after the last dose of trial treatment.

i. CT/MRI scan to document disease status at baseline to include chest abdomen and pelvis and other regions as clinically indicated. Brain scan is required to rule out brain metastases if clinically indicated. A screening CT/MRI is not necessary if the patient's last scan was obtained within 28 days before the screening visit.

j. The same radiographic procedures used to document disease status at baseline must be used throughout the study. Tumor assessments will be conducted using CT or MRI, approximately every 9 weeks until study discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response.

k. CA19-9 (or CA125, CEA if not expressers of CA 19-9) assessments will be taken at baseline and approximately every 3 weeks during the trial treatment period. All CA 19-9 assessments must be assayed by the same laboratory for each patient. The Investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression, in order to confirm or refute the clinical impression.

l. Baseline biopsy to be obtained up to 4 weeks prior to first dose of trial medication. If possible, an optional biopsy will also be collected on C2 day15 (+2 days).

m. Each patient will have 3 X 10 mL vials of blood collected at the following time points: Pre-treatment (0-14 days prior to cycle1/day1), prior to treatment on day 1 of cycles 1, 2, 4, 6, and every 2 cycles thereafter.

n. A test dose of 15 g AA will be given between days -7 and -1 prior to receiving AA on C1/D1 to preclude hypersensitivity reactions. If no hypersensitivity is observed then the first high dose of AA (25-75 grams/m^2) will be given in accordance with the protocol on Cycle 1/Day1.

o. Neulasta® injection on Day 9, or Neulasta OnPro® may be given on **Day 8** if patient is not returning for Day 9 hydration. If chemotherapy is held on day 8, Neulasta® injection on Day 9, or Neulasta OnPro® day 8 will be held.

p. All treatment related activities may be done 3 days prior to cycle 1, day 1, excluding plasma ascorbic acid to be collected within 60 minutes prior to start of AA infusion on day 1.

Table 12. End of Treatment – Survival Follow-Up

EOT thru Survival Follow-Up Period	**EOT**	**30 days post EOT**	**Survival FU**
Scheduling Window (Days)	**14 -28 ±2 days of last dose**		Approximately every 12 weeks
Post-study anticancer therapy status		X	
Survival Status		X	X
Directed Physical Examination [a]	X		
Concomitant Medication Review	X		
Review Adverse Events	X	X	
Vital Signs	X		
ECG	X		
ECOG (see appendix 3)	X		
CBC with Differential	X		
Comprehensive Serum Chemistry Panel	X		
Urinalysis	X		
Tumor Imaging [b]	X		
CA19-9 (or CA125, CEA if not expressers of CA 19-9)[c]	X		
MDASI-GI and BPI	X		
Contact information Review [d]	X	X	X

Footnotes for Table 12. End of Treatment-Survival Follow-up

a. Directed physical exam at the EOT, if deemed necessary.

b. The same radiographic procedures used to document disease status at baseline must be used throughout the study. Tumor assessments will be conducted using CT or MRI, approximately every 9 weeks until study discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response. An EOT CT/MRI is not necessary if the patient's last scan was obtained within 28 days before the EOT visit.

c. All CA19-9 (or CA 125, CEA if not expressers of CA 19-9) assessments must be assayed by the same laboratory for each patient.

d. At EOT trial staff is to confirm contact information for patient and a designated family member and remind patient of FU telephone contact that will be made every 12 weeks after EOT visit to determine date of death.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart - Section 5 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to patient safety.

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential patient prior to participating in a clinical trial.

6.1.1.1.1 General Informed Consent

Consent must be documented by the patient's dated signature. A copy of the signed and dated consent form should be given to the patient before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB/ERC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature or by the patient's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the patient qualifies for the trial.

6.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the patient within 28 days before starting the trial. Treatment for the disease for which the patient has enrolled in this study will be recorded separately and not listed as a prior medication.

6.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the patient during the trial. All medications related to reportable SAEs should be recorded as defined in Section 6.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

6.1.1.5.2 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a patient initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the EOT visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the patient will move into survival follow-up.

6.1.1.6 Assignment of Screening Number

A patient will be assigned a screening number once they provide written informed consented for the study. This screening number will be site specific and maintained on a Screening log in the Investigator Site File.

6.1.1.7 Assignment of Enrollment Number

Eligible patients will be assigned an enrollment number that will serve as the patient's number throughout the trial. This enrollment number will be site specific and maintained on an Enrollment log in the Investigator Site File.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each patient to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

6.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

6.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 5.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.1.2.6 Tumor Imaging and Assessment of Disease

Assessment of the patient's pancreatic cancer will evaluated based on tumor assessments using RECIST 1.1 [22] (Appendix 4)

Tumor assessments for evaluation of response will be conducted using contrast enhanced multiphase (delayed arterial phase and portal venous phase) CT or MRI, approximately every 9 weeks until study discontinuation or disease progression, whichever is later. All sites of disease must be followed using the same baseline assessment method. Confirmatory assessment of complete response (CR) or partial response (PR) must be performed no less than 4 weeks after the initial documentation of response.

All target lesions will be measured by consistent imaging techniques for each patient throughout the study. Suitable imaging techniques include CT-scan, or MRI. The same technique should be used for each evaluation in an individual patient. Copies of the scans must be available for review.

CA19-9 (or CA 125, or CEA if not expressers of CA 19-9) assessments will be taken at baseline and approximately every 3 weeks during the trial treatment period. All tumor marker assessments must be assayed by the same laboratory for each patient.

6.1.3 Quantitative Textural Analysis

Quantitative Textural Analysis (QTA) will be used to explore imaging based tumor and tissue texture baseline, on treatment, and post treatment radiology scans. Such information may provide a basis for establishing a diagnostic biomarker that could 1) measure and complement radiologic based treatment response assessments, 2) discover a non-invasive method for detecting tumor and tissue texture changes related to Vitamin C and its metabolite exposure and 3) identify other correlations of imaging to tumor biology, response to treatment, and laboratory assessments.

CT (or MRI if CT is medically contraindicated) scans will be performed at each investigative site as per protocol schedule.

De-identified imaging scans may be sent to an imaging core lab for quantitative textural analysis at a later day. Images may be reviewed to ensure appropriate series, images and anatomic coverage is available and that all PHI has been removed. Only query-free studies will be forwarded for analysis. Refer to Appendix 7 for specific information on the planned QTA analysis to be performed.

