Phase 1 Study of VE800 and Nivolumab in Patients with Selected Types of Advanced or Metastatic Cancer

Investigational Product(s)	VE800
Protocol Number	VE800-001
Version Number	2.0
Version Date	11 December 2019
Amendment	[IND 19293]1
IND Number	
Sponsor	*Vedanta Biosciences, Inc.* *19 Blackstone Street* *Cambridge, MA 02139* *Phone: (857) 706-1427* [redacted]

Confidentiality Statement

CONFIDENTIAL INFORMATION: This protocol contains trade secrets and other confidential information. Accordingly, this protocol shall be treated as confidential and restricted to its intended use, namely, the guidance of the clinical Investigator. This material is the sole property of Vedanta Biosciences, Inc and shall not be disclosed or used by others except as authorized in writing by Vedanta Biosciences, Inc. This material may be disclosed to and used by your staff and associates only to the extent necessary to conduct the clinical study.

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by International Council for Harmonisation (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential study patients.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled study patients may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study patients.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	Phase 1 Study of VE800 and Nivolumab in Patients with Selected Types of Advanced or Metastatic Cancer
Protocol Number	VE800-001
Version Number	Version 2.0
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Amendment	1

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

Medical Representative			
Name:	**Title:**	**Signature:**	**Date:**
[redacted]	[redacted] Vedanta Biosciences, Inc.		

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study VE800-001 and agree to the following:

- To conduct this study as described by the protocol
- To protect the rights, safety, and welfare of the patients under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2).
- To obtain approval for the protocol and all written materials provided to patients prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all patients enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those patients
- To maintain records of each patient's participation and all data required by the protocol

Name	**Title**	**Institution**
[Insert last name, first name]	[Insert title (at institution)]	[Insert address]
Signature		**Date**
		[DD Month YYYY]

1 SYNOPSIS

Name of Sponsor/Company: Vedanta Biosciences, Inc.

Name of Investigational Product: VE800

Name of Active Ingredient: Live biological product of 11 commensal bacterial strains

Title of Study: Phase 1 Study of VE800 and Nivolumab in Patients with Selected Types of Advanced or Metastatic Cancer

Study Center(s): Up to 45 centers /United States (US)

Planned Study Period (years):

Estimated date first patient enrolled: December 2019
Estimated date last patient completed: February 2022

Objectives:

Primary objectives:

- To evaluate the safety and tolerability of VE800 in combination with nivolumab in terms of adverse event (AE) rates using Common Terminology Criteria for Adverse Events (CTCAE, v. 5.0)
- To evaluate clinical activity as measured by objective response rate (ORR) of the study drug combination using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary objectives:

- To evaluate additional measures of clinical benefit, including:
  - Duration of response (DOR) according to RECIST 1.1
  - Best overall response according to RECIST 1.1
  - Disease control rate (DCR) according to RECIST 1.1
  - Progression-free survival (PFS) according to RECIST 1.1
  - Overall survival (OS)
- To evaluate the pharmacokinetics (PK) of VE800
  - Detection of each VE800 strain in stool
  - Degree and duration of VE800 strain colonization

Exploratory objectives:

- [redacted]

Methodology:

This is a first-in-human multicenter, open-label study evaluating the safety and clinical activity of VE800 in combination with nivolumab in patients with selected types of advanced or metastatic cancer, regardless of programmed death ligand 1 (PD-L1) expression status, where efficacy of an anti-programmed cell death protein 1 (PD-1) antibody is expected to be modest to null (e.g., in colorectal cancer - metastatic microsatellite-stable [CRC-MSS]). Safety, clinical activity, PK, and pharmacodynamics (stool, blood and/or tumor biomarker changes) will be evaluated.

Eligible patients will receive a 5-day course of vancomycin followed by daily VE800 dosing in combination with nivolumab administered every 4 weeks, as described in the Dosage and Administration Section.

Initial safety monitoring and dose-limiting toxicity (DLT) evaluation period:

The safety committee, comprising investigators and the Sponsor, will oversee the emerging safety data.

Patients will be evaluated for safety for a DLT period encompassing 28 days of VE800 dosing with nivolumab starting on Day 1.

[redacted]

Safety information collected throughout the entire treatment period, i.e., beyond 28 days of DLT period, will be reported and taken into account for decisions of recommended dose for later phases of development.

Patients who do not complete study treatment (vancomycin, VE800, and nivolumab) and/or scheduled safety assessments required for the DLT period, for reasons other than study treatment-related safety event, will not be considered towards the DLT-evaluable safety population. Additionally, AEs observed during the vancomycin administration phase or an

event clearly attributed by the Investigator to an alternative cause will not be considered a DLT.

Dose-limiting toxicity (DLT) criteria

The following treatment related AEs will be considered dose-limiting if determined to be at least possibly related to VE800 or to the combination of VE800 and nivolumab:

- ≥ Grade 2 uveitis or eye pain, that does not resolve with topical therapy (i.e., corticosteroids) within 2 weeks
- Grade 4 rash, or Grade 3 if no improvement (i.e., resolution to ≤ Grade 1 after a 1-2 week dose delay)
- Grade ≥ 4 hypersensitivity reaction, or Grade 3 that does not resolve to Grade 1 in <6 hrs
- Grade 2 or 3 colitis or diarrhea that persists without resolution to ≤ Grade 1 for ≥7 days despite adequate immune suppressive and anti-diarrheal therapy
- Grade 3 or 4 immune-mediated adverse event (imAE) without resolution to Grade ≤ 1 or baseline within 8 days despite adequate immune suppressive therapy
- Any grade clinically significant imAE (e.g., myocarditis, encephalitis) requiring treatment discontinuation
- Any other ≥ Grade 3 non-hematologic clinical (non-laboratory) toxicity excluding:
  - Nausea and vomiting resolving to ≤ Grade 1 within 48 hours with adequate treatment
  - Grade 3 fatigue with duration <7 days
  - Grade 3 or Grade 4 electrolyte abnormalities that last less than 48 h with adequate treatment
  - Grade 3 fever not associated with hemodynamic compromise
  - Grade 3 endocrinopathy that is well controlled by hormone replacement
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Any clinically-significant Grade ≥ 3 non-hematologic laboratory abnormality, except Grade 3 or Grade 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
- Any clinically-significant hematologic toxicity specifically defined as:
  - Grade 4 thrombocytopenia for ≥7 days, or Grade 3 or 4 associated with bleeding or requiring platelet transfusion
  - Grade 4 neutropenia for ≥7 days, or Grade 3 or 4 associated with infection or febrile neutropenia
  - Grade 4 anemia, or Grade 3 requiring blood transfusion
- Any death that is not clearly attributed to the underlying disease or extraneous causes

Toxicities will be assessed according to CTCAE v5.0. If multiple toxicities occur, the presence of DLT will be graded based on the most severe toxicity observed.

Patients will be treated with nivolumab 480 mg every 4 weeks (Q4W) in combination with daily VE800. All patients will continue study treatment until progression, unacceptable

toxicity, withdrawal of consent, study discontinuation criteria are met, completion of 2 years of treatment, or the study ends, whichever occurs first.

In each disease-specific expansion cohort, a Simon's two-stage design will be used to provide an initial assessment of the clinical activity at Stage 1 and advancement into Stage 2.

Reporting of AEs:

All AEs and SAEs will be collected and recorded for each patient from the day of signing the informed consent form (ICF) until 100 days after the last dose of the study treatment or until alternate anticancer therapy is initiated, whichever occurs first. Thereafter, only SAEs will be collected and recorded during the survival follow-up period or until alternate anticancer therapy is initiated. Any SAE occurring after the start of a new treatment that is considered to be related to study treatment by the investigator will be reported. All AEs and SAEs experienced by a study patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved or stabilized (e.g., until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed), until the patient is lost to follow-up, until the patient has died, or for at least 30 days after onset of AE/SAE, whichever is earlier.

Biomarker sample collection and analysis:

Archival tumor tissue is required for all patients entering the study and fresh tumor biopsies are optional but recommended; one biopsy will be obtained prior to VE800 administration. Archival tissue will be acceptable as the fresh baseline biopsy if collected within 60 days of dosing. Archival tissue must be requested and confirmed available prior to dosing. In melanoma patients previously treated with iCPI, the archival tissue will be acceptable if no intervening therapy was given to a patient since obtaining the biopsy, otherwise, fresh biopsy will be required. Additional tumor biopsies will be highly recommended but optional after approximately 4-6 weeks of study treatment and at the time of progression.

Biomarker analyses will be conducted on fresh and/or archival tumor tissue samples, and stool samples to correlate with the clinical outcome to identify the biomarker signature of treatment outcomes to the combination treatment. Stool samples will be collected for VE800 bacterial components detection, colonization duration, and evaluation of other microbiome components such as overall diversity.

The study will be conducted in conformance with Good Clinical Practice (GCP).

Number of Patients Planned:

A total of up to approximately 111 evaluable patients will be enrolled: 42 patients with melanoma, 42 patients with gastric/gastroesophageal junction (GEJ) adenocarcinoma, and 27 patients with microsatellite-stable (MSS) colorectal cancer (CRC).

Study population:

Inclusion Criteria:

1. Patients able and willing to provide written informed consent prior to initiation of any study-specific procedure or study drug administration and that understand the potential risks and benefits of study enrollment and study drug administration.
2. Patients with advanced or metastatic cancer who have received no more than 3 lines of prior systemic therapy for advanced/metastatic disease:

   a. Patients with advanced or metastatic melanoma who have progressed while receiving an anti-PD-1 or anti-PD-L1 antibody or within 3 months of discontinuation

      i. Patients must have RECIST 1.1 confirmed progressive disease (PD) (at least 2 consecutive scans at least 4 weeks apart) on or within 3 months of discontinuation of prior PD-1 or PD-L1 antibody either as a single agent or in combination with a standard or an investigational therapy
      ii. Patients who progressed on/within 3 months of adjuvant therapy with iCPI will be allowed; an adjuvant therapy will count as 1 prior line of therapy
      iii. Prior treatment with an anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody will be allowed
      iv. An anti-PD-1/PD-L1 must be the most recent therapy received

   b. Patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after at least one line of therapy including fluoropyrimidine-and platinum-containing chemotherapy and, if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy

   c. Patients with histologically confirmed advanced/metastatic CRC-MSS based on either an analysis of tissue from a prior biopsy or based on tissue from a new biopsy (patient's microsatellite/mismatch repair status should be known); who have progressed following at least one line of standard treatment for advanced/metastatic disease which must include fluoropyrimidine, oxaliplatin, or irinotecan, unless contraindicated. Patients who relapse within 6 months of adjuvant chemotherapy composed of oxaliplatin and a fluoropyrimidine will have their adjuvant therapy count as one prior regimen.
3. Age at least 18 years; any gender
4. Histologically diagnosed advanced (unresectable) or metastatic cancer with at least one measurable lesion as per RECIST 1.1
5. Tumor lesions amenable for biopsy, if deemed safe by the investigator
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
7. Adequate organ function, defined as
   a. Absolute neutrophil count (ANC) ≥1,500/µL
   b. Platelets ≥100,000/µL
   c. Hemoglobin ≥9 g/dL

d. Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using Cockcroft-Gault equation

e. Total bilirubin ≤1.5 × ULN; for patients with documented/suspected Gilbert's disease, total bilirubin ≤3 × ULN

f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN

g. Serum albumin ≥3 g/dL

8. Toxicity from prior cancer therapy should resolve to CTCAE Grade ≤ 1 (excluding alopecia and neuropathy, where up to Grade 2 residual is allowed)
9. Expected to be able to take daily oral medications including the size 0 VE800 capsules for the entire study duration
10. Women of childbearing potential must use adequate birth control for the duration of study participation and for 5 months after last dose of study drug (nivolumab)
11. Men must use contraception for 7 months following the last dose of study drug (nivolumab)

Exclusion Criteria:

1. Prior total colectomy or current ileostomy.
2. Prior treatment with immune checkpoint inhibitor (iCPI), which is defined as an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (Note: this criterion does not apply to patients with melanoma)
3. History of life-threatening toxicity related to prior immune therapy (e.g., anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g., hypo/hyperthyroidism)
4. Palliative radiotherapy within 1 week of the first dose of study drug administration
5. Receipt of any conventional or investigational systemic anti-cancer therapy within 21 days prior to the first dose of vancomycin
6. Concurrent chemotherapy, immunotherapy, biologic, or hormonal anti-cancer therapy. Agents such as bisphosphonates or denosumab are acceptable as prophylaxis for bone metastasis.
7. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, prostate cancer, or carcinoma in situ of the cervix or breast

8. Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [e.g., radiation or chemotherapy at least 1 month prior to study entry]. The patient must have no new or progressive signs or symptoms related to the CNS disease and must no longer be on corticosteroids for this indication.) For these patients, a scan to confirm the absence of new lesions or stability of brain metastases is required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days.
9. Major surgery within 28 days of first dose of the study drug
10. Patients considered a poor risk due to a serious, uncontrolled medical condition, nonmalignant systemic disease, or active uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
11. Clinically significant ascites (requiring drainage every 14 days or less)
12. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study drug administration, or is not in the best interest of the patient to participate
13. History or current evidence of celiac disease, inflammatory bowel disease, short gut, or current gastrointestinal tract fistulas or ischemia
14. Patients must not have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment
15. Treatment with botanical preparations (e.g., herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to start of the study treatment. Use of medical marijuana is allowed if legally permitted in the State where the patient is treated.
16. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study
17. Patients with an active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.
18. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the start of study treatment. Inhaled or topical steroids and adrenal replacement steroid doses of 10 mg daily prednisone equivalent are permitted in the absence of autoimmune disease (e.g., inflammatory bowel disease, celiac, vasculitis, systemic lupus erythematous, Grave's).

