Clinical Study Protocol 747-308

OBETICHOLIC ACID (OCA)

A Randomized, Double-blind, Placebo-controlled, Phase 2/3 Study to Assess the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Obeticholic Acid Compared to Placebo in Pediatric Subjects with Biliary Atresia, Post-hepatoportoenterostomy

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EU CT number: 2023-503926-37

Sponsor

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SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and Approved by:

[redacted] *Electronically signed by: [redacted]*
Reason: I have reviewed this document
Date: Sep 14, 2023 08:30 EDT

14-Sep-2023

[redacted] MD
[redacted] Clinical Development
Intercept Pharmaceuticals, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for obeticholic acid (OCA) and this Protocol 747-308. Having fully considered all the information available, I agree that it is ethically justifiable to give OCA to selected subjects according to this protocol.

I understand that all information concerning OCA supplied to me by the Sponsor, Intercept Pharmaceuticals, Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, electronic case report forms (eCRF), and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol 747-308 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____

Investigator's Name (Printed)

_____ _____

Investigator's Signature Date

STUDY PERSONNEL CONTACT INFORMATION

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2. SYNOPSIS

Name of Sponsor/Company:

Intercept Pharmaceuticals, Inc.

Name of Investigational Product:

Obeticholic acid

Name of Active Ingredient:

Obeticholic acid (OCA); 6α-ethyl-chenodeoxycholic acid (6-ECDCA); INT-747

Title of Study:

A Randomized, Double-blind, Placebo-controlled, Phase 2/3 Study to Assess the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Obeticholic Acid Compared to Placebo in Pediatric Subjects with Biliary Atresia, Post-hepatoportoenterostomy

Study Center(s):

Up to 50 investigational sites, globally

Studied Period:	**Phase of Development:**
The total duration of the study (first subject consented to last subject completing the last study visit of the double-blind [DB] phase) will be approximately 4 years.	Phase 2/3

Objectives:

Primary Objectives

To evaluate the effect of OCA compared to placebo in conjunction with established local standard of care on clinical outcomes in subjects with biliary atresia who have had a successful Kasai procedure as measured by time to first occurrence of any component of a composite endpoint comprised of the following adjudicated events:

- Death (all-cause)
- Liver transplant
- Pediatric end-stage liver disease (PELD) score ≥17/model of end stage liver disease (MELD) ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Clinically evident ascites related to portal hypertension (diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

Secondary Objectives:

To evaluate the:

- Pharmacokinetics (PK) of OCA as measured by unconjugated plasma OCA (parent), glyco-OCA, tauro-OCA, and total OCA (molar sum of OCA and its active conjugates)

- Pharmacodynamics (PD) of OCA as measured by: Biomarkers of farnesoid X receptor (FXR) activation: plasma fibroblast growth factor 19 (FGF-19), 7-hydroxy-4-cholesten-3-one (C4), and endogenous bile acids
- Biomarkers of hepatobiliary function: gamma-glutamyl transferase (GGT), total and direct (conjugated) bilirubin
- Effect of OCA on liver stiffness by transient elastography (if available at site)
- Disease progression as measured by plasma levels of fat-soluble vitamins (Vitamins D and K)
- Safety and tolerability of OCA

Exploratory Objectives:

- To evaluate the acceptability and swallowability of the dosing regimen
- To evaluate the palatability of the dosing regimen

Type of Study Control:

Double-blind, randomized, placebo-controlled study

Number of Subjects (Planned):

Approximately 144 pediatric subjects will be enrolled in the trial; an interim analysis will be conducted after the initial 25 to 30 subjects are enrolled and reach Month 4.