6.1.4 Blood and Tumor Tissue Collection

Each patient will have 30 mL vials of blood collected at the following timepoints: Pre-treatment (0-14 days prior to cycle1/day1), and during the trial prior to treatment on days 1 of cycles 1, 2, 4, 6, and every 2 cycles thereafter.

A baseline tumor biopsy will be taken from each patient and used for profiling

(collected within the 4 weeks prior to cycle 1/day1). Optional and if possible (patient condition permitting) this will be repeated on Cycle 2 /day 15 (+ 2 days). Tissue samples will be sent to the Sponsor and will be centrally analyzed by the Sponsor or a third party vendor contracted by the Sponsor.

Tumor and blood samples will be collected pre-treatment and during treatment. These biomarker assessments will potentially aid in understanding the drug effect. All patients will be consented for the collection and use of these samples. All samples will be linked anonymized and only identified by the trial ID and unique sample number allocated by the Sponsor. The results of any exploratory analysis will not be included in the clinical study report and may be reported separately from the main study results.

The assays described below may be performed with the material derived from each patient (if available). It is likely that not all assays will be performed on samples provided by each patient (possibly because of insufficient tumor material or inadequate sample quality). Outcome measures may include but are not limited to:

- Tumor sample analyses: metabolic profiles, whole exome and whole genome CN, ChIP-seq/ATAQ seq, IHC and PCR assays on immune cell populations, CAFs, stem cell content (CD133, Aldh) and Musashi.
- Blood sample analyses: CTCs/circCSC enumeration, Single CTC/circCSC transcription profiling, immune profiling [CD4+CD8+ T cells, MDSC (IDO-1+HLR-DR-/lowCD33+CD11b+CD14+), Immunosuppressive plasmocytes (CD19+CD138+IgA+IL-10+PD-L1+), Th17 (CD3+gdTCR+IL-17A+), Treg (CD4+Foxp3+), Hypo-responsive NK cells (CD3-CD56+KIR-NKG2A-), cfDNA, GPC1+ exosomes.

6.1.5 Plasma Ascorbic Acid levels

Plasma concentration of ascorbic acid will be assessed at screening, and during treatment on days 1, 3, and 17 of Cycles 1 and Cycle 2, at the following time points:

- Within 60 minutes prior to start of ascorbic acid infusion
- 5-10 minutes (+/- 5 minutes) prior to the end of ascorbic acid infusion
- 60 minutes (+/- 5 minutes) post the end of ascorbic acid infusion

The plasma ascorbic acid assay will be performed by the site's local laboratory and will require an additional collection of 1 mL of blood.

6.1.6 Laboratory Procedures/Assessments

Safety laboratory tests for hematology, chemistry, urinalyses, and serum or urine pregnancy tests (if applicable) will be performed by the local laboratory at each investigational site at screening, baseline, and throughout the trial treatment period.

Table 13. Laboratory Tests – performed locally

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	β-hCG†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		
	Uric Acid		
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		

† Perform on women of childbearing potential only.

‡ If considered standard of care in your region.

6.1.7 Quality of life and Pain Assessments

Two well-known tools will be utilized to assess patient's self-reported quality of life and pain levels during this study. The MD Anderson Symptom Inventory (MDASI-GI) and Brief Pain Inventory (BPI) are valid, reliable, and sensitive instruments for assessing the severity of symptoms and their interference in patients' daily functioning. The MDASI asks patients to rate the worst severity of symptoms during the past 24 hours (0 not present to 10 as bad as you can imagine). It also rates the extent to which symptoms interfere with various aspects of life (e.g., general activity, mood, relations with other people, and enjoyment of life) using a scale ranging from 0 (did not interfere) to 10 (interfered completely). The BPI uses four pain severity items rated with a 0 to 10 numeric rating scale (NRS); the interference scale is similar to the MDASI (0 = no interference to 10 = interferes completely). Internal consistency measures (reliability) in prior studies were high at 0.80 or more (Cronbach alpha) for the BPI and MDASI (Atkinson et al, 2010; Cleeland et al, 2000; Janjan et al, 2007; Wang et al, 2010).

Instruments will be administered at screening, weekly throughout treatment and at end of study. Please see Appendix 8 and 9 for information on instruments.

6.1.8 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.8.1 Screening

Screening of potential patients will be performed only after informed consent is obtained and within 21 days prior to first dose of trial medication (unless stated otherwise below). All necessary laboratory values and assessment reports must be available prior to cycle1/ day 1.

The following will be completed as part of the screening visit:

1. Written informed consent

2. Medical history including concurrent baseline conditions (using NCI CTCAE version 4.0; Appendix 2), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).

3. Complete physical examination including height (cm) and weight (kg).

4. ECOG Performance Status (see Appendix 3)

5. Vital signs (blood pressure, pulse, respiratory rate, and temperature).

6. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain

metastases if clinically indicated only). If a CT scan was taken within 28 days prior to first dose, new scans are not necessary. However, if new scans are to be done, they should be performed within 5 days prior to starting trial medication. Obtain de-identified Dicomm encoded CT scan for central lab (Appendix 7).

7. Electrocardiogram (ECG)

8. PT/INR and aPTT

9. Complete blood count (CBC) with differential and platelet count.

10. Comprehensive serum chemistries (refer to Table 12).

11. CA 19-9 (or CA125 or CEA if not expressers of CA19-9)

12. Plasma ascorbic acid level

13. G6PD Enzyme

14. Iron studies including serum ferritin and transferrin saturation

15. Urinalysis (refer to Table 12)

16. Serum β-HCG pregnancy test for women of child-bearing potential (refer to Section 4.6.2 for more details)

17. Concomitant medication notation (to include all medications taken within 30 days prior to enrollment)

18. Baseline biopsy is to be obtained up to 4 weeks prior to first dose of trial medication (C1/D1). Refer to Section 6.1.2.8

19. Central Blood Sample at time of biopsy, 3 X 10 mL vials (must be collected within 14 days of Cycle 1/Day 1)

20. Patient to complete MDASI-GI and BPI questionnaires

6.1.8.2 Treatment Period

Patients will be treated at 21 ± 3 day intervals. Patient must begin cycle 1 within 21 days of signing the IRB approved informed consent document and after the screening assessments.

Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other outpatient setting appropriate for chemotherapeutic infusions.

For subsequent cycles, all assessments must be conducted within 72 hours (except those noted), or if medical or scheduling conditions require a delay.

Screening clinical evaluations and laboratory assessments may be used as the Cycle 1 /Day 1 evaluations if they are completed within 72 hours of trial treatment administration.