19. Patients with known active hepatitis (e.g., hepatitis B or C) or any positive test result for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating presence of virus (e.g., hepatitis B surface antigen [HBsAg, Australia antigen] positive or hepatitis C antibody [anti-HCV] positive [except if HCV-RNA negative]). NOTE: Patients with previously treated hepatitis B or C are permitted to enroll if there is evidence of documented resolution of infection.
20. Patients with a condition requiring any live/attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) within the last 30 days. Vaccines are permitted after the first 28 days of study treatment.
21. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.
22. Known hypersensitivity to VE800 components, nivolumab, vancomycin, or excipients contained in these products
23. Received a fecal transplant, spore or other preparation of fecal material, isolated bacterial products, genetically modified bacteria, or VE800

Investigational Product, Dosage, and Mode of Administration:

All patients will receive vancomycin followed by concurrent VE800 and nivolumab as described below:

VE800 is a live biotherapeutic product (LBP) consisting of 11 distinct nonpathogenic, nontoxigenic, commensal bacterial strains clonally derived from healthy donor stool. [redacted]

[redacted]

Nivolumab will be administered intravenously (IV) at a dose of 480 mg as a 30-minute IV infusion on Day 1 of each 4-week treatment cycle. Patients may be dosed within a ±3-day window.

Patients will be instructed to take their dose of VE800 at the same time of the day, preferably in the morning after an overnight fast. Patients must swallow all capsules whole and not chew any. [redacted].

Dose modifications:

In patients for whom a safety issue arises that is assessed as related to VE800, depending on the type and severity of AE, treatment with VE800 may be withheld permanently or

temporarily upon consultation with the Sponsor. These patients may continue on nivolumab as a single agent. These patients will have an end of VE800 visit in addition to the end of treatment (EOT) visit.

Dose and schedule modifications of VE800 (modified dose or frequency of administration) will be allowed, if warranted by the study safety findings, after consultation with the Sponsor. The Sponsor in consultation with the study investigators may consider introducing additional dosing regimen/s if warranted based on emerging overall safety, tolerability, and biomarker data.

[redacted]

Nivolumab dosing delays up to 28 days are permitted for medical/surgical events, logistical reasons, or reasons unrelated to study treatment after discussion with the medical monitor.

Nivolumab will be administered until progression, unacceptable toxicity, withdrawal of consent or until the study ends, whichever occurs first. No dose and schedule modifications of nivolumab will be allowed, except as described in Section 7.1.3. In patients for whom a safety issue arises that is related to nivolumab, nivolumab should be withheld permanently and/or supportive care measures as described in Appendix 1. In such a case, continuing VE800 may be allowed upon consultation between Investigator and Sponsor.

Duration of Study:

Patients benefiting from study treatment, as judged by the Investigator, may continue study treatment for up to 2 years or Sponsor decision to discontinue the study.

Criteria for Evaluation:

Efficacy:

ORR will be evaluated using RECIST 1.1, including the following:

- Antitumor response based on change in measurable tumor burden
- Time-point response assessment: percentage changes in tumor burden per assessment time point
- Best overall response assessment (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD])
- DCR (CR+PR+SD)
- DOR, defined as the time from first documentation of CR or PR until the time of first documentation of PD
- Landmark PFS at 6 and 12 months
- PFS, defined as the time from start of treatment to the earlier date of assessment of progression or death by any cause in the absence of progression

[redacted]

All radiographic images/scans will be sent to a central imaging vendor upon acquisition and archival for potential future evaluation.

OS as measured from the date of start of treatment to the date of death by any cause will also be evaluated.

Safety:

- Incidence of treatment-emergent AEs (TEAEs) occurring while patients are on study drug and any SAEs occurring while patients are on treatment or up to 100 days after EOT
- Changes in clinical laboratory parameters (hematology, chemistry), vital signs, electrocardiogram (ECG) parameters, ECOG performance status, physical examinations, and usage of concomitant medications

Pharmacokinetics/Biomarkers:

[redacted]

Statistical Considerations:

The study will use a Simon two-stage design. In each disease-specific expansion cohort, a Simon two-stage design will be used to provide an initial assessment of the clinical activity at Stage 1 for continuation to Stage 2. ORR will be evaluated using RECIST 1.1.

[redacted]

1.1 Schedule of Events

The schedule of events is presented in Table 1.

Table 1 Schedule of Events for Study VE800-001

Dose/Visit:	**Screen -ing**	**Vancomycin**		**VE800 daily and Nivolumab Q4W**									**EOT**		**Survival Every 90 days (±2w) Visit / Phone Call (b)**
Day:	**-21 to -5**	**-4**	**D -3-0**	**C1/D1**	**C1/D3**	**C1/D7**	**C1/D14 (±1d)**	**C1/D21**	**C2/D1 (1 mo) (±3d)**	**C3/D1 (2 mo) (±3d)**	**C4/D1 (3 mo) (±3d)**	**C5-n/ D1 (Q4W) (±3d)**	**Within 7 days of Decision to DC**	**At least 100 days from end of nivolumab treatment**	
Visit #	**Screen -ing**	**BL (V 1)**		**V 2**	**At home stool collection**	**At home stool collection**	**V 2a**	**At home stool collection**	**V 3**	**V 4**	**V 5**	**V6 to EOT**	**EOT (a)**	**Safety Visit**	
Procedure:															
ICF	X														
Inclusion/Exclusion Review	X	X		X											
Demographics	X														
Medical, surgical, and cancer history	X	X													
Concomitant medications	X	X		X					X	X	X	X	X	X	
AE monitoring	X	X		X			X		X	X	X	X	X	X(c)	X(c)
Sample Collection:															
Tumor assessment and imaging		X (d)								X (d)		X (d)			
Biopsy		X (e)							X (f)	X (f)	X (f)	X (f)	X(f)		
[redacted]															
Labs and Assessments:															
CBC w/differential (safety lab)	X			X (i)			X (j)		X	X	X	X	X	X	
Serum chemistry (safety lab)	X			X (i)			X (j)		X	X	X	X	X	X	
Coagulation (k)	X														
Serum Pregnancy Test	X								X	X	X	X	X	X	
Urinalysis	X			X					X	X	X	X	X	X	
Serum-based tumor markers (l)	X									X		X			
Thyroid Panel (k)	X														

Dose/Visit:	Screen-ing	Vancomycin		VE800 daily and Nivolumab Q4W									EOT		Survival Every 90 days (±2w) Visit / Phone Call (b)
Day:	-21 to -5	-4	D -3-0	C1/D1	C1/D3	C1/D7	C1/D14 (±1d)	C1/D21	C2/D1 (1 mo) (±3d)	C3/D1 (2 mo) (±3d)	C4/D1 (3 mo) (±3d)	C5-n/ D1 (Q4W) (±3d)	Within 7 days of Decision to DC	At least 100 days from end of nivolumab treatment	
Visit #	Screen-ing	BL (V 1)		V 2	At home stool collection	At home stool collection	V 2a	At home stool collection	V 3	V 4	V 5	V6 to EOT	EOT (a)	Safety Visit	
ECG	X								X				X		
ECOG PS	X			X					X	X	X	X	X		
Physical exam	X												X	X	
Symptom-directed physical exam				X			X (j)		X	X	X	X			
Vital signs, weight, and height (height at screening only) (m)	X	X		X			X (j)		X	X	X	X	X	X	
Collection of microsatellite stability data (MSS/MSI-high); PD-L1 expression(n)	X														
[redacted]															
[redacted]															
[redacted]															
[redacted]															
Drug Administration:															
Vancomycin		X	X												
VE800 [redacted]				X	X	X	X	X	X	X	X	X			
Nivolumab				X					X	X	X	X			
Telephone contact (y)						X									

Abbreviations: AE = adverse event; BL = baseline; C = cycle; CBC = complete blood count; CRC= colorectal cancer; D or d = day(s); DC = discontinue; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; GEJ = gastroesophageal junction; ICF = informed consent form; mo = month(s); MSI = microsatellite instable; MSS = microsatellite-stable; [redacted] Q4W = every 4 weeks; V = visit; w = weeks.

Footnotes on next page

Footnotes:

a. Patients that discontinue VE800 but continue with nivolumab treatment will have an end of VE800 visit within 7 days after the decision to discontinue VE800 and an EOT visit within 7 days after the decision to discontinue nivolumab. Likewise, patients that discontinue nivolumab but continue with VE800 treatment will have an end of nivolumab visit within 7 days after the decision to discontinue nivolumab and an EOT visit within 7 days after the decision to discontinue VE800. The same assessments will be done at the end of VE800/nivolumab and EOT visits. Patients that discontinue VE800 and nivolumab at the same time will have only one EOT visit.
b. If patient cannot return to clinic for this visit, a phone call is allowed. Subsequent follow-up assessments are via phone call.
c. All AEs and SAEs will be collected until 100 days after the last dose of study treatment or until alternate anticancer therapy is initiated, whichever occurs first. Only SAEs will be collected during survival follow-up or until alternate anticancer therapy is initiated. Any SAE occurring after the start of a new treatment that is considered to be related to study treatment by the investigator will be reported..
d. Baseline assessment may be done during the screening period. Should be obtained every 8 weeks after baseline (every 12 weeks after 1 year); confirmation of change should be at least 4 weeks between previous tumor assessment/imaging and confirmation. Tumor assessment per RECIST via CT or MRI.
e. Archival tissue will be acceptable as the fresh baseline biopsy if collected within 60 days of dosing. Archival tissue must be requested and confirmed available prior to dosing. In melanoma patients previously treated with iCPI the archival tissue will be acceptable if no intervening therapy was received to a patient since obtaining the biopsy, otherwise, fresh biopsy will be required.
f. Additional tumor biopsies will be highly recommended but optional after approximately 4-6 weeks of study treatment and at the time of progression. If possible, biopsy should be from the same lesion as pre-treatment biopsy.

[redacted]

i. These safety assessments may be drawn 24 hours prior to C1/D1.
j. Symptom directed physical exam, CBC with differential, and serum chemistry at C1/D14 visit required for first 12 patients only.
k. At screening or if clinically indicated.
l. After baseline, this assessment will be done if applicable per standard of care at the time of radiological tumor assessment. For the radiological tumor assessment at baseline, these assessments can be taken at screening or baseline.
m. On dosing days, vital signs will be measured prior to administration of study drug.
n. Collection of microsatellite stability data only for patients with gastric/GEJ adenocarcinoma or CRC. MSS/MSI status for CRC is mandatory for inclusion. MSS/MSI status and PD-L1 expression is to be collected for all cohorts, if available.

[redacted]

y. Telephone call on C1D7 to review symptoms and ensure compliance with oral dosing.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AVMN	Ampicillin, vancomycin, metronidazole, and neomycin
BATF3	Basic leucine zipper ATF-like transcription factor 3
BTLA	B and T lymphocyte attenuator
CBC	Complete blood count
cHL	Classic Hodgkin lymphoma
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRA	Clinical research associate
CRC	Colorectal cancer
CRO	Clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DC	Dendritic cells
DCR	Disease control rate
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
E-R	Exposure-response
FSH	Follicle stimulating hormone
fT3	Free triiodothyronine

fT4	Free thyroxine
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
GF	Germ-free
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICOS	Inducible co-stimulatory molecule
iCPI	Immune checkpoint inhibitor
IFN-γ	Interferon-gamma
IL	Interleukin
IND	Investigational New Drug (Application)
imAE	Immune-mediated adverse event
[redacted]	[redacted]
IRB	Institutional Review Board
iUPD	Immune-unconfirmed progressive disease
IV	Intravenous(ly)
LBP	Live biotherapeutic product
LP	Lamina propria
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimal inhibitory concentration
MMR	Measles, mumps, rubella
MSI	Microsatellite-instable
MSS	Microsatellite-stable
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease

PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PO	Oral
PPK	Population pharmacokinetic
PR	Partial response
Q4W	Every 4 weeks
QD	Once a day
QID	Four times a day
QTc	Heart-rate corrected QT interval
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SD	Stable disease
SI	Small intestine
SPF	Specific-pathogen-free
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WOCBP	Women of childbearing potential

2 INTRODUCTION

2.1 Background

2.1.1 Target Population

VE800 was shown to enhance tumor growth inhibition of immune checkpoint inhibitors (iCPIs) in preclinical models. This study will enroll patients with advanced/metastatic cancer for whom efficacy of an anti-programmed cell death protein 1 receptor (PD-1) antibody is expected to be modest to null.

2.1.2 Description of VE800

VE800 is an orally administered (PO) live biotherapeutic product (LBP) consisting of 11 distinct nonpathogenic, nontoxigenic, commensal bacterial strains clonally derived from healthy donor stool.



2.1.3 Description of Nivolumab

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses (Pardoll, 2003; Zitvogel, 2006; Dunn, 2002). Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) (Greenwald, 2004). Collectively, these signals govern the balance between T-cell activation and tolerance.

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), inducible co-stimulatory molecule (ICOS), and B and T lymphocyte attenuator (BTLA) (Freeman, 2000). PD-1 signaling has been shown to inhibit CD28-mediated upregulation of interleukin (IL)-2, IL-10, IL-13, IFN-γ and B-cell lymphoma-extra large (Bcl-xL). PD-1 expression also been noted to inhibit T-cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes (Sharpe, 2007). These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV) re stimulation assay with human peripheral blood mononuclear cells (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (Wolchok, 2009).