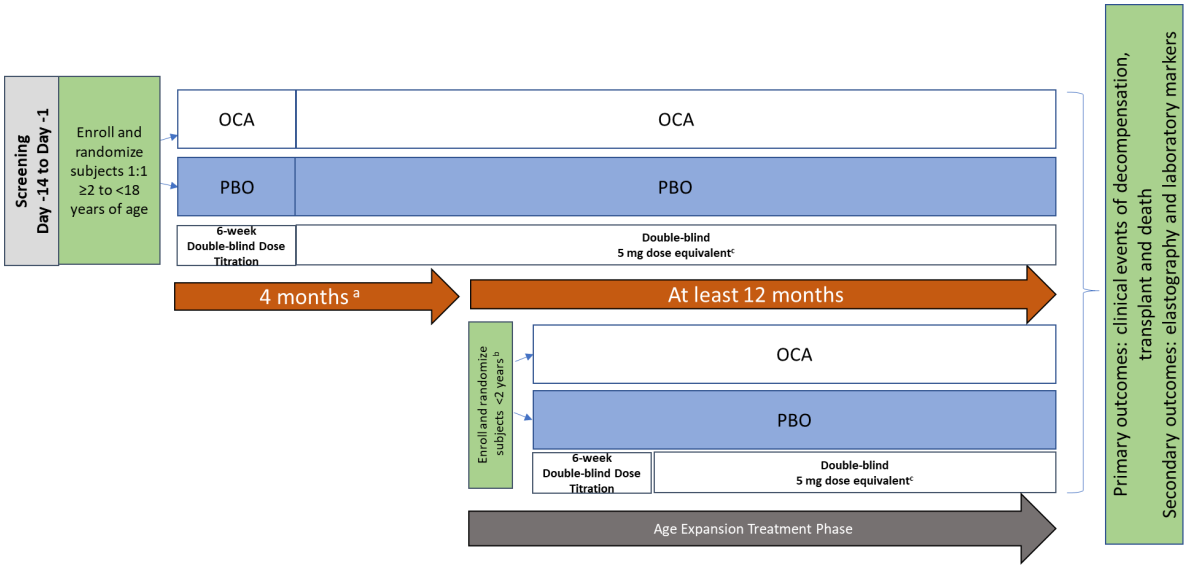
Methodology:

Overall Study Design:

This is a global, multicenter, DB, placebo-controlled Phase 2/3 study to evaluate the efficacy, safety and tolerability, as well as PK/PD of OCA in eligible pediatric subjects with biliary atresia with successful hepatoportoenterostomy (HPE, also known as a Kasai portoenterostomy).

Screening Phase: The Screening Visit assessments must be performed within 14 days before Day 1 to determine the eligibility for enrollment and allow for the analysis and reporting of the Screening hematology, serum chemistry, radiology testing, and urinalysis results. Subjects must be able to swallow the placebo tablets to be included in the study. Thus, subjects will receive placebo tablet(s) at the Screening Visit to evaluate acceptability and the ability to swallow. The number of placebo tablets will be determined based on the 5 mg adult equivalent dose (AED) using individual subject weight. The study will initiate enrollment with pediatric subjects aged 2 to <18 years to be randomized to receive OCA or placebo in a DB manner. Following the interim analysis and assessment of safety in older children, enrollment of subjects <2 years of age will be considered.

Study Design:



AED=adult equivalent dose; DSMB=Data Safety Monitoring Board; OCA=obeticholic acid; PBO=placebo
Note: n=approximately 144 subjects
[a] Following the 6-week dose titration phase, subjects will continue on the tolerated dose for 12 months, inclusive of the titration phase. An interim analysis of safety and biochemical markers to determine potential study futility will be completed after approximately 25 to 30 subjects have been enrolled in the study for 4 months. The DSMB will be consulted for timing of a second interim analysis.
[b] Subjects aged <2 years will be enrolled only if supported by safety and efficacy data from the interim analysis.
[c] Subjects may be maintained at a lower, maximum tolerated dose than OCA 5 mg AED, as deemed necessary.

Double-Blind Phase

Dose Titration Phase: Subjects who satisfy the inclusion and exclusion criteria will be randomized to receive placebo or OCA (starting at 1.5 mg AED) in a 1:1 ratio. Investigational medicinal products (OCA or placebo) will be taken orally, with water, once daily. Doses of investigational product (i.e., OCA or placebo) will be titrated every 2 weeks in a stepwise manner for the first 6 weeks, starting at 1.5 mg AED and titrating through 3 mg AED to a maximum of 5 mg AED, as tolerated; a discussion with the Medical Monitor is encouraged when determining uptitration, if considerable signs or symptoms have arisen. Key PK parameters will be measured predose at Weeks 2, 4, and 6 (C_{trough}). Subjects who do not tolerate higher OCA doses may revert to their previous lower dose for the remainder of the study after discussion with the Medical Monitor.

Age Expansion Treatment Phase: Following the 6-week dose titration phase, subjects will continue at the tolerated dose. Blood samples will be collected predose at Weeks 10, 18, 30, end of treatment (EOT), and end of study (EOS)/early termination (ET) for PK characterization. The duration of dosing is expected to be approximately 24 months.

The first interim analysis will be conducted after approximately 25 to 30 subjects reach Month 4; assessments of GGT, total and direct (conjugated) bilirubin, and total plasma bile acids will be evaluated. Responders are defined as the subjects with ≥40% reduction from baseline in GGT and ≥25% reduction from baseline in direct bilirubin at Month 4.