Day 1 of each cycle (except where noted)

- **Cycle 1 only:** Inclusion/exclusion review
- Directed physical exam
- Vital signs
- Measurement of weight (kg) and BSA calculation prior to dosing (After Cycle 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Cycle 1 /Day 1
- ECOG Performance Status (Appendix 3)
- Hematology: CBC with differential and platelet count
- Serum chemistries (refer to Table 12)
- CA19-9 (or CA 125, or CEA if not expressers of CA 19-9).
- **Cycles 1 and 2 only:** Plasma ascorbic acid levels, within 60 minutes prior to start of AA infusion, 5-10 minutes (+/- 5 min) prior to end of AA infusion, and again 60 minutes (+/- 5 min) post end of AA infusion.
- Urinalysis
- Serum β-HCG pregnancy test. Results must be reviewed prior to treatment initiation confirming a negative serum β-HCG for women of child-bearing potential and documentation of the patient's confirmation of preferred acceptable method of contraception starting from the day of trial treatment initiation or 14 days prior to the initiation of trial medication for oral contraception (refer to Section 4.4.2 for more details).
- **Cycles 1, 2, 4, 6 and every 2 cycles thereafter:** Central Blood Sample 3 X10 mL vials – collected prior to treatment.
- AEs using the NCI CTCAE V4.0 (Appendix 2)

- Concomitant medication notation
- Patient to complete MDASI-GI and BPI questionnaires
- Ascorbic Acid administration
- NabPlaGem administration

Day 3, 8, 10, 15,17 (± 1 day) of each cycle

- Vital signs
- AEs using the NCI CTCAE (Appendix 2)
- Concomitant medication notation
- Ascorbic Acid administration
- **Day 2 and 9:** Optional intravenous hydration
-
- **Day 3 and 17 of cycle 1 & 2 only:** Plasma ascorbic acid levels, within 60 minutes prior to start of AA infusion, 5-10 minutes (+/- 5 min) prior to end of AA infusion, and again 60 minutes (+/- 5 min) post end of AA infusion.
- **Day 8 and 15 of each cycle only:** Directed physical exam if clinically indicated, including weight
- **Day 8 and 15 of each cycle only**: ECOG Performance Status
- **Day 8 and 15 of each cycle only:** Hematology: CBC with differential and platelet count - results must be reviewed on day 8 prior to chemotherapy administration
- **Day 8 and 15 of each cycle only:** Serum chemistries (refer to Table 12) - results must be reviewed on day 8 prior to chemotherapy administration

  Day 8 and 15 of each cycle only: Patient to complete MDASI-GI and BPI questionnaires
- **Day 8 of each cycle only:** NabPlaGem administration
- **Day 9 of each cycle only:** Neulasta® injection, or Neulasta OnPro® may be given on Day 8 if patient is not returning for Day 9 hydration.

Cycle 2 /day 15 (+ 2 days)

- Repeat biopsy (refer to Section 6.1.2.7). Optional

Every 9 ± 1 weeks until disease progression or end of trial, whichever comes first

- CT/MRI scan to evaluate disease status (using same imaging method as Baseline). Obtain De-identified dicomm encoded CT scan for central lab (Appendix 7).

Note: In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression. In order to either confirm or refute the clinical impression.

6.1.8.3 End of Treatment (EOT)

The patient will continue on study treatment until there is evidence of clear-cut tumor progression, has treatment ending toxicities, or withdraws from treatment (refer to section 4.5). The following assessments will be performed 14-28 (+/- 2) days after completing the last dose of trial medication or before the initiation of a new anti-cancer treatment, whichever comes first:

- Directed physical exam, if deemed necessary
- ECOG Performance Status (see Appendix 3)
- Vital signs
- ECG
- Hematology: CBC with differential and platelet count
- Serum chemistries
- CA 19-9 (or CA125 or CEA if not expressers of CA19-9)
- Urinalysis
- Concomitant medication
- Patient to complete MDASI-GI and BPI questionnaires
- CT/MRI scan to evaluate disease status (using same imaging method as Baseline). If a CT scan was taken within 28 days prior to visit, new scans are not necessary.
- AEs using the NCI CTCAE Version 4.0 (see Appendix 2)

Patients with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

6.1.8.4 Survival Follow-up

Once a patient experiences confirmed disease progression or starts a new anti-cancer therapy, the patient moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the any of the component of trial treatments, is also an adverse event.

Progression of the cancer under study (pancreatic cancer) is not considered an adverse event.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 6.2.2.1. The investigator will make every attempt to follow all patients with non-serious adverse events for outcome.

6.2.1 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the patient to be excluded from the trial, or are the result of a protocol-specified

intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through trial treatment or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor.

6.2.2 Immediate Reporting of Adverse Events to the Sponsor

In addition, all SAEs must be reported promptly to HonorHealth after the Investigator recognizes/classifies the event as a SAE. The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE within 24 hours/ 1 business day of becoming aware of the event, preferably by fax or alternatively by phone or email; at a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report. If an SAE is reported by phone or by e-mail, the Investigator must fax a completed SAE report form to HonorHealth within 1 business days. The Investigator should follow all AEs/SAEs observed during the study until they resolve or stabilize, the patient is lost to follow-up, or the events are otherwise explained. The HonorHealth Drug Safety Team is responsible for notifying the relevant regulatory authorities and study partners of certain Serious Adverse Events.

For any additional questions regarding reporting requirements of a SAE, please contact the following individual:

HonorHealth Drug Safety Team
After hours, weekends, holidays: 480-323-1350
Business hours phone: 480-323-1323
E-mail: DrugSafety@honorhealth.com

6.2.2.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;

- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

For the time period beginning when the consent form is signed until treatment initiation any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any patient must be reported within 24 hours to the Sponsor and within 2 working days if it causes the patient to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment initiation through 30 days following cessation of treatment, or until the patient initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the trial treatment, must be reported within 24 hours to the Sponsor.

Additionally, any serious adverse event, considered by an investigator to be related to trial treatment that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All patients with serious adverse events must be followed up for outcome.

6.2.3 Evaluating Adverse Events

An investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP website at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

When specific adverse events are not listed in the CTCAE they will be graded by the investigator according to the following grades and definitions, consistent with the CTCAE Version 4.0.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

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

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

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

- Grade 5: Death related to AE.

Duration

The investigator will record the start and stop dates of the adverse event. If less than1 day, this will be indicated in the appropriate length of time in units.

Action Taken

Did the adverse event cause the trial treatment to be discontinued? This is to be recorded for each trial treatment including ascorbic acid, nab-paclitaxel, cisplatin, and gemcitabine.