Overall, the safety profile of nivolumab is manageable and generally consistent across completed and ongoing clinical trials with no maximum tolerated dose (MTD) reached at any dose tested up to 10 mg/kg. Most adverse events (AEs) were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab Investigator's Brochure (IB).



[redacted]



3 OBJECTIVES

Primary objectives:

- To evaluate the safety and tolerability of VE800 in combination with nivolumab in terms of AE rates using Common Terminology Criteria for Adverse Events (CTCAE, v. 5.0)
- To evaluate clinical activity as measured by objective response rate (ORR) of the study drug combination using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Secondary objectives:

- To evaluate additional measures of clinical benefit, including:
  - Duration of response (DOR) according to RECIST 1.1
  - Best overall response according to RECIST 1.1
  - Disease control rate (DCR) according to RECIST 1.1
  - Progression-free survival (PFS) according to RECIST 1.1
  - Overall survival (OS)
- To evaluate the pharmacokinetics (PK) of VE800
  - Detection of each VE800 strain in stool
  - Degree and duration of VE800 strain colonization

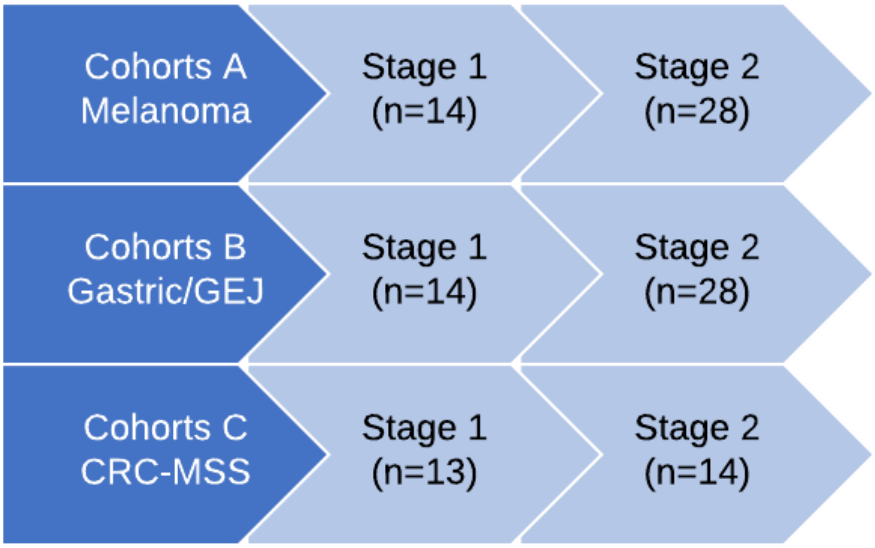
Exploratory objectives:



4 DETERMINATION OF GLOBAL CHANGES IN MICROBIOME COMPOSITION, STUDY PLAN

4.1 Study Schematic

Figure 1 Flow Diagram of Study VE800-001—Simon Two-Stage Design



Abbreviations: CRC = Colorectal cancer; GEJ = Gastroesophageal junction; MSS = Microsatellite-stable

4.2 Study Design

This is a first-in-human multicenter, open-label study evaluating the safety and clinical activity of VE800 in combination with nivolumab in patients with selected types of advanced or metastatic cancer, where efficacy of an anti-PD-1 antibody is expected to be modest to null. Safety, clinical activity, PK, and pharmacodynamics (stool, blood and/or tumor biomarker changes) will be evaluated.

The following cohorts of patients with advanced/metastatic cancer will be enrolled:

- Melanoma
- Gastric/gastroesophageal junction (GEJ) adenocarcinoma
- Colorectal cancer microsatellite-stable (CRC-MSS)

Forty-two patients each are planned for enrollment in the melanoma cohort and in the gastric/GEJ adenocarcinoma cohort, and 27 patients are planned for enrollment in the CRC-MSS cohort. The study will use a Simon two-stage design; the number of patients planned for each stage are shown in Figure 1.

Eligible patients will receive a 5-day course of PO vancomycin (125 mg 4 times a day [QID]) to modulate the intestinal microbiota, followed by VE800 dosing. [redacted]

[redacted] All patients will continue study treatment until progression, unacceptable toxicity, withdrawal of consent, study discontinuation criteria are met, completion of 2 years of treatment, or the study ends, whichever occurs first. Patients benefiting from study treatment, as judged by the Investigator, may continue study treatment for up to 2 years.

The safety committee, comprising Investigators and the Sponsor, will oversee the emerging safety data.

Patients will be evaluated for safety for a dose-limiting toxicity (DLT) period encompassing 28 days of VE800 dosing with nivolumab starting on Day 1.

[redacted]

In each disease-specific expansion cohort, a Simon two-stage design will be used to provide an initial assessment of the clinical activity at Stage 1. ORR will be evaluated using RECIST 1.1.

As VE800 is a consortium of commensal bacteria derived from healthy donor and shown to be present in healthy human population, no significant toxicity is expected, but not excluded. Patients will be monitored for safety throughout duration of the study to identify a potential increase in incidence and/or severity of immune-mediated adverse events (imAEs).

In patients for whom a safety issue arises that is assessed as related to VE800, depending on the type and severity of AE, treatment with VE800 may be withheld permanently or temporarily upon consultation with the Sponsor. These patients may continue on nivolumab as a single agent. These patients will have an end of VE800 visit in addition to the end of treatment (EOT) visit.

In patients for whom a safety issue arises that is related to nivolumab, nivolumab should be withheld permanently, as described in Section 6.2.1, and/or supportive care measures should be administered per the Management Algorithms for Nivolumab in Appendix 1. In such a case, continuing VE800 as a single agent may be allowed upon consultation between Investigator and Sponsor. These patients will have an end of nivolumab visit in addition to the EOT visit.

5 POPULATION

5.1 Recruitment

A total of up to approximately 111 patients will be enrolled at up to 45 centers in the United States (US).

Before recruitment of patients, written Institutional Review Board (IRB)/Ethics Committee (EC) approval of the protocol, informed consent documents, advertising and patient-facing documents will be obtained.

5.2 Inclusion Criteria

To be included in this study, each individual must satisfy all the following criteria:

1. Patients able and willing to provide written informed consent prior to initiation of any study-specific procedure or study drug administration and that understand the potential risks and benefits of study enrollment and study drug administration.
2. Patients with advanced or metastatic cancer who have received no more than 3 lines of prior systemic therapy for advanced/metastatic disease:
    a. Patients with advanced or metastatic melanoma who have progressed while receiving an anti-PD-1 or anti-PD-L1 antibody or within 3 months of discontinuation
        i. Patients must have RECIST 1.1 confirmed Progressive Disease (PD) (at least 2 consecutive scans at least 4 weeks apart) on or within 3 months of discontinuation of prior PD-1 or PD-L1 antibody either as a single agent or in combination with a standard or an investigational therapy
        ii. Patients who progressed on/within 3 months of adjuvant therapy with iCPI will be allowed; an adjuvant therapy will count as 1 prior line of therapy
        iii. Prior treatment with an anti-CTLA-4 antibody will be allowed
        iv. An anti-PD-1/PD-L1 must be the most recent therapy received
    b. Patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after at least one line of therapy including fluoropyrimidine-and platinum-containing chemotherapy and, if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy
    c. Patients with histologically confirmed advanced/metastatic microsatellite-stable (MSS) Colorectal cancer (CRC) based on either an analysis of tissue from a prior biopsy or based on tissue from a new biopsy (patient's microsatellite/mismatch repair status should be known); who have progressed following at least one line of standard treatment for advanced/metastatic disease which must include fluoropyrimidine, oxaliplatin, or irinotecan, unless contraindicated. Patients who relapse within 6 months of adjuvant chemotherapy composed of oxaliplatin and a fluoropyrimidine will have their adjuvant therapy count as one prior regimen.
3. Age at least 18 years; any gender

4. Histologically diagnosed advanced (unresectable) or metastatic cancer with at least one measurable lesion as per RECIST 1.1
5. Tumor lesions amenable for biopsy, if deemed safe by the investigator
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
7. Adequate organ function, defined as
    a. Absolute neutrophil count (ANC) ≥1,500/µL
    b. Platelets ≥100,000/µL
    c. Hemoglobin ≥ 9 g/dL
    d. Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using Cockcroft-Gault equation
    e. Total bilirubin ≤1.5 × ULN; for patients with documented/suspected Gilbert's disease, total bilirubin ≤3 × ULN
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN
    g. Serum albumin ≥ 3 g/dL
8. Toxicity from prior cancer therapy should resolve to CTCAE Grade ≤ 1 (excluding alopecia and neuropathy, where up to Grade 2 residual is allowed)
9. Expected to be able to take daily oral medications including the size 0 VE800 capsules for the entire study duration
10. Women of childbearing potential must use adequate birth control for the duration of study participation and for 5 months after last dose of study drug (nivolumab)
11. Men must use contraception for 7 months following last dose of study drug (nivolumab)

5.3 Exclusion Criteria

Individuals who meet any of the following criteria are ineligible for this study:

1. Prior total colectomy or current ileostomy
2. Prior treatment with iCPI, which is defined as an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (Note: this criterion does not apply to patients with melanoma.)
3. History of life-threatening toxicity related to prior immune therapy (e.g., anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g., hypo/hyperthyroidism)
4. Palliative radiotherapy within 1 week of the first dose of study drug administration
5. Receipt of any conventional or investigational systemic anti-cancer therapy within 21 days prior to the first dose of vancomycin

6. Concurrent chemotherapy, immunotherapy, biologic, or hormonal anti-cancer therapy. Agents such as bisphosphonates or denosumab are acceptable as prophylaxis for bone metastasis.
7. Prior malignancy active within the previous 2 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, prostate cancer, or carcinoma in situ of the cervix or breast
8. Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [e.g., radiation or chemotherapy at least 1 month prior to study entry]. The patient must have no new or progressive signs or symptoms related to the CNS disease and must no longer be on steroids for this indication.) For these patients, a scan to confirm the absence of new lesions or stability of brain metastases is required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days.
9. Major surgery within 28 days of first dose of the study drug
10. Patients considered a poor risk due to a serious, uncontrolled medical condition, nonmalignant systemic disease, or active uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.
11. Clinically significant ascites (requiring drainage every 14 days or less)
12. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study drug administration, or is not in the best interest of the patient to participate
13. History or current evidence of celiac disease, inflammatory bowel disease, short gut, or current gastrointestinal tract fistulas or ischemia
14. Patients must not have received a transfusion (platelets or red blood cells) within 4 weeks of the first dose of study treatment
15. Treatment with botanical preparations (e.g., herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to start of the study treatment. Use of medical marijuana is allowed if legally permitted in the State where the patient is treated.
16. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study
17. Patients with an active, known or suspected autoimmune disease. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.

18. Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the start of study treatment. Inhaled or topical steroids and adrenal replacement steroid doses of 10 mg daily prednisone equivalent are permitted in the absence of autoimmune disease (e.g., inflammatory bowel disease, celiac, vasculitis, systemic lupus erythematous, Grave's).
19. Patients with known active hepatitis (e.g., hepatitis B or C) or any positive test result for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating presence of virus (e.g., hepatitis B surface antigen [HBsAg, Australia antigen] positive or hepatitis C antibody [anti-HCV] positive [except if HCV-RNA negative]). NOTE: Patients with previously treated hepatitis B or C are permitted to enroll if there is evidence of documented resolution of infection.
20. Patients with a condition requiring any live/attenuated vaccine (e.g., varicella, zoster, yellow fever, rotavirus, oral polio, and measles, mumps, rubella [MMR]) within the last 30 days. Vaccines are permitted after the first 28 days of study treatment.
21. Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.
22. Known hypersensitivity to VE800 components, nivolumab, vancomycin, or excipients contained in these products (see Section 7.1)
23. Received a fecal transplant, spore or other preparation of fecal material, isolated bacterial products, genetically modified bacteria, or VE800

6 STUDY CONDUCT

6.1 Study Procedures

The schedule for completing study procedures and assessments is detailed in Table 1 (Schedule of Events).

6.1.1 Informed Consent

Informed consent must be obtained before any study-specific procedure is performed. For patients who sign a documented informed consent form (ICF) but are not enrolled, the reason for screen failure will be recorded.

6.1.2 Screening Assessments

Results from screening evaluations are required to confirm eligibility and must be available before study drug administration.

Screening assessments include collection of demographics, medical and medication history, safety assessments, and stool sample collection.

6.1.3 Efficacy Assessments

6.1.3.1 Tumor Assessment and Imaging

Tumor assessment should be obtained at baseline and every 8 weeks thereafter and confirmation of change should be at least 4 weeks between previous tumor assessment/imaging. After 1 year, patients who remain on treatment will have imaging performed every 12 weeks (84 ±7 days). Primary response evaluation will be done by using RECIST 1.1, including the following (see Appendix 2):

- ORR: The primary efficacy endpoint is ORR defined as the proportion of patients achieving complete response (CR) or partial response (PR) as determined by the Investigator
- DOR: DOR will be assessed as a secondary endpoint defined as the time from first documentation of CR or PR until the time of first documentation of progressive disease (PD)
- Progression-free survival (PFS): PFS will be assessed as a secondary endpoint defined as the time from start of treatment to the earlier date of assessment of progression or death by any cause in the absence of progression
- OS: OS will be assessed as a secondary endpoint defined as the time from the date of start of treatment to the date of death by any cause
- DCR (CR+PR+SD): DCR will be assessed as a secondary endpoint defined as the percentage of patients achieving CR, PR, or stable disease (SD)
- Antitumor response based on change in measurable tumor burden
- Time-point response assessment: percentage changes in tumor burden per assessment time point
- Best overall response assessment (CR, PR, SD, PD)

[redacted]

OS will be assessed as a secondary endpoint defined as the time from the date of start of treatment to the date of death by any cause.