An unblinded Data Safety Monitoring Board (DSMB) will assess these results, along with overall safety of the drug, and will advise on: 1) any safety concerns that would prohibit inclusion of subjects <2 years of age into the study, and 2) evidence of failure to sufficiently impact biomarkers, which would indicate futility of the study.

The timing of the second interim analysis based on the primary clinical outcome will be at approximately 12 months and will be confirmed by the DSMB following the first interim analysis.

The DSMB will continue to oversee the data throughout the study.

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria

1. Male or female pediatric subjects from birth to <18 years old

   Note: Subjects aged <2 years old will not be enrolled until after review of safety data during the planned interim analysis and agreement from the DSMB that there is sufficient safety data to enroll this age group.

2. Diagnosis of non-syndromic biliary atresia
3. Demonstrated successful HPE as defined by total bilirubin <2 mg/dL (34.2 µmol/L) at least 3 months post-HPE procedure.

Key Exclusion Criteria

1. Prior liver transplant or active status on transplant list
2. Participants diagnosed with biliary atresia splenic malformation (BASM)
3. Conjugated (direct) bilirubin ≥ upper limit of normal (ULN) of site-specific reference range. If conjugated bilirubin is not available: total bilirubin ≥2 mg/dL (34.2 µmol/L)
4. Platelets <120,000/µL
5. International normalized ratio (INR) ≥1.5
6. Current or history of complications of decompensated chronic liver disease including:
   a. gastroesophageal varices and/or variceal bleeding
   b. clinically evident ascites related to portal hypertension
   c. hepatic encephalopathy
   d. prior placement of portosystemic shunt
   e. hepatopulmonary syndrome or portopulmonary hypertension
   f. hepatorenal syndrome
   g. any evidence of portal hypertension based on imaging (e.g., cavernous transformation of portal vein, abdominal varices, etc.)
   h. Hepatocellular carcinoma
   i. Childs-Pugh B or C
7. Height and weight Z-score <-2 per site-specific reference ranges
8. Acholic (pale) stools
9. Aspartate aminotransferase (AST) >4x ULN
10. Alanine aminotransferase >4x ULN
11. GGT >500 U/L
12. Anticoagulation therapy
13. Albumin <3.5 g/dL
14. Inability to swallow tablets (i.e., tablet or mini-tablet formulations)

Investigational Product, Dosage and Mode of Administration:

Investigational Product Formulation:

- OCA 0.1 mg mini-tablet and matching placebo mini-tablet
- OCA 1.5 mg tablet and matching placebo tablet

Dosage and Mode of Administration

OCA or matching placebo tablets will be administered orally daily starting at a dose below the minimum effective primary biliary cholangitis (PBC) adult equivalent dose and titrating to up to the effective PBC adult equivalent dose every 2 weeks as tolerated.

Mini-Tablets and Dispensing Aids

OCA 0.1 mg mini-tablets may be provided for subjects who require them. Optional dispensing aids, such as counting trays and tweezers, may be provided to subjects/parents/guardians to assist in dispensing the mini-tablets.

Reference Therapy, Dosage and Mode of Administration:

Reference Therapy and Dosage: Placebo mini-tablets and placebo tablets, matched in size and appearance to OCA mini-tablets (0.1 mg) and 1.5 mg tablets, respectively.

Mode of Administration: Oral

Duration of Treatment:

The total expected duration for each individual subject will be at least 24 months, including a screening period of 14 days, and at least 16 months of treatment.

Criteria for Evaluation:

The assessments and endpoints supporting the primary, secondary, and exploratory objectives of the study are as follows:

Primary Endpoint	**Assessments**
Time to the first occurrence of any of the following clinical events.	Time to first occurrence of: • Death • Liver transplant • PELD score ≥17/MELD ≥15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Clinically evident ascites related to poral hypertension (diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
Secondary Endpoints	**Assessments**

PK exposure of OCA	Plasma unconjugated OCA (parent), glyco-OCA, tauro-OCA, and total OCA
Biomarkers of hepatobiliary function	GGT, total and direct (conjugated) bilirubin
Biomarkers of FXR activation (PD)	Plasma FGF-19, C4, endogenous bile acids
Noninvasive assessment of liver stiffness (if available at site)	Transient elastography
Disease progression	Plasma levels of fat-soluble vitamins (D and K)
Safety and tolerability of OCA	Treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs), electrocardiogram (ECG), physical exam, clinical laboratory results, and vital signs
Exploratory Endpoints	**Assessments**
Acceptability and swallowability	Subject's ability to swallow the dose regimen and overall acceptability of the dose regimen will be evaluated via a five-point criteria evaluation (see protocol).
Palatability	At the Week 6 visit, palatability of OCA will be assessed using a five-point facial hedonic scale with a correlated 100-point visual analog scale (facial hedonic scale [FHS]/VAS-5) in children ≥4 years of age. Children <4 years will evaluate palatability using a four-point criteria evaluation (refer to protocol).