Relationship

All adverse events regardless of CTCAE grade must also be evaluated for relationship (in regards to each trial treatment including/ trial interventions). This is to be recorded for each trial treatment including ascorbic acid, nab-paclitaxel, cisplatin, and gemcitabine.

The determination of the likelihood that trial treatment caused the adverse event will be provided by an investigator. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame.

The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the trial treatment and the adverse event based upon the available information.

The following components are to be used to assess the relationship between trial treatment and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the trial treatment caused the adverse event (AE):

Exposure: Is there evidence that the patient was actually exposed to trial treatment such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Time Course: Did the AE follow in a reasonable temporal sequence from administration of trial treatment? Is the time of onset of the AE compatible with a drug-induced effect?

Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

Dechallenge: Was trial treatment discontinued or dose/exposure/frequency reduced? This is to be recorded for each trial treatment including ascorbic acid, nab-paclitaxel, cisplatin, and gemcitabine.

If yes, did the AE resolve or improve? **If yes,** this is a positive dechallenge.

If no, this is a negative dechallenge.

Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the trial treatment; or (3) the trial is a single-dose drug trial); or (4) trial treatment is/are only used one time.

Rechallenge: Was the patient re-exposed to trial treatment in this study? This is to be recorded for each trial treatment including ascorbic acid, nab-paclitaxel, cisplatin, and gemcitabine.

If yes, did the AE recur or worsen?

If yes, this is a positive rechallenge.

If no, this is a negative rechallenge.

Note: If a rechallenge is planned for an adverse event which was serious and which may have been caused by either of the trial treatments, or if reexposure to trial treatment poses additional potential significant risk to the patient, then the rechallenge must be approved in advance by the Sponsor as per dose modification guidelines in the protocol.

Consistency with Trial Treatment Profile: **Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding trial treatment or drug class pharmacology or toxicology?**

Relationship	Attribution	Description
Unrelated to the trial treatment/intervention	Unrelated	The AE is clearly NOT related to the trial treatment/intervention
	Unlikely	The AE is *doubtfully related* to the trial treatment/intervention
Related to the trial treatment/intervention	Possible	The AE *may be related* to trial treatment/intervention
	Definite	The AE *is clearly related* to trial treatment/intervention

6.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design

This is a phase 1B/ II Pilot Trial. Up to 15 patients will be enrolled in Phase IB and up to 21 patients in Phase II. Eligible patients will be treated with high dose ascorbic acid (escalating doses) + NABPLAGEM (paclitaxel protein bound + cisplatin + gemcitabine). The dose of ascorbic acid used in the Phase II study will be determine from the safety and ascorbic acid concentration responses occurring in the Phase 1B dose escalation study.

Trial treatment will be administered per the schedule as described in 4.2. The primary endpoint will be response rate, objective response rate (CR+ PR), as well as disease control rate (CR+ PR+ SD x 18 weeks).

The secondary endpoint will be incidence of toxicities, percent of patients who normalized their CA19-9, progression free survival, and overall survival.

7.2 Sample Size Considerations

The sample size of this pilot study will be up to 24 patients in the Phase IB and up to 21 patients in the Phase II (total of 45). If a complete response rate is noted in at least one of the first 10 patients in the phase II portion, then the study size can be increased up to 21 patients. This is based on a test of a null hypothesis of a 5% complete response or less, versus an alternative hypothesis of a 30% complete response rate or greater. Four or more complete responders out of 21 patients will be sufficient evidence for rejection of the null hypothesis of insufficient activity of the regimen. This design has a power of 90% at a one-sided Type I error rate of 2.5%.

7.3 Statistical Analysis Plan

7.3.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and discontinuations for the study will be summarized using a CONSORT diagram.

7.3.2 Analysis of Patient Characteristics

Demographic and baseline characteristics, such as age, race, BSA, duration of pancreatic cancer, site(s) of metastatic disease, prior cancer treatment, and baseline ECOG performance status will be summarized using means (± standard error) or medians (range) for continuous variables and proportions for categorical variables.

7.3.3 Analysis of Trial Treatment Administration

Trial treatment (Ascorbic Acid + NABPLAGEM) administration will be listed and dose modifications will be flagged. Mean and standard deviations will be used to summarize the average dose received.

7.3.4 Analysis of Toxicities

Incidence of toxicity will be assessed through summaries of adverse events, clinically relevant changes in laboratory results, and vital signs. All patients who receive any amount of trial treatment will be included in the analysis.

All adverse events occurring on or after Cycle 1/day 1 will be summarized by body systems and per grade according to NCI-CTC Version 4. Additionally, all serious adverse events as defined in section 6.2.2.1 will be listed separately and tabulated.

7.3.5 Analysis of Primary Endpoint

The objective response for each patient (complete response, partial response or stabilization of disease) will be assessed at the determined evaluation time points as detailed in 6.1.2.6. The duration of objective response as determined by the investigator and the time to disease progression and duration of survival will be assessed for each patient.

Progression-free survival is defined as the interval from the date of registration (i.e. assignment of patient number) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. Patients who do not progress and remain alive will be censored at their last radiographic assessment date. Overall survival will be measure from the date of registration (i.e. assignment of patient number) to the date of death due to any cause, or the date of last contact (censored observations).

The efficacy analysis will include summaries for the following parameters: complete response rate (CR), objective response rate (CR + PR), disease control rate (CR +

PR + SD at 18 weeks), percent of patients who normalize their CA 19-9 (or CA 125 or CEA if these are used to follow the patient disease), progression-free survival (PFS), and overall survival (OS). The efficacy analysis will only be conducted on patients who have received at least one dose of ascorbic acid, albumin-bound paclitaxel, cisplatin, gemcitabine and have at least one post baseline tumor assessment. All proportions will be estimated using an exact 95% binomial confidence interval. For the estimation of progression-free and overall survival, a Kaplan-Meier analysis will be performed.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Trial treatment will not be provided directly to the site as part of this trial but will be obtained directly from the treating investigator's designated pharmacy supply. Therefore the labeling, storage, handling, and disposal of the trial treatment will follow the dispensing pharmacy's own standard operating procedures.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Institutional Review Board/Ethics Committee Approval

Before trial initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by the Sponsor prior to submission to the IRB. The Investigator will forward to the Sponsor or their nominated designee a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CRF 56 of the *Code of Federal Regulations,* as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S.