6.1.4 Biomarkers

6.1.4.1 Biopsy

Archival tumor tissue is required for all patients entering the study and fresh tumor biopsies are optional but recommended; one biopsy will be obtained prior to VE800 administration. Archival tissue will be acceptable as the fresh baseline biopsy if collected within 60 days of dosing. Archival tissue must be requested and confirmed available prior to dosing. In melanoma patients previously treated with iCPI the archival tissue will be acceptable if no intervening therapy was received to a patient since obtaining the biopsy, otherwise, fresh biopsy will be required.

Additional tumor biopsies will be highly recommended but optional after approximately 4-6 weeks of study treatment and at the time of progression.

Biomarker analyses will be conducted on fresh and/or archival tumor tissue samples, and stool samples to correlate with the clinical outcome to identify the biomarker signature of treatment outcomes to the combination treatment. Stool samples will be collected for VE800 bacterial components detection, colonization duration, and evaluation of other microbiome components such as overall diversity.

[redacted]

[redacted] Table 1 [redacted]

6.1.4.4 Serum Tumor Markers

Serum tumor markers (carcinoembryonic antigen [CEA] for CRC or gastric cancer) will be done if the Investigator deems applicable per standard of care at the time of radiological tumor assessment.

6.1.5 Safety Assessments

Safety will be assessed throughout the study and the safety data will include reported AEs, SAEs, clinical laboratory data, electrocardiograms (ECGs), ECOG performance status, concomitant medications, physical examinations, and vital signs.

If a patient shows pulmonary-related signs (hypoxia, fever) or symptoms (e.g., dyspnea, cough, fever) consistent with possible pulmonary AEs, the patient should be immediately evaluated to rule out pulmonary toxicity.

6.1.5.1 Adverse Events

Adverse events will be assessed by direct observation and patient assessments/interviews. All nonserious AEs and SAEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following discontinuation of study treatment or until alternate anticancer therapy is initiated, whichever occurs first. Thereafter, only SAEs will be recorded through the survival follow-up period or until alternate anticancer therapy is initiated. Complete details on the definition, reporting, and management of AEs are provided in Section 8.2. Additional details on management of AEs related to nivolumab are provided in Appendix 1.

Every AE must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the patient's case report form. ImAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. ImAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the participant's case report form.

6.1.5.2 Laboratory Assessments

All laboratory assessments below will be done by local laboratories.

The following laboratory tests will be performed according to the schedule in Table 1:

Hematology – Complete Blood Count (CBC)
Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count
Coagulation - at screening only, or if clinically indicated
Prothrombin time (PT)/international normalized ratio (INR)
Activated partial thromboplastin time (aPTT)
Chemistry
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Amylase
Alkaline phosphatase (ALP)
Total bilirubin

Albumin - screening only
Sodium
Potassium
Lactate dehydrogenase (LDH)
Lipase
Creatinine
Blood urea nitrogen (BUN) or serum urea
Fasting glucose - at screening only, or if clinically indicated
Chloride
Calcium
Phosphorus
Thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) – at screening only, or if clinically indicated
Serology
Hepatitis B/C, (HBsAG, anti-HCV, or HCV RNA) – at screening only, or if clinically indicated
HIV testing (where mandated locally)
Other Analyses
Pregnancy test (women of childbearing potential only: minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG])
Follicle stimulating hormone (FSH) screening (only required to confirm menopause in women <55 years of age)

6.1.5.3 Physical Examination

Physical examinations will be performed by trained medical personnel. A complete physical examination will be performed at screening and at the EOT and Safety visits. Symptom-directed physical examinations are to be performed according to Table 1. Abnormal physical examination findings will be recorded as AEs only if they are considered to be clinically significant by the Investigator.

6.1.5.4 Vital Signs, Weight, and Height

Vital signs, including pulse, blood pressure, and body temperature, will be collected according to the schedule in Table 1, as well as at unscheduled times as medically indicated. On dosing days, vital signs will be measured prior to administration of study drug. Abnormal vital sign measurements will be recorded as AEs only if they are considered to be clinically significant by the Investigator.

Height will be collected at screening only. Weight will be collected according to the schedule in Table 1. Weight is to be measured consistently in the same manner each time and noted in the source – with or without heavy items/shoes/bulky clothing, etc.

6.1.5.5 Electrocardiogram

Single 12-lead ECGs will be performed at scheduled time points (see Table 1), as well as at unscheduled time points as medically indicated. ECG parameters to be evaluated include heart rate, QT interval corrected for heart rate (QTc), QRS, and PR intervals. Post-baseline abnormal ECG measurements will be recorded as AEs if they are considered to be clinically significant by the Investigator.

6.1.5.6 ECOG Performance Status

Performance status will be determined according to the ECOG performance status scale (see Appendix 4) at scheduled time points in Table 1.

6.1.5.7 Imaging Scan (Radiographic Disease Assessments)

Imaging scans, or radiographic evaluations (computed tomography [CT]/magnetic resonance imaging [MRI] of chest, abdomen, and pelvis or other regions known to have disease involvement) will be used to assess extent of disease. Scans will be taken at baseline and will be conducted every 8 weeks after the first scan. [redacted]

[redacted]

6.1.7 Survival Follow-up

In this study, survival is an important endpoint. Post-treatment follow-up is of critical importance and is essential to preserving patient safety and the integrity of the study. Patients who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Table 1 until death or the conclusion of the study, unless the patient has withdrawn consent for all contacts or is lost to follow-up. Patients are to return for a clinic visit for the first survival follow-up assessment and subsequent assessments are via phone contact. If the patient is unable to return to the clinic for the first follow-up visit, assessment via phone call is allowed.

6.2 Discontinuation or Withdrawal

6.2.1 Individual Patients

Patients may withdraw their consent at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a patient withdraws consent, the date and stated reason for consent withdrawal will be documented. Patient data, including samples (e.g., blood, serum), collected up to the date of consent withdrawal (i.e., early termination) will be included in the analyses.

[redacted]

Patients who discontinue study drug prematurely for reasons other than withdrawal of consent, lost to follow-up, or AEs with an outcome of death will continue to be followed for the intended duration of the study as outlined in the schedule of events. Further attempts to contact the patient are allowed if safety findings require communicating or follow-up. The Sponsor will be notified of all study withdrawals.

Patients meeting any of the following criteria will discontinue study drug dosing:

- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity prior to next scheduled nivolumab treatment OR requires systemic treatment
- Any Grade 3 non-skin, drug-related AE lasting >7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Grade 3 adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
    - Grade ≥3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
    - Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN

  *In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the Investigator and Sponsor/Medical Monitor must occur.
- Any allergic reaction during study drug administration, regardless of grade, should prompt study drug discontinuation unless there is a clear alternative etiology for the event. The study drug may be restarted if a clear alternative etiology for the event is identified.
- Disease progression as determined by Investigator, as defined in the Section 6.2.2
- Any other AE, laboratory abnormality, incurrent illness where continued treatment could be detrimental to patient's well-being
- Withdrawal of consent
- Pregnancy
- Lost to follow-up
- Discretion of the Investigator (e.g., protocol violations, noncompliance, continued study drug administration not in the patient's best interest)
- Termination of the study or a study site by the Sponsor

6.2.2 Nivolumab Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of participants treated with immunotherapy may derive clinical benefit despite initial evidence of PD (Wolchok, 2009). Participants treated with nivolumab will be permitted to continue nivolumab treatment beyond initial RECIST 1.1 defined

PD, assessed by the investigator up to a maximum of 24 months from date of first dose as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)
- Participant provides written informed consent prior to receiving additional nivolumab treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the participant is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the nivolumab participant continues to achieve clinical benefit by continuing treatment, the participant should remain on the trial and continue to receive monitoring according to Table 1.

For the participants who continue nivolumab study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD.

Nivolumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

6.2.3 Replacement of Patients

After consultation between the Investigators and Sponsor, enrollment may be extended to replace patient(s) that become non-evaluable for safety or if there is insufficient PK data.

6.3 Study Termination

This study may be discontinued at any time due to safety concerns, failure to meet expected enrollment goals, administrative reasons, or at the discretion of the Sponsor. Should the study be terminated prematurely, the Sponsor will provide written notification to the Investigator and regulatory authorities and will specify the reason(s) for early termination. The Investigator must inform the IRB/EC promptly and provide the reason(s) for the termination as well as patient status of all patients at their site.

7 INVESTIGATIONAL MEDICAL PRODUCT

7.1 Description of Products

7.1.1 VE800

7.1.1.1 Formulation, Storage, Preparation, and Handling

VE800 is an orally administered LBP consisting of 11 well characterized, clonally-derived nonpathogenic, nontoxigenic, commensal bacterial strains. [redacted]

7.1.1.2 Dosing and Administration

[redacted]

Patients will be instructed to take their dose at the same time of the day, preferably in the morning after an overnight fast (i.e., on an empty stomach). Patients must swallow all capsules whole and not chew the capsules. [redacted]

In patients for whom a safety issue arises that is related to VE800, depending on the type and severity of the AE, dose of VE800 may be reduced, or treatment with VE800 may be withheld permanently or temporarily upon consultation with the Sponsor, while a patient continues on nivolumab.

A patient who becomes unable to ingest VE800 may be allowed to continue single agent nivolumab, after discussion between the Sponsor and Investigator.

[redacted]

7.1.2 Vancomycin

7.1.2.1 Dosing and Administration

Eligible patients will receive vancomycin PO, 125 mg QID for 5 days prior to start of dosing with VE800 PO QD.

7.1.3 Nivolumab

7.1.3.1 Dose Rationale

A nivolumab dose of 480 mg given every 4 weeks (Q4W) was selected for this study based on available PK, safety, and efficacy data.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, non-small cell lung cancer (NSCLC), renal cell cancer (RCC), classic Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck, CRC, and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was recently updated to 240 mg Q2W or 480 mg Q4W in multiple indications (OPDIVO package insert, 2019; OPDIVO Summary of Product Characteristics, 2018). Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

The benefit-risk profiles of nivolumab 240 mg Q2W, 360 mg Q3W and 480 mg Q4W are predicted to be comparable to 3 mg/kg Q2W. This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response (E-R) relationships across indications. Population PK (PPK) analyses have shown that the PK of nivolumab is linear with proportional exposures over a dose range of 0.1 to 10 mg/kg; no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a flat dose were simulated, including 240 mg Q2W, 360 mg Q3W and 480 mg Q4W. The simulated average serum concentration at steady state (C_{avg}) following administration of nivolumab 360 mg Q3W and 480 mg Q4W are predicted to be similar to those following administration of nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W administered to participants over a wide body weight range (34-180 kg) across tumor types.

Extensive E-R analyses of multiple PK measures (maximum serum concentration at Day 1[$C_{max}1$], average serum concentration at Day 28 [$C_{avg}28$], and trough serum concentration at Day 28 [$C_{min}28$]) and efficacy and safety endpoints indicated that the efficacy of the flat-dose 480 mg IV regimen are similar to that of 3 mg/kg Q2W IV regimen. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using $C_{avg}28$ as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for IV 480 mg Q4W were similar to that of IV 3 mg/kg Q2W. In E-R safety analyses, it was demonstrated that the exposure margins for safety are maintained following nivolumab 480 mg Q4W, and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and imAEs Grade 2+ are similar following nivolumab 480 mg Q4W relative to nivolumab 3 mg/kg Q2W across tumor types. In addition, nivolumab exposures with 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W

flat-dose IV regimens across tumor types are maintained well below the corresponding exposures observed with the well-tolerated 10 mg/kg IV nivolumab Q2W dose regimen.

Additional details on nivolumab and nivolumab risk-benefit can be found in the nivolumab IB.

7.1.3.2 Formulation, Storage, Preparation and Handling

Nivolumab is supplied as 240 mg/24 mL solution in a single-dose vial.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

Nivolumab is shipped to clinical sites and stored at 5°C ± 3°C. Nivolumab should be protected from light.

7.1.3.3 Dosing and Administration

Nivolumab will be administered at a dose of 480 mg as a 30-minute IV infusion on Day 1 of each 4-week treatment cycle until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. Patients may be dosed within a ±3-day window.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dosing visits are not skipped, only delayed.

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. Nivolumab infusion must be promptly followed by a flush of diluent to clear the line.

Patients should be carefully monitored for infusion reactions during nivolumab administration.

No dose and schedule modifications of nivolumab will be allowed, except as noted below. In patients for whom a safety issue arises that is related to nivolumab, nivolumab should be withheld permanently and/or supportive care measures administered per the Management Algorithms for Nivolumab in Appendix 1. Nivolumab dosing delays up to 28 days are permitted in case of medical/surgical events or logistical reasons or unrelated to study treatment after discussion with the medical monitor.

Nivolumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities
- Grade 3 skin, drug-related AE
- Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, Total Bilirubin will require dose discontinuation
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Participants who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

If nivolumab is discontinued, continuing VE800 may be allowed upon consultation between Investigator and Sponsor.