Summary of Safety Criteria for Mandatory Treatment Interruption or Discontinuation:

Subjects who meet the following criteria will have investigational product interrupted and re-evaluated:

- If liver biochemistries (AST, ALT, or total bilirubin) indicative of potential hepatic injury exceed ULN:
  a. Increasing conjugated (direct) bilirubin ≥2x baseline and >ULN
  (If conjugated bilirubin is not available, then increasing total bilirubin ≥2x baseline and >ULN)
  b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x baseline that is >ULN, OR ALT or AST >300 U/L
  c. GGT >3x baseline and >ULN
- Clinical events indicative of hepatic injury or decompensation

Subjects who meet any of the following criteria will be discontinued from investigational product permanently:

- INR >1.5
- 25% decrease in platelets from baseline value and <120,000/μL
- Pregnancy
- Organ failure requiring hospitalization

Subjects who are discontinued for a clinical or laboratory adverse event (AE) will be followed for as long as necessary to adequately evaluate the safety of the subject or until the event stabilizes, resolves, or is no longer of clinical concern.

Statistical Methods:

A Statistical Analysis Plan (SAP) providing details about the specific planned analyses (interim and final), including efficacy, safety, and PK analyses will be prepared and approved by the Sponsor or its designees prior to study database lock. The PK modeling will be included in a separate clinical pharmacology analysis plan (CPAP).

Analysis Populations:

Intent-to-Treat (ITT) Population

The ITT Population will include all randomized subjects. The treatment assignment will be based on randomized treatment. The ITT Population will be the primary population used for all efficacy analyses and PD analyses.

Modified ITT (mITT) Population

The mITT Population will include all subjects from the ITT Population who took at least one dose of investigational product (OCA or placebo) and who received treatment for at least 4 months. The mITT population will serve as a secondary analysis population for the efficacy and PD analyses.

Pharmacokinetic Population

The PK Population will consist of all subjects who receive OCA, have at least one confirmed analyzable sample, and have no major protocol deviations that may potentially affect the PK analysis.

Safety Population

The Safety Population will include all subjects who receive at least one dose of investigational product (OCA or placebo). Treatment assignment will be based on the actual treatment that is received.

Primary Efficacy Analysis

The primary efficacy analysis is time to first occurrence of any component of the composite clinical endpoint. The 2 treatment groups will be compared using the log-rank test stratified by age group using median as the cutoff value. A Cox regression model, including the treatment group and the age group, will be used to estimate the hazard ratio, along with a 95% confidence interval (CI). Kaplan-Meier estimates of the distribution of the time to event will be tabulated and presented by treatment group.

Secondary Efficacy Analyses

Responder endpoints (e.g., proportion of subjects with improvement in biomarkers, GGT, and direct bilirubin) will be analyzed by Cochran Mantel Haenszel (CMH) test, stratifying by age group.

Continuous variables (e.g., change from baseline in GGT) will be evaluated using a mixed model for repeated measures (MMRM). The model will include the terms of treatment group, visit, treatment by visit interaction, and age as factors, and the corresponding baseline value as covariates.

Exploratory Analyses

Acceptability and swallowability of a subject's dose regimen will be determined using the five-point criteria evaluation and will be summarized by the treatment group. A by-age subgroup summary will also be presented. Palatability will be assessed at the Week 6 visit using a five-point facial hedonic scale with a correlated 100-point visual analog scale (FHS/VAS-5) in children ≥4 years of age. Children <4 years will have palatability assessed using a four-point criteria evaluation.

Interim Analyses

The first interim analysis will be conducted after approximately 25 to 30 subjects reach Month 4; assessments of GGT, total and direct (conjugated) bilirubin, and total plasma bile acids will be evaluated. Responders are defined as having a ≥40% reduction from baseline in GGT and ≥25% reduction from baseline in direct bilirubin at Month 4.

Assuming a 10% and 55% response rate for the placebo and OCA groups, respectively, and a total sample size of 30, the mean (95% CI) for the treatment difference is 45% (16% to 74%). The treatment difference of at least 15% is considered to be a clinically important difference.

The study will be terminated for futility if the futility boundary of 15% is crossed (i.e., if the treatment difference falls outside of the lower bound of the 95% CI).

Safety will be evaluated by the DSMB at the time of the interim analysis. Subjects <2 years of age will be recruited into the study following advice of the DSMB after the interim analysis.