In addition, the Investigator will be responsible for forwarding to the Sponsor or their nominated designee a description of the IRB members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet the FDA and other appropriate regulatory requirements. In addition, the labeling for all approved trial medications should be submitted to the IRB for information purposes.

9.2 Investigators protocol agreement

The Investigator must sign the Investigator's Protocol Agreement. The original must be kept on file at the Sponsor and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed if and when a protocol amendment is issued by the Sponsor.

9.3 Confidentiality

The Investigator and any other personnel involved in this trial shall not disclose, or use for any purposes (other than for the performance of this trial any data, records, or other information (hereinafter collectively "information") disclosed to the Investigator or other trial personnel. Such information shall remain the confidential and proprietary property of the Sponsor, and shall be disclosed only to the Investigator or other designated trial personnel.

Patient confidentiality will be ensured by using assigned site-specific Screening and Randomization numbers (refer to Section 6.1) throughout the trial.

9.4 Compliance with Financial Disclosure Requirements

All Investigators will be required to submit written financial disclosures to the Sponsor prior to participating in this clinical trial and any changes in disclosures during the course of the trial as per 21 CFR part 54.

9.5 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are patient to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

9.6 Quality Management System

All aspects of the study will be carefully monitored by The HonorHealth Research Institute and/or its authorized representative for compliance with applicable government regulations with respect to current ICH GCP guidelines as well as other applicable regulations and guidelines.

9.7 Data Monitoring Plan

The HonorHealth Research Institute shall ensure that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. Prior to enrolling patients into the study, a The HonorHealth Research Institute representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator.

Monitoring will include on-site visits with the Investigator and study team as well as any appropriate communications by mail, email, fax, or telephone.

Data monitoring procedures will be carried out by each site and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documents (including radiology review), review of trial-related regulatory documents and logs (e.g. enrollment, trial site staff), would be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

At the conclusion of the monitoring visit, the monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The site Clinical Research Coordinator responsible for the trial will be provided with a copy of the written monitoring notes for resolution of the findings.

The monitor will complete a written monitoring report and forward it to the Principal Investigators and to the Sponsor. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to the Sponsor or their designee and the site monitor. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site monitor's trial file follow up at the next monitoring session.

9.8 Data Management

9.8.1 Case Report Forms

All the clinical data will be captured by the site on electronic case report forms (eCRFs). The eCRFs will be used for all consented patients. The investigator and trained trial personnel will enter and edit the data via a secure network, with secure identification and password requirement. A complete electronic audit trial will be maintained. The investigator will be required to provide approval of all data to confirm

accuracy. Copies of the eCRFs will be provided to the investigator at the conclusion of the trial.

9.8.2 Source Documents

Source documents serve as the evidence of the existence of the patient and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed by to the sponsor, or assigned clinical monitor.

Data captured on the eCRF is to be transcribed from source document and must be consistent with any discrepancies explained and documented.

9.9 Data Safety and Monitoring Committee

An independent Data Safety and Monitoring Committee (DSMC) will be formed to evaluate the safety and effectiveness of the study medication for each subject as well as study conduct of each site. The DSMC will also review all SAEs reported by each site. The DSMC will review study data to determine if endpoints are being met and if the study can continue with or without changes to the protocol or if the study should be terminated immediately due to safety concerns or lack of data to support study endpoints. Findings and recommendations of the DSMC will be reported to the Sponsor after each meeting. The DSMC will meet on a quarterly basis or more frequently as needed if safety concerns are raised. Furthermore, prior to opening the Phase II portion of the study a review by the DSMC will be conducted. This treatment regimen combines 3 chemotherapeutic agents with known toxicity profiles and high-dose ascorbic acid with unknown toxicities. Because cancer is a life-threatening disease, treatments that result in Grade 3 and 4 toxicities are considered to have an acceptable risk profile. Data reported to the sponsor will be received by sponsor representatives on a regular basis and not less than once a month. In addition, SAEs will be reported to the sponsor immediately and reviewed as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the sponsor, the site Principal Investigators and DSMC members who will decide jointly whether the study should be modified, interrupted, or stopped. A monthly conference call will be held with investigators participating in the study. The statistical group will provide listings of toxicities on a regular basis.

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APPENDICES

Appendix 1 - Ascorbic Acid Product Insert

ASCORBIC ACID- ascorbic acid injection, solution
Mylan Institutional LLC

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.

ASCORBIC ACID
Injection, USP

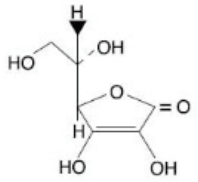
FOR INTRAVENOUS, INTRAMUSCULAR OR SUBCUTANEOUS USE.

CONTAINS NO PRESERVATIVES.

DESCRIPTION

Ascorbic Acid (vitamin C) is a water-soluble vitamin. It occurs as a white or slightly yellow crystal or powder with a light acidic taste. It is an antiscorbutic product. On exposure to air and light it gradually darkens. In the dry state it is reasonably stable in air, but in solution it rapidly oxidizes. Ascorbic Acid is freely soluble in water; sparingly soluble in alcohol; insoluble in chloroform, ether, and benzene.

The chemical name of Ascorbic Acid is L-ascorbic acid. The molecular formula is $C_6H_8O_6$ and the molecular weight is 176.13. The structural formula is as follows:



Ascorbic Acid injection is a clear, colorless to slightly yellow sterile solution of Ascorbic Acid in Water for Injection, for intravenous, intramuscular or subcutaneous use. **Each ml contains:** Ascorbic Acid 500 mg, Disodium Edetate 0.25 mg, Sodium Hydroxide 110 mg, in Water for Injection q.s. pH (range 5.5 to 7.0) adjusted with Sodium Bicarbonate and Sodium Hydroxide. Contains no preservatives.

CLINICAL PHARMACOLOGY

In humans, an exogenous source of ascorbic acid is required for collagen formulation and tissue repair. Ascorbic acid is reversibly oxidized to dehydroascorbic acid in the body. These two forms of the vitamin are believed to be important in oxidation-reduction reactions. The vitamin is involved in tyrosine metabolism, conversion of folic acid to folinic acid, carbohydrate metabolism, synthesis of lipids and proteins, iron metabolism, resistance to infections, and cellular respiration.

Ascorbic acid deficiency results in scurvy. Collagenous structures are primarily affected, lesions develop in bones and blood vessels. Administration of ascorbic acid completely reverses the symptoms of ascorbic acid deficiency.