7.2 Dose-limiting Toxicity Criteria

The following treatment related AEs will be considered dose-limiting if determined to be at least possibly related to VE800 or to the combination of VE800 and nivolumab:

- ≥ Grade 2 uveitis or eye pain, that does not resolve with topical therapy i.e., corticosteroids within 2 weeks
- Grade 4 rash, or Grade 3 if no improvement (i.e., resolution to ≤ Grade 1 after a 1-2 week dose delay)
- Grade ≥ 4 hypersensitivity reaction, or Grade 3 that does not resolve to Grade 1 in <6 hrs
- Grade 2 or 3 colitis or diarrhea that persists without resolution to ≤ Grade 1 for ≥7 days despite adequate immune suppressive and anti-diarrheal therapy
- Grade 3 or 4 imAE without resolution to Grade ≤ 1 or baseline within 8 days despite adequate immune suppressive therapy
- Any Grade clinically significant imAE (e.g., myocarditis, encephalitis) requiring treatment discontinuation
- Any other ≥ Grade 3 non-hematologic clinical (non-laboratory) toxicity excluding:
  - Nausea and vomiting resolving to ≤ Grade 1 within 48 hours with adequate treatment
  - Grade 3 fatigue with duration <7 days
  - Grade 3 or Grade 4 electrolyte abnormalities that last less than 48 h with adequate treatment
  - Grade 3 fever not associated with hemodynamic compromise
  - Grade 3 endocrinopathy that is well controlled by hormone replacement
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor
- Any clinically-significant Grade ≥ 3 non-hematologic laboratory abnormality, except Grade 3 or Grade 4 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
- Any clinically-significant hematologic toxicity specifically defined as:
  - Grade 4 thrombocytopenia for ≥7 days, or Grade 3 or 4 associated with bleeding or requiring platelet transfusion
  - Grade 4 neutropenia for ≥7 days, or Grade 3 or 4 associated with infection or febrile neutropenia
  - Grade 4 anemia, or Grade 3 requiring blood transfusion
- Any death that is not clearly attributed to the underlying disease or extraneous causes

Toxicities will be assessed according to CTCAE v5.0. If multiple toxicities occur, the presence of DLT will be graded based on the most severe toxicity observed.

7.3 Treatment Assignment and Bias Minimization

This is an open-label, non-randomized study.

Patients will be enrolled in cohorts based on cancer type. The study will use a Simon two-stage design.

7.4 Assessment and Verification of Compliance

Patients will be instructed to return all study drug supplies (including empty, partially empty, and full bottles) at each scheduled clinic visit for accountability and compliance review by study personnel. Study personnel will reinforce dosing instructions and answer patient questions at each clinic visit and during telephone follow-up.

7.5 Prior and Concomitant Therapies

All medications and supplements administered within 14 days prior to Screening through the last follow-up visit will be recorded in the electronic case report forms (eCRFs) using generic drug names when possible. All antibiotics used within the 60 days prior to Screening will be recorded in the eCRF.

7.5.1 Permitted Therapies

Concomitant medications may be administered at the Investigator's discretion to conform to standard practice, including routine medications a patient will continue during study participation as well as newly prescribed medications, except for those excluded medications described in

[redacted]

8 SAFETY MONITORING

8.1 Definitions

- **Adverse event** – An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
- **Serious adverse event** – An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (An event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- **Adverse reaction** – An adverse reaction is any AE caused by a drug
- **Suspected adverse reaction** (SAR) – An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.
- **Treatment-emergent adverse event** (TEAE) **–** A TEAE is an undesirable event not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following study treatment.
- **Immune-mediated adverse event** – An imAEs is an AE consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. ImAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity
- **Unexpected adverse event** – An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed, or is not consistent with the risk information described in the General Investigational Plan. Unexpected also

refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

8.2 Documenting Adverse Events

Adverse events will be assessed by direct observation and patient assessments/interviews.

Abnormal clinical laboratory values and vital sign and ECG measurements will be recorded as AEs only if they are considered to be clinically significant by the Investigator. If a laboratory abnormality is the sole potential AE, the abnormality must be confirmed (if possible) with a repeat laboratory test performed as soon as possible.

8.2.1 Timeframe for Collection

All AEs and SAEs will be collected and recorded for each patient from the day of signing the ICF until 100 days after the last dose of the study treatment or until alternate anticancer therapy is initiated, whichever occurs first. Thereafter, only SAEs will be collected and recorded during the survival follow-up period or until alternate anticancer therapy is initiated. Any SAE occurring after the start of a new treatment that is considered to be related to study treatment by the investigator will be reported.

All AEs and SAEs experienced by a study patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved or stabilized (e.g., until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed), until the patient is lost to follow-up, or until the patient has died, whichever is earlier.

8.2.2 Classification of Events

8.2.2.1 Assessment of Toxicity Grade

The toxicity grade of an AE refers to its severity. The severity of AEs will be categorized using the National Cancer Institute (NCI) CTCAE, version 5.0 (CTCAE, 2017), which is appropriate for grading and assessing the range of potential AEs that may be observed in the targeted study population. For any term that is not specifically listed in the CTCAE scale, severity must be assigned a grade of 1 through 5 using the following CTCAE guidelines:

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

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

8.2.2.2 Assessment of Causality

Medical judgment will be used to determine the cause of the AE, considering all relevant facts such as (but not limited to) the underlying study indication, comorbidities, concomitant medication(s), medical history, pattern of the AE (e.g., continuous, intermittent), temporal relationship to the study drug, and de challenge or re-challenge.

The Investigator will be responsible for selecting "Yes" or "No" as detailed below for the relationship of each AE to the study drug.

Yes: there is a reasonable possibility that there is a causal relationship to the study drug and one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from the time of administration of the study drug
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The event follows a known pattern of response to the study drug
- The event disappears or decreases on cessation or reduction in dose. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study dosing despite other clear indications of relatedness).

No: there is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of the study drug to the time of the AE
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environmental or toxic factors, or other modes of therapy administered to the patient
- The event does not follow a known pattern of response to the study drug
- The event does not disappear or decrease on cessation, and it does not reappear or worsen when dosing is resumed

8.2.2.3 Action Taken with Study Drug(s)

For each AE reported, the action taken with the study drug as a result of the AE will be recorded as one of the following:

- None
- Dose reduced
- Dose delayed
- Drug interrupted
- Drug discontinued

8.2.2.4 Outcome of Adverse Event

The outcome of each AE at the time of last observation will be reported as one of the following:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved/ongoing (e.g., for irreversible congenital anomalies)
- Recovered/resolved with sequelae (e.g., for other irreversible medical conditions)
- Fatal (i.e., death is at least possibly related to the AE)
- Unknown

8.3 Reporting Serious Adverse Events

All SAEs, regardless of relationship to study drug, must be reported to the clinical research organization (CRO) within 24 hours of site personnel knowledge. This will be done by faxing or emailing the completed SAE Report Form to the CRO at the number provided on the SAE Report Form.

Contact information for safety reporting is as follows:

Safety Reporting

[redacted]

Investigators must follow patients with SAEs until event resolution or stabilization, withdrawal of consent, patient is lost to follow-up, or death, whichever occurs first.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB. For fatal or life-threatening SAEs for which important or relevant information is missing, active follow-up must be undertaken immediately.

The Sponsor, or their representatives, will provide the health authority; IRB, as appropriate; and participating investigators with clinical safety updates/IND safety reports according to local requirements.

Any SAEs considered to have at least a possible relationship to the study drug and discovered by the Investigator at any time period after the patient's study treatment has ended should be reported according to the timeframe described above.

8.3.1 Submission and Distribution of Serious Unexpected Suspected Adverse Reaction Reports

Per regulatory requirements, if an SAE is assessed by the Sponsor as a serious unexpected suspected adverse reaction (SUSAR), it will be submitted to the Regulatory Authorities. In addition to this, a copy of the report (CIOMS or MedWatch 3500A) will be distributed to the Investigators/site. A copy of the report will be submitted to the respective IRB/EC and Investigators as per local regulation. Reporting will be conducted in compliance with 21 CFR 312.32.

[redacted]

8.5 Clinical Laboratory Findings

It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the appropriate reference range(s). All abnormal values assessed to be of clinical concern and at least possibly related to the study drug or of uncertain causality will be repeated. Persistent abnormal values or changes of possible clinical concern that remain within the normal range will be followed up and further evaluated at the discretion of the Investigator.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE if:

- A repeat test is performed when possible to confirm the abnormality
- An action on study drug dosing is made as a result of the abnormality
- An intervention for management of the abnormality is required
- The Investigator considers the abnormality to be an AE

Abnormal test results must not be recorded as AEs unless they fulfill the aforementioned criteria. All abnormal laboratory values, even if reported as an AE, will be categorized by the Investigator as not clinically significant (NCS) or clinically significant (CS) and a severity grade will be included in the eCRF.

8.6 Pregnancy

Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at Screening, prior to dosing in Cycle 2 and each subsequent 28-day dosing cycle, and at EOT. Definitions of WOCBP and methods of contraception are provided in Appendix 5. Men must use contraception for 7 months following the last dose of study drug (nivolumab or VE800).

Pregnancies occurring on study that involve a study patient must be brought to the attention of the treating physician immediately, and pregnant patients must discontinue study dosing. Site personnel will notify the Sponsor within 24 hours of the Investigator's knowledge of the

pregnancy using a Pregnancy Notification Form per contact details noted in Section 8.3. Such pregnancies will be followed to outcome, as possible.

The outcome of all pregnancies that occur from the date of the first dose until 5 months after the last dose of study treatment should, if possible, be followed up and documented. When a report of pregnancy is received, the Investigator must obtain the consent of the patient's partner prior to obtaining information about the pregnancy (using a suitably approved consent form in accord with local procedures).

Pregnancy in a female patient or female partner of a male patient is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (e.g., spontaneous abortion, which may qualify as an SAE).

8.7 Overdose or Misuse

Overage in dosing of either the study drug or a concomitant medication without overdose signs or symptoms unless the event meets SAE criteria (e.g., hospitalization) are excluded from SAE reporting; however, dosing that is not within 95-105% of a planned dose should be recorded on the appropriate eCRF page.

9 ANALYSIS

An overview of planned analyses is presented in this section. Details will be provided in the statistical analysis plan (SAP).

Data from 3 cohorts will be analyzed and reported separately by cohort.

9.1 Sample Size Determination

The study will use a Simon two-stage design. In each disease-specific expansion cohort, a Simon two-stage design will be used to provide an initial assessment of the clinical activity at Stage 1 for continuation to Stage 2. ORR will be evaluated using RECIST 1.1.



9.2 Analysis Sets

The following patient populations (i.e., analysis sets) will be evaluated and used for presentation of the data:

- Full Analysis Set: All patients who were enrolled and received any dose of any study drug (vancomycin, VE800, or nivolumab). The Full Analysis Set will be the default analysis set for all analyses, unless otherwise specified.
- Safety Analysis Set: All patients who were enrolled and received at least 1 dose of any study drug (VE800 or nivolumab). The Safety Analysis Set will be the primary set for the analysis of safety data.
- DLT-evaluable population: The first 12 patients to complete the first 28 days of combination treatment of VE800 and nivolumab administration or experience a DLT
- PK population: All patients who receive at least 1 dose of VE800 and have at least 1 PK sample.
- Efficacy Population: all patients who receive one dose of the combination treatment of VE800 and nivolumab and have a valid baseline and post baseline tumor assessment (death or documented clinical progression without imaging may be considered a valid post-baseline assessment).

9.3 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the ORR defined as the proportion of patients achieving a best overall response of CR or PR evaluated using RECIST 1.1.

[redacted]

9.4 Analysis of Secondary Efficacy Endpoints

Additional measures of ORR will be evaluated using RECIST 1.1, including the following

- Antitumor response based on change in measurable tumor burden
- Time-point response assessment: percentage changes in tumor burden per assessment time point
- Best overall response assessment (CR, PR, SD, PD)
- DCR, defined as CR+PR+SD
- DOR, defined as the time from first documentation of CR or PR until the time of first documentation of PD

PFS according to RECIST (v1.1) is defined as the time from enrollment to the earlier date of assessment of progression or death by any cause in the absence of progression. [redacted]

9.6 Population Analysis

9.6.1 Disposition

A tabulation of the disposition of patients will be presented, including the number of patients who fail Screening after signing informed consent, receive study drug, and complete or prematurely discontinue, and the reasons for study discontinuation. Entry criteria eligibility and protocol deviations will be listed.

9.6.2 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline disease characteristic will be generated. Data to be tabulated will include sex, age, race, and ethnicity, as well as cancer history and prior treatments.

9.6.3 Disease History

For disease history the following will be documented:

- Date of first diagnosis
- Cancer diagnosis and Stage at the time initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- For patients with CRC: microsatellite stability status (MSS or microsatellite instable [MSI] high)
- Information on first anticancer treatment:
  - Intent (adjuvant, neoadjuvant, curative, palliative)
  - Date of start of first treatment
  - Agents used in first treatment
  - Date of last dose of first treatment
- Information on second and subsequent anticancer treatments:
  - Intent (adjuvant, neoadjuvant, curative, palliative)
  - Dates of start of all subsequent treatments
  - Agents in all subsequent treatments
  - Dates of last dose of all subsequent treatments
- Best response to prior anticancer treatment
- (For melanoma only) best response to iCPI
- Date of recurrence for each prior anticancer treatment

9.7 Safety Analysis

9.7.1 Adverse Events

Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) at the time of study initiation. A by-patient AE data listing, including verbatim term, preferred term, system organ class, study drug arm, severity, and relationship to study drug, will be provided. The number of patients experiencing a DLT will be summarized by study cohort, system organ class, and preferred term. Additionally, the number of patients experiencing TEAEs and the number of individual TEAEs will be summarized by study cohort, system organ class, and preferred term. TEAEs will also be summarized by severity and by relationship to study drug.

9.7.2 Clinical Laboratory Analysis

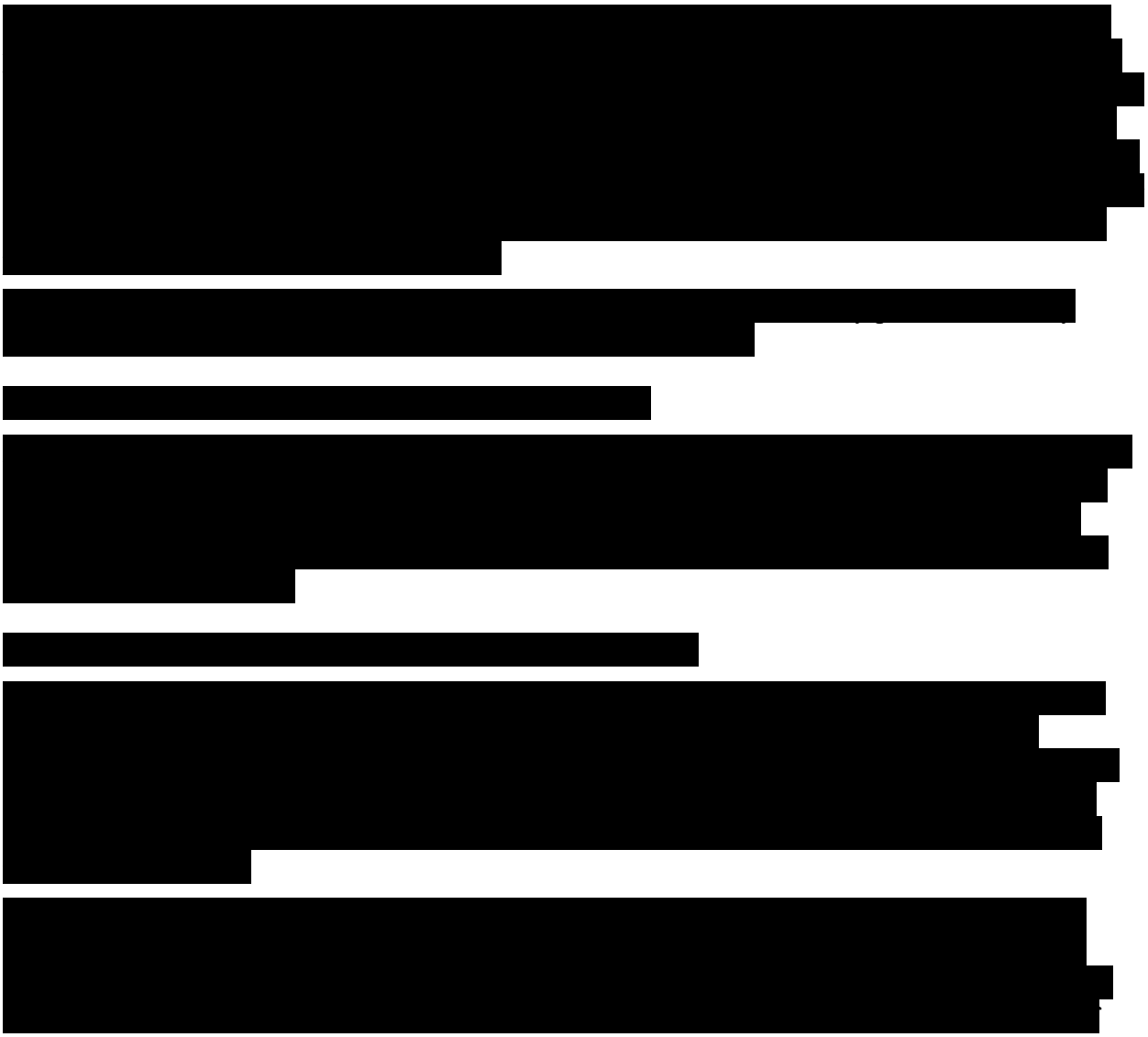
Changes in clinical laboratory parameters (hematology, chemistry) will be summarized by protocol-specified collection time point. A summary of changes from baseline will also be presented for each protocol-specified time point.

9.7.3 Other Safety Endpoint

Vital signs, ECG parameters, ECOG performance status, and physical examinations be summarized by protocol-specified collection time point. A summary of changes from baseline will also be presented for each protocol-specified time point.

9.8 Pharmacokinetics Analysis

Results from stool microbiota composition and VE800 detection analyses will be presented in by-patient listings and summarized by cohort and study day, including absolute values and changes from baseline.



[redacted]

9.11 Procedures for Reporting Changes to the Planned Analysis

All deviations from the SAP will be provided in the clinical study report.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be performed in accordance with the protocol, guidelines for GCP established by the International Council for Harmonisation (ICH), and applicable local regulatory requirements and laws.

The Sponsor is committed to designing, implementing, conducting, analyzing, and reporting this trial in compliance with the highest ethical and scientific standards. Protection of patient safety is the overriding concern in the design of clinical trials. In all cases, Vedanta clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

10.2 Ethics Review

The Investigator must inform and obtain approval from the IRB/EC for study conduct at named sites, the protocol, informed consent documents, and any other written information that will be provided to the patients and any advertisements that will be used. Written approval must be obtained prior to recruitment of patients and shipment of study drugs.

Proposed amendments to the protocol and aforementioned documents must be submitted to the Sponsor for review and approval, then to the IRB/EC. Amendments may be implemented only after a copy of the approval letter from the IRB/EC has been transmitted to the Sponsor.

Per GCP guidelines, the Investigator will be responsible for ensuring that an annual update is provided to the IRB/EC until the study is completed (i.e., finalization of the clinical study report) to facilitate continuing review of study conduct and that the IRB/EC is informed about the end of the study. Copies of the update, subsequent approvals, and final letter must be sent to the Sponsor.

In addition to IRB/EC and regulatory authority approval, all other required approvals (e.g., approval from the local research and development board or scientific advisory committee) will be obtained prior to recruitment of patients and shipment of study drugs.

10.3 Informed Consent

Informed consent is a process that is initiated prior to the patient's agreeing to participate and continues throughout the patient's participation. It is the Investigator's (or designee's) responsibility to obtain written informed consent from each patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards before any study procedures are initiated. Each patient must be given a copy of the signed informed consent documents and associated materials. The original copy of the signed and dated informed consent documents must be retained at the site and is subject to inspection by representatives of the Sponsor or regulatory authorities. If any amendments affect the ICF (e.g., when new study procedures or assessments have been added), all active patients must be reconsented using the same process for the initial consent.

10.4 Data Privacy

The Investigator must ensure that the patient's privacy is maintained. On eCRFs and other documents submitted to the Sponsor, patients will be identified by their assigned patient number only and any other information that may reveal the patient's identity must be redacted (e.g., first and last name). Documents that are not submitted to the Sponsor (e.g., signed informed consent documents) must be kept in a confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory authorities, and IRBs/ECs to review the portion of the patient's medical record that is directly related to the study. As part of the required content of informed consent documents, patients must be informed that their medical records will be reviewed in this manner.

10.5 Disclosure

Information concerning the study, patent applications, processes, scientific data, or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may only use this information for the purposes of the study.

It is understood by the Investigator that the Sponsor will use information obtained in this study in connection with the clinical development program, and therefore may disclose it as required to other clinical Investigators and to regulatory authorities. In order to allow the use of the information derived from this study, the Investigator understands the obligation to provide complete test results and all data obtained to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting must be undertaken only with written consent from the Sponsor.

10.6 Biological Specimens and Data

Following the conclusion of the study, patient samples that have not been depleted may be stored and used for additional future research. This research will help understand disease subtypes, drug response, and toxicity, and possibly to identify new biomarkers that predict patient response to treatment.

This use of the samples for internal research will be done in accordance with the guidelines defined by the FDA document "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable" (issued 25 April 2006) and European Medicines Agency's (EMEA's) Reflection Paper on Pharmacogenetic Samples, Testing, and Data Handling (EMEA, April 2008). If a patient requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the Sponsor (or central laboratory) will destroy the samples as described in this FDA guidance. The Sponsor (or central laboratory) will notify the Investigator in writing that the samples have been destroyed.

11 OVERSIGHT

11.1 Quality Control and Assurance

Quality control procedures will be conducted according to the Sponsor and CRO's internal procedures. The study site may be audited by a quality assurance representative of the Sponsor. All necessary data and documents will be made available for inspection along with any required study staff.

11.1.1 Monitoring

This study will be closely monitored by representatives of the Sponsor or designee throughout its duration. Monitoring will include personal visits with the Investigator and study staff as well as appropriate communications by telephone, fax, mail, email, or use of the electronic data capture (EDC) system, as applicable. It is the monitor's responsibility to inspect all eCRFs at regular intervals throughout the study to verify the completeness, accuracy, and consistency of the data and to confirm adherence to the study protocol and to GCP guidelines. The Investigator agrees to cooperate with the monitor to ensure that any problems detected are resolved promptly. The Investigator and site will permit study-related monitoring, audits, IRB/EC review, and regulatory inspection, including direct access to source documents.

It is understood that study monitors and any other personnel authorized by the Sponsor may contact and visit the Investigator and will be permitted to inspect all study records (including eCRFs and other pertinent data) on request, provided that patient confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

Every effort will be made to maintain the anonymity and confidentiality of patients. However, because of the experimental nature of the investigational product, the Investigator agrees to allow representatives of the Sponsor and authorized representatives of regulatory authorities to inspect the facilities used in the conduct of this study and to inspect, for purposes of verification, all hospital or clinic records of all enrolled patients relevant to study participation.

11.1.2 Audits

Regulatory authorities, the IRB/EC, and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

11.1.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or ICH GCP requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. Deviations must be reviewed by the site, clinical research associate (CRA), Sponsor and designee, as appropriate for potential corrective actions development. Corrective actions will be implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3;
- 5.1 Quality Assurance and Quality Control, Section 5.1.1; and
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the Investigator to use continuous vigilance to identify and promptly report deviations. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing IRB/EC per their policies. The Investigator is responsible for knowing and adhering to IRB/EC requirements.

11.1.4 Records

11.1.4.1 Data Capture and Management

Medical records and/or study visit worksheets will be used by the Investigator or designee as source documents for recording data specified in the protocol for each patient enrolled. Data recorded in the eCRF derived from source documents must be consistent with the data recorded on the source documents. All source documents must be completed in a neat, legible manner to ensure accurate interpretation of data. Additional data will be collected through clinical laboratories.

Clinical data derived from source documents will be entered into a 21 CFR Part 11-compliant EDC system at the clinical sites. The data system will include password access, consistent backup, and an audit trail. Internal and external quality checks will be applied to identify data that appear inconsistent, incomplete, or inaccurate. Data not captured on eCRFs will be received and stored as external files by the Sponsor or designee.

Study plans will describe internal and external quality checks and cross functional data monitoring to identify and address data issues via a risk-based approach. Needed queries will be issued by the system (some fields may require immediate correction for form submission), CRO, or authorized Sponsor staff in an attempt to clarify and/or correct missing, incomplete, or illogical data. Changes or corrections to eCRFs will be made by the Investigator or an authorized member of the study staff.

Data entered and compiled for interim analysis and/or DMC review will be monitored as closely as possible for accuracy and quality but may not undergo final data cleaning and verification.

It is the Investigator’s responsibility to ensure eCRFs are complete and accurate, regardless of whether this responsibility has been delegated in whole or in part. Following review and approval, the Investigator or designee will electronically sign and date the pages, which certifies that the Investigator has thoroughly reviewed and confirmed all data on the eCRF.

A read-only copy of the eCRFs will be provided to study sites after the study has ended and the EDC system has been locked.

11.1.4.2 Records Retention

Data retention practices will follow ICH guidelines, which note that essential documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents must be retained for a longer period if required by the applicable local requirements.

12 PUBLICATION POLICY

The Sponsor encourages the scientific publication of data from clinical research studies. However, an Investigator(s) may not present or publish partial or complete study results without participation and written agreement of the Sponsor. The Investigator and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. All proposed publications must be reviewed and commented on by the Sponsor before submission for publication. The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the Sponsor in connection with this study. These procedures are in place to ensure coordination of study data publication and adequate review of data for publication against the validated study database for accuracy.