INDICATIONS AND USAGE

Ascorbic acid is recommended for the prevention and treatment of scurvy. Its parenteral administration is desirable for patients with an acute deficiency or for those whose absorption of orally ingested ascorbic acid is uncertain.

Symptoms of mild deficiency may include faulty bone and tooth development, gingivitis, bleeding gums, and loosened teeth. Febril states, chronic illness, and infection (pneumonia, whooping cough, tuberculosis, diphtheria, sinusitis, rheumatic fever, etc.) increases the need for ascorbic acid.

Hemovascular disorders, burns, delayed fracture and wound healing are indications for an increase in the daily intake.

CONTRAINDICATIONS

There are no contraindications to the administration of ascorbic acid.

WARNINGS

Diabetics, patients prone to recurrent renal calculi, those undergoing stool occult blood tests and those on sodium restricted diets or anticoagulant therapy should not take excessive doses of ascorbic acid over an extended period of time.

PRECAUTIONS

General Precautions

Too-rapid intravenous injection is to be avoided.

Laboratory Tests

Diabetics taking more than 500 mg of ascorbic acid daily, may obtain false reading of the urinary glucose test. No exogenous ascorbic acid should be ingested for 48 to 72 hours before amine dependent stool occult blood tests are conducted because possible false negative results may occur.

Drug Interactions

Limited evidence suggests that ascorbic acid may influence the intensity and duration of action of bishydroxycoumarin.

Usage in Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Ascorbic Acid Injection. It is also not known whether Ascorbic Acid Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ascorbic Acid Injection should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Caution should be exercised when Ascorbic Acid Injection is administered to a nursing woman.

ADVERSE REACTIONS

Transient mild soreness may occur at the site of intramuscular or subcutaneous injection. Too-rapid intravenous administration of the solution may cause temporary faintness or dizziness.

DOSAGE AND ADMINISTRATION

Ascorbic acid is usually administered orally. When oral administration is not feasible or when malabsorption is suspected, the drug may be administered intramuscularly, intravenously or

subcutaneously. When given parenterally, utilization of the vitamin reportedly is best after IM administration, which is the preferred parenteral route.

For intravenous injection, dilution into a large volume parenteral such as Normal Saline or Glucose is recommended to minimize the adverse reactions associated with intravenous injection.

The average protective dose of ascorbic acid for adults is 70 to 150 mg daily. In the presence of scurvy, doses of 300 mg to 1 gram daily are recommended. However, as much as 6 grams have been administered parenterally to normal adults without evidence of toxicity.

To enhance wound-healing, doses of 300 to 500 mg daily for a week to ten days, both preoperatively and postoperatively, are generally considered adequate, although considerably larger amounts have been recommended. In the treatment of burns, doses are governed by the extent of tissue injury. For severe burns, daily doses of 1 to 2 grams are recommended. In other conditions in which the need for ascorbic acid is increased, three to five times the daily optimum allowances appear to be adequate.

WARNING

PRESSURE MAY DEVELOP WITHIN THE VIAL UPON STORAGE.

Exercise care when withdrawing and/or relieve pressure by first inserting sterile empty syringe into vial thus allowing pressure to equilibrate.

When using dispensing vials use aseptic technique. Dispense entire contents in aliquots under a laminar flow hood without delay or within 4 hours after entry or discard remaining content after first withdrawal. Prepare stoppers with a suitable antiseptic solution. Do not use unless solution is clear and seal is intact.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

HOW SUPPLIED

Ascorbic Acid for Injection USP, 500 mg/mL, is available in:

NDC 67457-118-50
carton containing a 50 mL sterile dispensing vial, individually packaged

PROTECT FROM LIGHT. STORE IN CARTON UNTIL TIME OF USE. Store between 2° to 8°C (36° to 46°F).

Manufactured for:
Mylan Institutional LLC
Rockford, IL 61103 U.S.A.

Manufactured by:
Mylan Institutional
Galway, Ireland

0921L100
Revised: 12/2016
MI:ASCOIJ:R3

PRINCIPAL DISPLAY PANEL - 50 mL Carton

NDC 67457-118-50 50 mL

Ascorbic

Acid
Injection, USP
500 mg/mL

For Intravenous,
Intramuscular or
Subcutaneous Use

Rx only Vial

Each mL contains: Ascorbic Acid 500 mg, Disodium Edetate 0.25 mg, Sodium Hydroxide 110 mg, in Water for Injection q.s. pH (range 5.5 to 7.0) adjusted with Sodium Bicarbonate and Sodium Hydroxide.

Contains no preservatives.

USUAL ADULT DOSAGE: See accompanying prescribing information.

WARNING: Use aseptic techniques. Dispense entire contents in aliquots under a laminar flow hood without delay or within 4 hours after entry, or discard remaining contents after first withdrawal. Prepare stoppers with a suitable antiseptic solution.

Do not use unless solution is clear and seal is intact.

STORE BETWEEN 2° TO 8°C (36° TO 46°F).

Store in carton until time of use.

PROTECT FROM LIGHT.

PRESSURE MAY DEVELOP UPON STORAGE. EXERCISE CARE WHEN WITHDRAWING.

Manufactured for:
Mylan Institutional LLC
Rockford, IL 61103 U.S.A.

Manufactured by:
Mylan Institutional
Galway, Ireland

MI:118:1C:R3

Mylan.com



ASCORBIC ACID

ascorbic acid injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:67457-118
Route of Administration	INTRAVENOUS, INTRAMUSCULAR, SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Ascorbic Acid (UNII: PQ6CK8PD0R) (Ascorbic Acid - UNII:PQ6CK8PD0R)	Ascorbic Acid	500 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Edetate Disodium (UNII: 7FLD91C86K)	0.25 mg in 1 mL
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	
Sodium Bicarbonate (UNII: 8MDF5V39QO)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67457-118-50	1 in 1 CARTON	06/01/1999	
1		50 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Unapproved drug other		06/01/1999	

Labeler - Mylan Institutional LLC (790384502)

Revised: 12/2016 Mylan Institutional LLC

Appendix 2 - NCI CTCAE version 4.0

The CTCAE Version 4.0 can be accessed and downloaded from the CTEP website at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Appendix 3 - ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Appendix 4 - RECIST 1.1 Criteria

1. Definitions

1.1. Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

1.2. Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

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 Tumours) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

See section 6.1.2.6 for criteria for continuing treatment past RECIST 1.1 disease progression.

2. RECIST 1.1 Response and Evaluation Endpoints

2.1. Measurable Disease. Measurable tumour lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) 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 ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

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.

2.3. Target Lesions. When more than one measurable tumour 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 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour 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.