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14 APPENDICES

APPENDIX 1 NIVOLUMAB MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

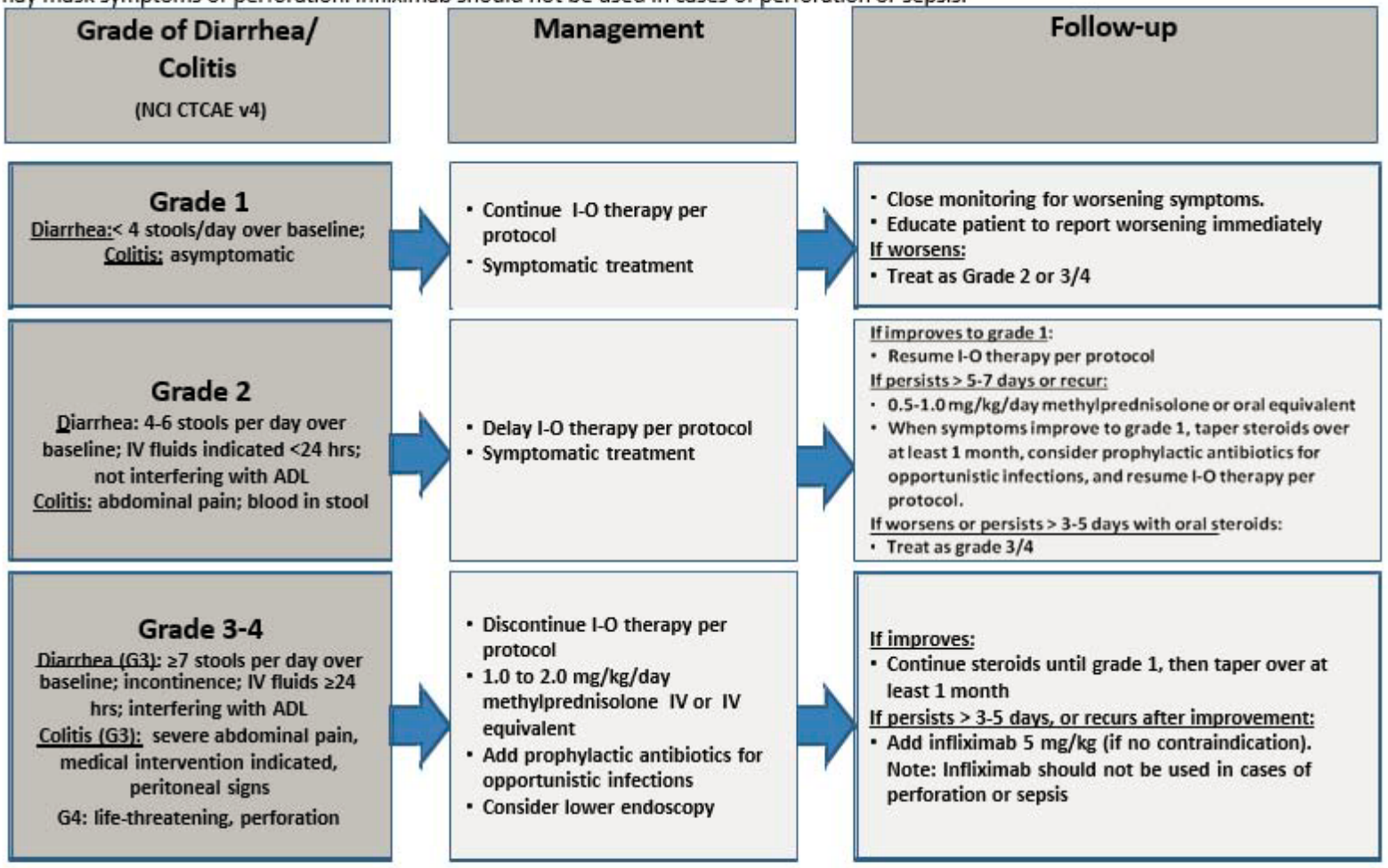
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

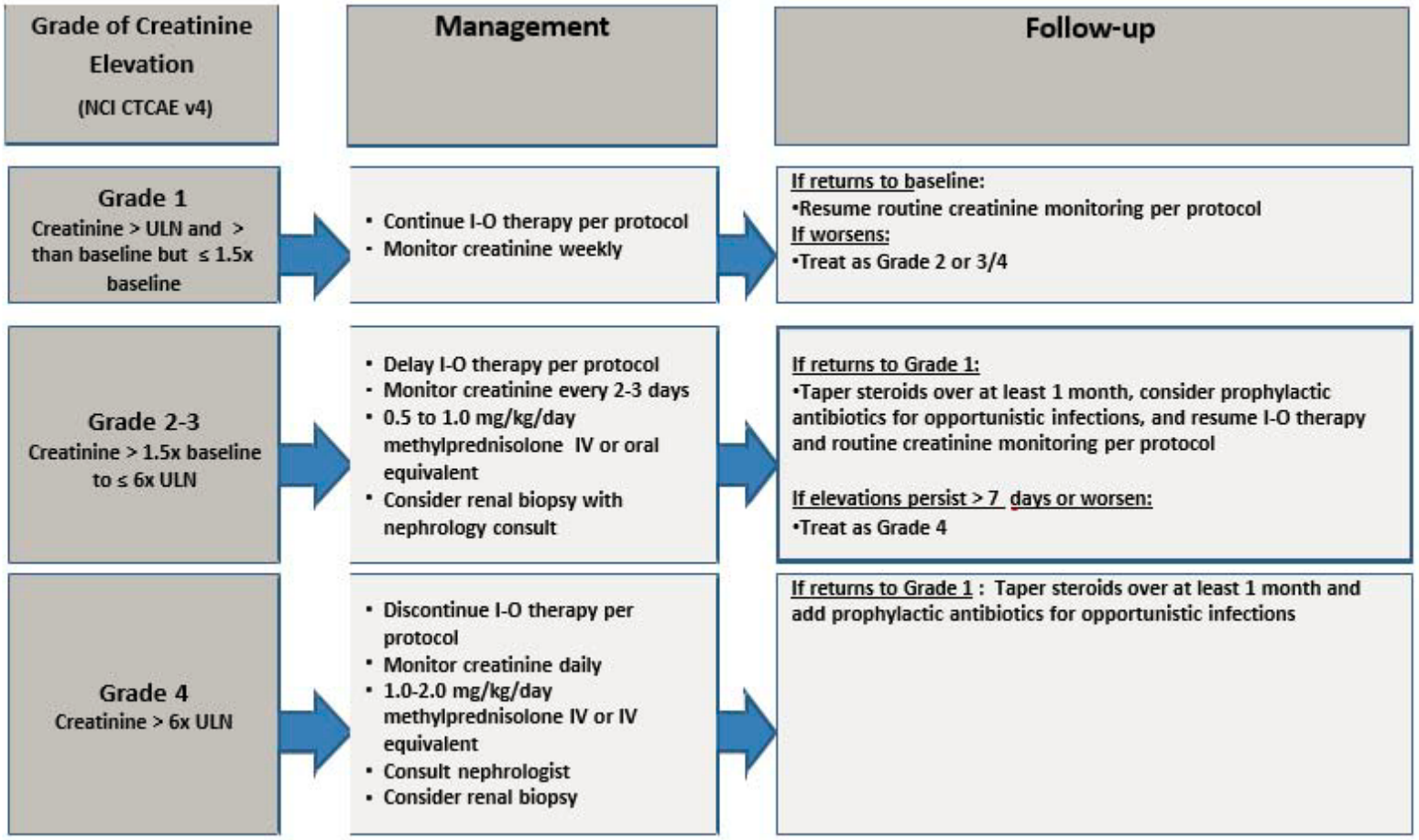


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

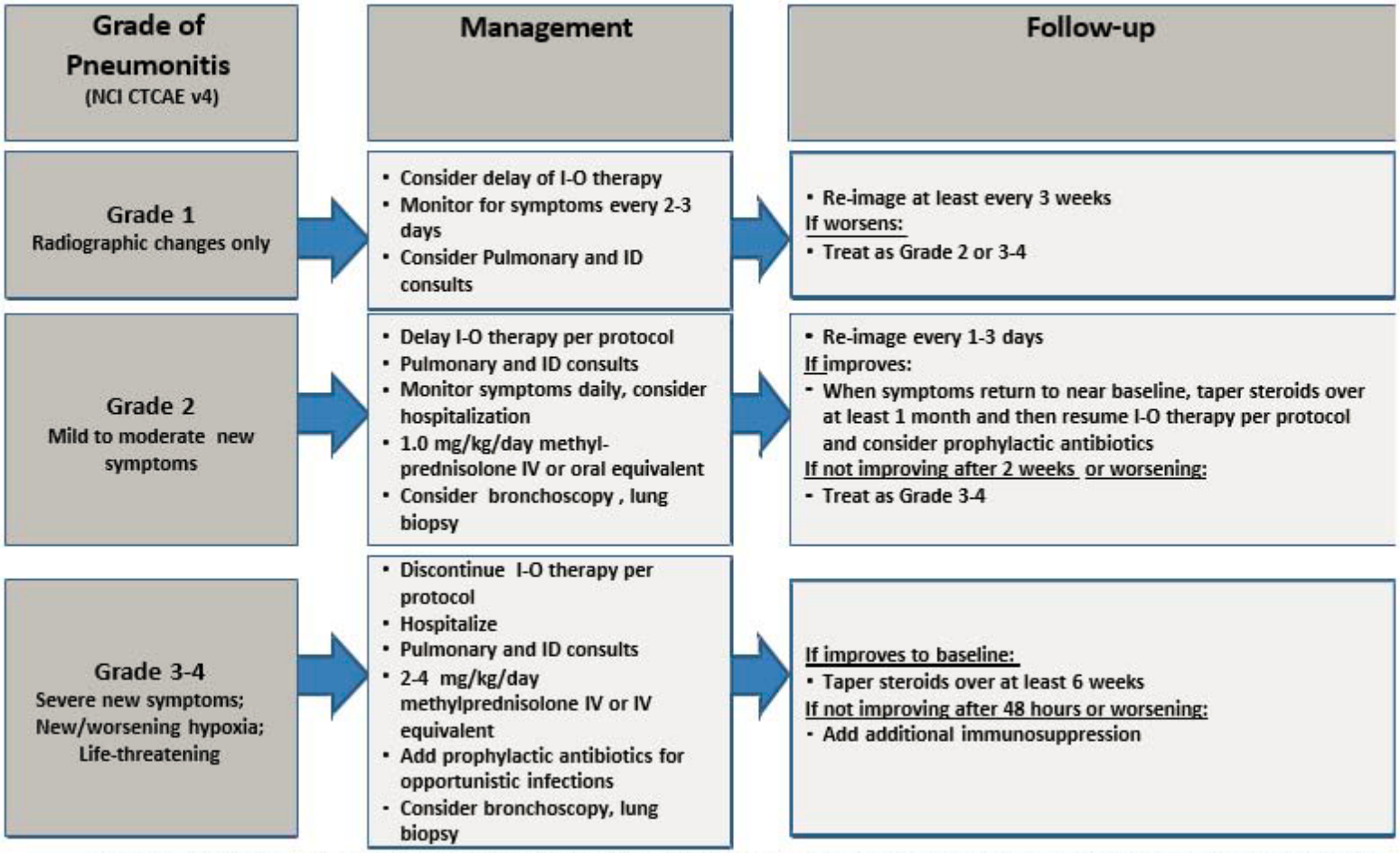


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

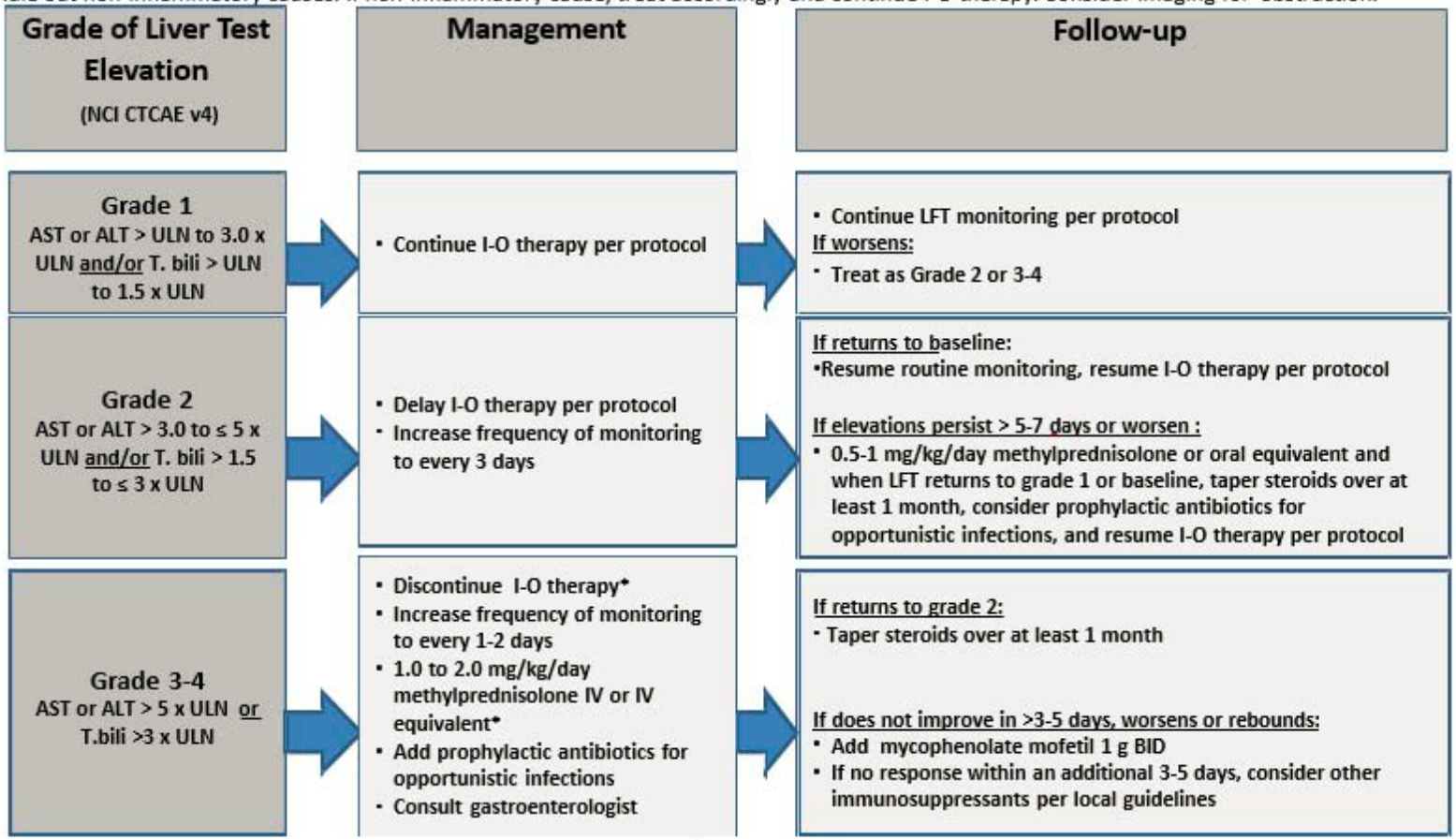


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

27-Jun-2019

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



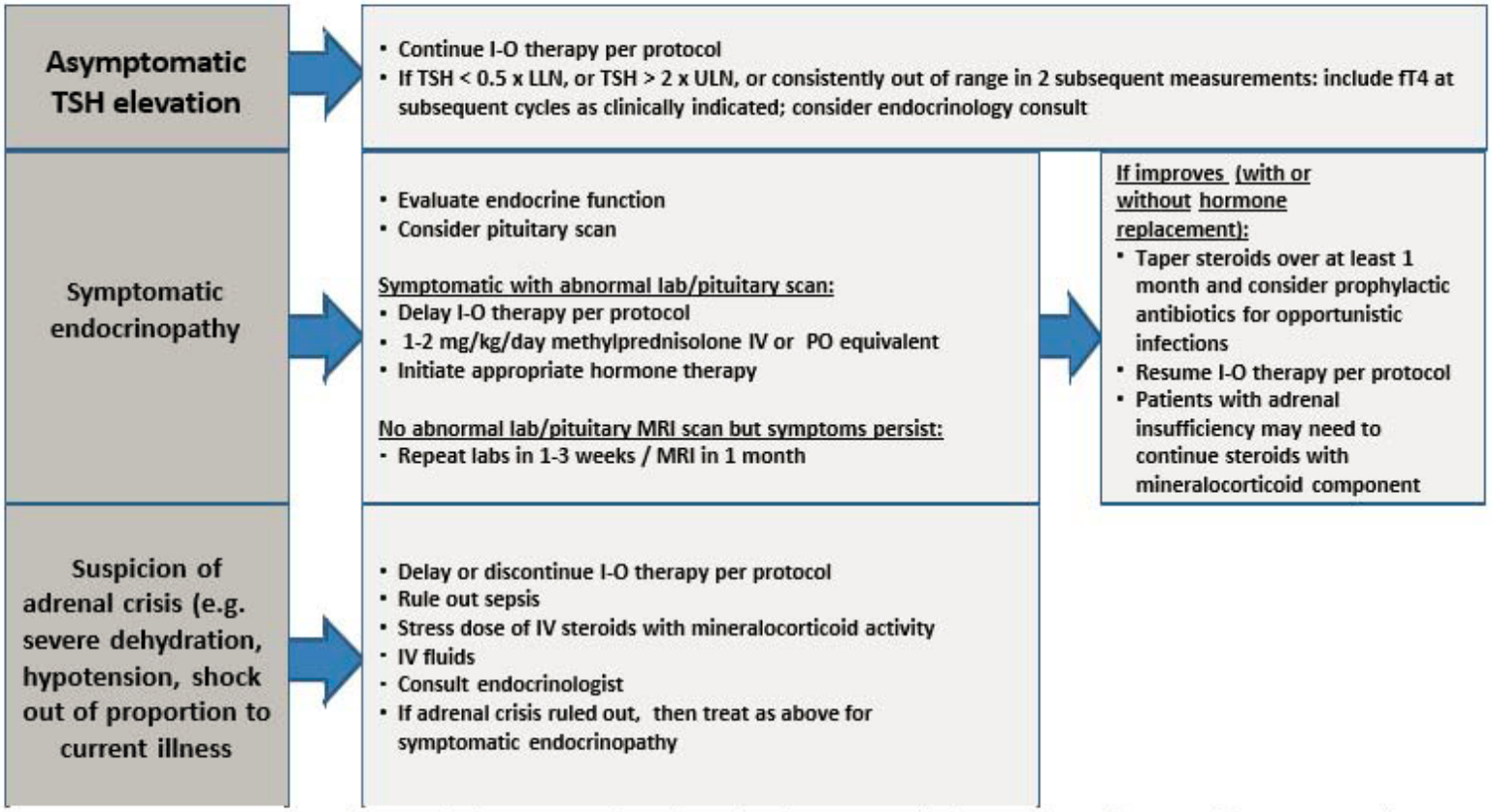
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

27-Jun-2019

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

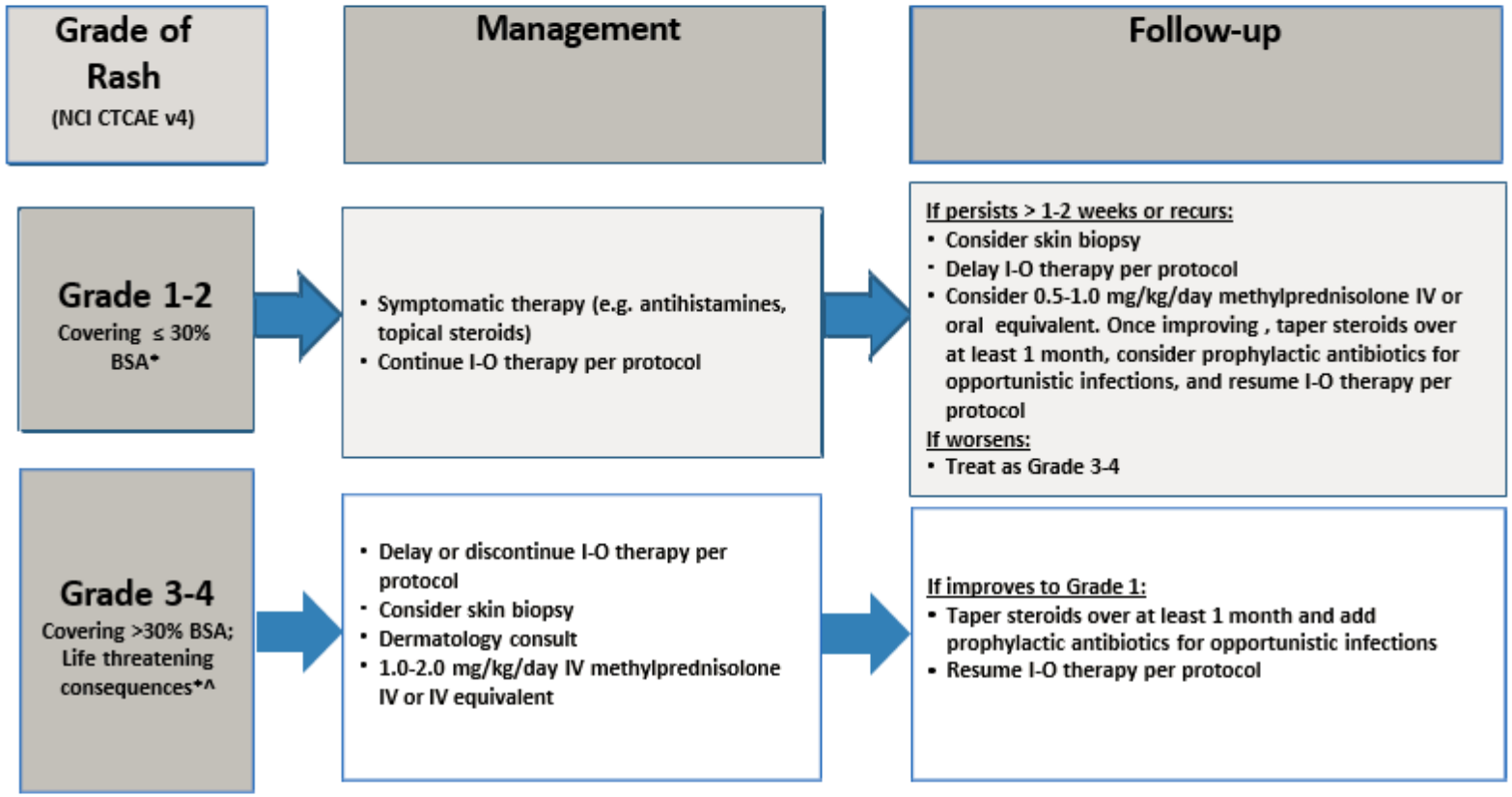


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

27-Jun-2019

Neurological Adverse Event Management Algorithm

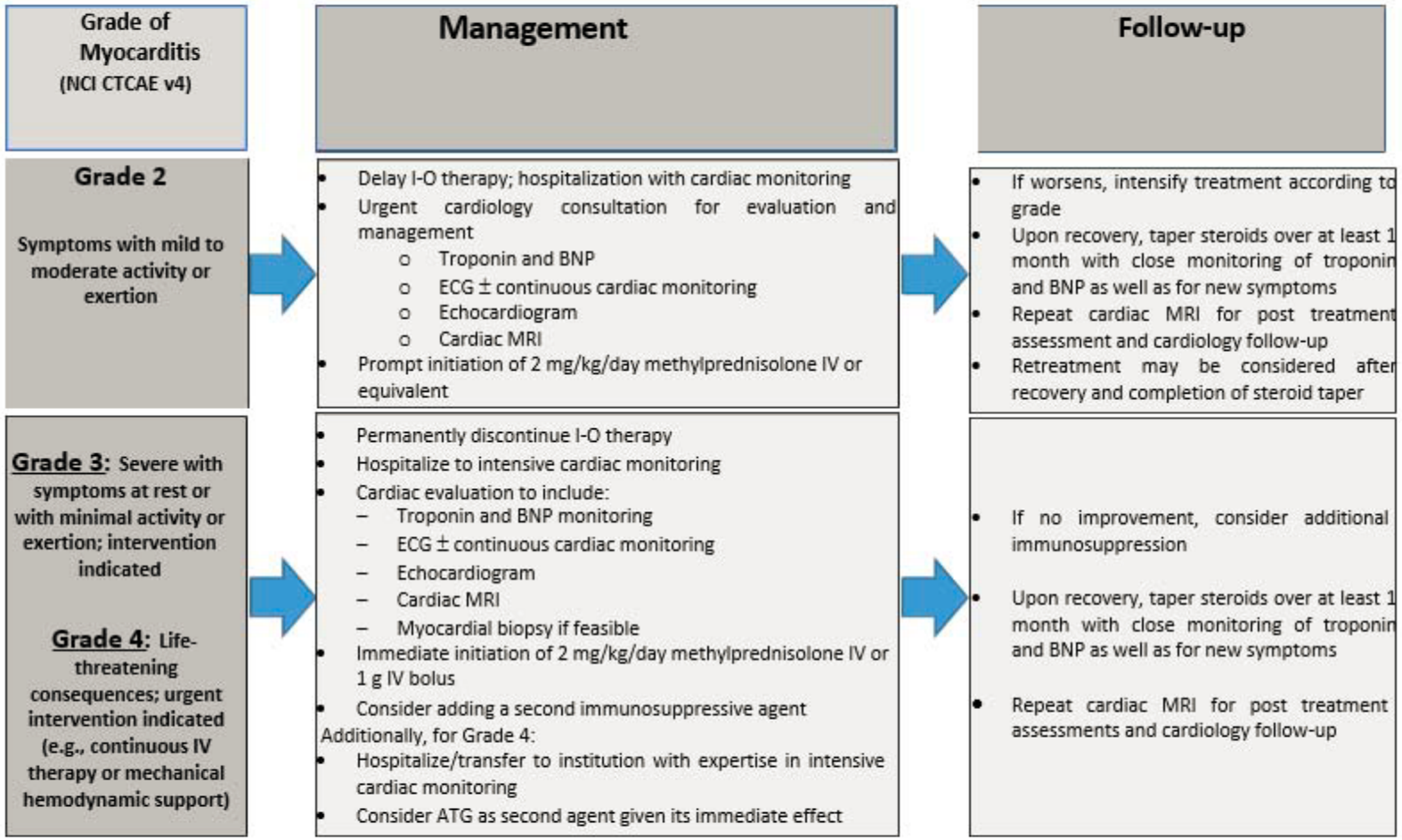
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: - Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

27-Jun-2019

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

27-Jun-2019

APPENDIX 2 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST), V1.1

Response Criteria by RECIST v1.1 (Eisenhauer, 2009)

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: 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 diameters while on study.

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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

RECIST Response for Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
CR	CR	No	CR	>4 wks. Confirmation[b]
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation[b]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline[b]
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD[c]	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

a See RECIST v1.1 publication for further details on what is evidence of a new lesion.

b Only for non-randomized trials with response as primary endpoint.

c In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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." Every effort should be made to document the objective progression even after discontinuation of treatment.

[redacted]

APPENDIX 4 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
Grade	
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken (1982)

APPENDIX 5 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level >40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.*

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progesterone-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable

Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP patients who choose complete abstinence must continue to have pregnancy tests, as specified in the protocol. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP patient chooses to forego complete abstinence.
NOTES: a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. c. Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction.

Unacceptable Methods of Contraception
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

*** Local laws and regulations may require use of alternative and/or additional contraception methods.**

CONTRACEPTION GUIDANCE FOR MALE PATIENTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male patients with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male patients are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male patient.
- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