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".

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 lesions and normalization of tumour markers. 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[4] before CR can be accepted. Confirmation of response is only required in non-randomised studies.

- Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour 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. Confirmation of response is only required in non-randomised studies.

- 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 ≥5 mm. 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 tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour 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.

Table S1: 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	Normalization of tumour markers, tumour nodes <10 mm
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 ≥4 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	Normalization of tumour markers, tumour nodes <10 mm
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 objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

Appendix 5 - Trial Drug Preparation, Dosing, Administration And Storage

Paclitaxel protein bound (Abraxane™) Prescribing Information (Updated 07/2015) – Accessed via Abraxane Website:
http://www.abraxane.com/downloads/Abraxane_PrescribingInformation.pdf

Cisplatin Prescribing Information (updated 02/2015) – Accessed via Daily Med (National Library of Medicine)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018057s083lbl.pdf

Gemcitabine (Gemzar™) Prescribing Information (Updated 9/2017) – Accessed via Gemzar Website:
http://pi.lilly.com/us/gemzar.pdf

Appendix 6 - 2006 Update Of ASCO Practice Guideline Recommendations For The Use Of White Blood Cell Growth Factors: Guideline Summary

Setting/Indication	Recommendation
Primary prophylaxis	Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For “dose-dense” regimens, CSF is required and recommended. Clinical Trial data support the use of CSF when the risk of FN is in the range of 20% or higher.
Primary prophylaxis: Special circumstances	Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age > 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor-producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate, even with regimens with FN rates of < 20%.
Secondary prophylaxis	Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
Therapeutic use: Afebrile neutropenia	CSF should not be routinely used for patients with neutropenia who are afebrile.
Therapeutic use: Febrile neutropenia	CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 × 109/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
Dose intensity/density of chemotherapy	Dose-dense regimens should only be used within an appropriately designed clinical Trial or if supported by convincing efficacy data.

Setting/Indication	Recommendation
Adjuncts to progenitor-cell transplantation	Administration of CSF to mobilize PBPC often in conjunction with chemotherapy, and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.
AML: Initial or repeat induction chemotherapy	CSF use following initial induction therapy is reasonable, though there has been no favorable impact on remission rate, remission duration, or survival. Patients > 55 years of age may be most likely to benefit from CSF use.
AML: CSF for priming effects	Use of CSF for priming effects is not recommended.
AML: Consolidation chemotherapy	CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive postremission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. As yet there is no information about the effect of longer-acting pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical Trials.
MDS	Intermittent administration of CSF may be considered in a subset of patients with severe neutropenia and recurrent infection.
ALL	CSF administration is recommended after the completion of the initial first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of < 1,000/mm^3 by approximately 1 week.
Acute leukemia in relapse	CSF should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia.
Radiotherapy ± chemotherapy	CSF should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSF may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.
Older patients	Prophylactic CSF for patients aged ≥ 65 years with lymphoma treated with curative chemotherapy (CHOP or

Setting/Indication	Recommendation
	more aggressive regimens) should be given to reduce the incidence of FN and infections.
Pediatric patients	As in adults, the use of G-CSF is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly, the use of G-CSF for secondary prophylaxis or for therapy should be limited to high-risk patients. However, the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with G-CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the specific use of G-CSF in children with ALL should be considered carefully.
Comparative clinical activity of G-CSF and GM-CSF	No guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents. Further Trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of GCSF and GM-CSF.
Treatment for radiation injury	Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.

Abbreviations: CSF, colony-stimulating factors; FN, febrile neutropenia; PBPC, peripheral-blood progenitor cell; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, filgrastim; GM-CSF, sargramostim; pegylated G-CSF, pegfilgrastim.

Appendix 7 - Quantitative Textural Analysis

A Quantitative Radiomics Approach

Recent data acquisition and analytical advances have expanded the traditional role of medical imaging beyond subjective/qualitative arenas. Radiomics refers to the comprehensive analyses of tumor phenotypes based on quantifiable image features (1). Quantitative CT-based tumor and tissue texture analysis (QTA) provides a comprehensive, 3-dimensional and temporal analyses of tumor heterogeneity (1). This approach represents an emerging technology that can conceivably monitor tumor development, progression, immune cell activity and response to treatment by identifying early and evolving measureable changes of on radiologic images (e.g CT, PET and MRI) as measured on individual voxel elements included of regions of interest. This is because tumor heterogeneity on cross-sectional imaging is manifested by histopathological differences in cell density, necrosis, and hemorrhage (2,3) that is readily detected by these radiologic exams. Image texture analyses assess tumor heterogeneity in accordance to the distribution and relationship of pixel or voxel-gray levels in the image (4). Findings from several studies have suggested that imaging texture reflects tumor-host interactive status within the tumor microenvironment (5,6). Radiologic tumor texture analysis has shown promise in predicting pathologic features, overall survival, and response to therapy in NSCLC (1,7-9), colorectal cancers (3,5), esophageal cancer (10), head and neck cancers (11) and metastatic renal cell cancer (13). In separate studies, we have shown prognostic QTA signature that differentiated K-ras mutant NSCLC tumors from pan-wild type NSCLCs (9). We have recently demonstrated that using QTA, a specific imaging QTA signature of kurtosis and entropy is associated with interchromosomal aberrations in mPDA as determined by NGS and that these imaging features are associated with PFS and OS (12). Furthermore, an analysis of the texture of tissue and tumors from mPDA subjects treated with paricalcitol showed a distinct texture pattern in the liver and pancreas of mPDA subjects on both the pre treatment and early post treatment scans leading to texture differences that may be distinctive based on vitamin D levels measured in patient serum. These encouraging results provide the rationale for using QTA to explore differences in tumor and tissue texture in this study using baseline to and post treatment scans. Such information would be informative and provide a basis for establishing a complementary diagnostic biomarker that could 1) predict early and evolving treatment related response on imaging 2) provide imaging biomarkers to allow a non invasive method for detecting tumor and tissue texture changes related to vitamin C exposure and 3) identify other correlations of imaging to tumor biology, response, laboratory assessments.

In order to perform Quantitative Textural Analysis (QTA) the following steps are required as will be detailed in the Imaging Manual sent to participating trial sites- De-identified dicomm encoded CT scans will loaded onto a QTA analysis platform for textural analysis. Standard reconstructed algorithm generated image series will be evaluated for presence or absence of evaluable tumor, i.e. tumor $\geq$10mm containing clearly defined tumor margins on at least two consecutive slices and on reference tissue.

QTA will be applied to regions of interest which uses an image filtration-histogram technique whereby the filtration technique applies a Laplacian of Gaussian band-pass filter enhanced algorithm leading to extracted features of different sizes based on the spatial scale filter (SSF) value varying from fine-texture (SSF2, 2 mm in radius), medium texture (SSF3, 3 mm in radius), and coarse-texture (SSF4, 4 mm in radius). This is followed by quantification of tumor texture from the filtered histogram based texture maps producing the following quantitative parameters

a) Mean (a measure of average brightness within the ROI)
b) Kurtosis (K, a measure of peakedness and tailedness)
c) Skewness (S, a measure of asymmetry of the frequency-intensity histogram)
d) Standard-deviation (SD, a measure of variation or dispersion that exists from the mean)
e) Mean Positive Pixel (MPP, a measure of pixels that contain non-fat/air densities)
f) Entropy (a measure of orderliness based upon co-occurrence matrix principles)

A Sample Output from QTA Analysis of Lung Metastasis Lesions is shown below:



Additional published Radiomics features may be extracted on the imaging slice as appropriate for tumor size, location and pattern features. A bioinformatics linkage using clinical, laboratory and molecular information will be integrated into the imaging

results for surrogate biomarker testing. The expected statistical analysis of the data will involve a non-parametric Mann Whitney test used to assess the ability of the QTA, clinical, and patient characteristics to differentiate between responders and non responders, vitamin C levels, molecular characterization and relapse risk. We anticipate using a recursive-type decision tree (or similar) approach to determine whether the differentiation between these outcomes could be improved by sequential application of QTA parameters. The QTA parameter that most accurately identifies the selected dependent variable will be used in the entire patient cohort as the first node, thereby generating two branches. The abilities of additional QTA parameters to identify outcomes will then be separately tested for each branch, adding further nodes to the tree. The diagnostic threshold values for the QTA parameters used at each node will be optimized using Receiver Operator Characteristic (ROC) analysis to maximize diagnostic accuracy. QTA parameters will be applied in order of overall accuracy for determination the biomarker usefulness in achieving the desired exploratory endpoints of this trial. If two modalities have the same accuracy, the modality with the highest sensitivity will be applied first. No further node will be added to a branch if the misclassification rate in that branch is less than 15%. The final decision tree will be applied to the whole cohort to determine the overall sensitivity, specificity, and accuracy. Since this is an exploratory study, General mixed linear modeling and/or computer simulation analysis will be sought to link response, vitamin C levels, molecular characterization and other clinically relevant endpoints with QTA results. In our prior work a Monte Carlo analysis using 1,000 iterations of the decision tree was used to assess the impact of uncertainty in the sensitivity and specificity for each QTA parameter (expressed as their 95% confidence intervals [CI]) on the overall diagnostic performance of the decision tree. For responses and survival data, univariate Kaplan-Meier survival (KM) analysis will assess the relationship between the above. An iterative procedure will also be applied to identify the optimal cut off for each marker that provides the best separation of the population into ‘good’ and ‘poor’ outcomes groups (indicated by the best p-value from log-rank test). Due to small numbers, we might need to censor reporting results for significant features yielding less than 10 patients per group for comparison to avoid overstating significant results. Multivariate Cox regression will be used to determine which significant univariate parameters along with their interactions are independent predictors of recurrence, metastasis and relapse, along with the hazard ratio (HR) and the CI. A two-tailed P value of less than 0.05 will be considered to indicate a significant difference.

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Appendix 8 - The MDAnderson Symptom Inventory Gastrointestinal Cancer Module (MDASI-GI)

(TO BE SUBMITTED SEPARATELY FROM PROTOCOL FOR IRB APPROVAL)

MD Anderson Symptom Inventory (MDASI) modules augment the 19 core MDASI symptom and interference items with additional items identified as unique to a particular patient population. MDASI modules may be disease-specific, disease-site-specific, or treatment-specific.

The MDASI gastrointestinal cancer module (MDASI-GI) is a site-specific module. Along with the core MDASI's 13 symptom items and 6 interference items, the MDASI-GI also assesses 5 symptoms specific to gastrointestinal cancer:

- Constipation
- diarrhea or watery stools
- difficulty swallowing
- change in taste
- feeling bloated

MDASI-GI Features

- Purpose: To assess the severity of multiple gastrointestinal cancer-related symptoms and the impact of these symptoms on daily functioning
- Population: Patients with symptoms caused by gastrointestinal cancer and its treatment
- Assessment areas: Severity of multiple symptoms and the impact of symptoms on daily functioning during the last 24 hours
- Method: Self-report; paper-and-pencil form or tablet PC (self-administered or via interview), or telephone-based interactive voice response (IVR) system
- Time required: Five minutes
- Scoring: Please see the MDASI User's Guide
- Reliability: Cronbach alpha reliability ranges from 0.80 to 0.87

Appendix 9 - The Brief Pain Inventory (BPI) Short Form

(TO BE SUBMITTED SEPARATELY FROM PROTOCOL FOR IRB APPROVAL)

The Brief Pain Inventory (BPI) is available in two formats: the BPI short form, which is used for clinical trials and is the version used for the foreign-language translations; and the BPI long form, which contains additional descriptive items that may be clinically useful (for example, items that expand the possible descriptors of pain, such as burning, tingling, etc.). For brevity's sake and for the patient's ease of use, however, we recommend the short form of the BPI.

In response to the US Food and Drug Administration (FDA) guidance for the pharmaceutical industry on the use of patient-reported outcome measures in medical product development to support labeling claims, we have prepared a BPI User's Guide to provide documentation of the BPI's development and psychometric properties. The information offered therein addresses the recommendations in the FDA guidance and establishes the BPI's adequacy as a measure to support medical product claims.

BPI Features

- Purpose: To assess the severity of pain and the impact of pain on daily functions
- Population: Patients with pain from chronic diseases or conditions such as cancer, osteoarthritis and low back pain, or with pain from acute conditions such as postoperative pain
- Assessment areas: Severity of pain, impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or the past week
- Responsiveness: Responds to both behavioral and pharmacological pain interventions
- Method: Self-report or interview
- Time required: Five minutes (short form), 10 minutes (long form)
- Scoring: No scoring algorithm, but "worst pain" or the arithmetic mean of the four severity items can be used as measures of pain severity; the arithmetic mean of the seven interference items can be used as a measure of pain interference
- Reliability: Cronbach alpha reliability ranges from 0.77 to 0.91