The second interim analysis will be performed based on the primary endpoint (time to first occurrence of clinical outcomes). A group sequential design and conditional power approach will be utilized. At the time of the interim analysis, the interim data will be analyzed to determine the conditional power. If the power is not acceptable, the trial will be terminated for futility.

PK/PD Analyses

Pharmacokinetic exposure parameters will be summarized for the OCA group. The PD endpoints will be analyzed to compare the treatment difference between OCA and placebo.

Further details of the planned PK analyses for all the evaluated plasma concentration data will be described in the CPAP.

Safety Analysis

Safety data will be summarized using descriptive statistics. The safety analysis will include the incidence of TEAEs. The incidence will be tabulated by system organ class (SOC) and preferred term, and similarly by severity and relationship to treatment.

Laboratory parameters, vital signs, and ECGs will be summarized using descriptive statistics at baseline and at each scheduled postbaseline visit. The change from baseline will also be summarized.

Data Oversight:

An independent DSMB will review efficacy and safety data on a regular schedule throughout the study.

The Sponsor, including the Medical Monitor, will provide ongoing monitoring of safety data.

Sample Size Justification:

The overall study sample size is estimated based on the clinical outcome composite endpoint analysis at the end of the study; time to the first occurrence of any component of the adjudicated clinical outcome (death, liver transplant, and markers of decompensated liver damage).

A total of 66 composite events will be required in the OCA and placebo groups in a 1:1 ratio, to provide about 80% power via two-sided log-rank test at the 0.05 significance level, assuming a hazard ratio of 0.50 between the OCA and placebo groups. Approximately 144 subjects for the 2 groups will be required to obtain the 66 events based on the additional assumptions:

- Total study duration of 4 years, allowing 1.5 years accrual and up to approximately 24 months of follow-up
- Placebo event rate of 52% over 1.5 years
- 20% discontinuation rate

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this protocol.

Abbreviation or Specialist Term	Explanation
6-ECDCA	6α-ethyl-chenodeoxycholic acid
ADL	activities of daily living
AE	adverse event
AED	adult equivalent dose
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
BAS	bile acid sequestrants
BASM	biliary atresia splenic malformation
BMI	body mass index
BP	blood pressure
C4	7-hydroxy-4cholesten-3-one
CDCA	chenodeoxycholic acid
CI	confidence interval
CMH	Cochran Mantel Haenszel
COVID-19	coronavirus disease 2019
CPAP	clinical pharmacology analysis plan
CPB	Child-Pugh B
CPC	Child-Pugh C
CRA	Clinical Research Associate
CRF	case report forms
CRN	Clinical Research Network
CTFG	Clinical Trial Facilitation Group
C_{trough}	pre-dose trough concentration
DB	double-blind
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EDC	electronic data capture
eCRF	Electronic Case Report Form

Abbreviation or Specialist Term	Explanation
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ET	early termination
FGF-19	fibroblast growth factor-19
FHS	facial hedonic scale
FSH	Follicle-stimulating Hormone
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GSC	general safety committee
HBV	Hepatitis B Virus
HCP	healthcare provider
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HDL	high-density lipoprotein
HPE	Hepatoportoenterostomy
HSAC	hepatic safety adjudication committee
IB	investigational brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
INR	international normalized ratio
IRB	Institutional Review Board
ISF	investigator site file
ITT	Intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LDL	low-density lipoprotein
LSM	least squares mean
LTSE	long-term safety extension

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary of Regulatory Activities
MELD	model of end-stage liver disease
mITT	Modified ITT
MMR	Mixed model for repeated measures
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OCA	obeticholic acid
PBC	primary biliary cirrhosis or primary biliary cholangitis
PBO	Placebo
PD	Pharmacodynamics
PELD	Pediatric End-Stage Liver Disease
PIS-IC	Patient Information Sheet and Consent Form
PK	Pharmacokinetics
PSC	primary sclerosing cholangitis
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plans
SAR	suspected adverse reaction
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
VAS	visual analog scale

5. INTRODUCTION

5.1. Overview of Pediatric Biliary Atresia and OCA

Biliary atresia is a progressive, idiopathic, fibro-obliterative disease of early infancy manifested by biliary obstruction due to maldevelopment of the extrahepatic biliary tree. Although the overall incidence rate is low (approximately 1 in 10,000 to 20,000 live births globally), biliary atresia is the most common cause of neonatal jaundice for which surgery is indicated and the most common indication for liver transplantation in children (Matsui 1994, Yoon 1997, McKiernan 2000, Lin 2011, Lupo 2017, Bezerra 2018).

Despite being the major form of serious pediatric liver disease in infancy and the main indication for liver transplantation in children, the etiology of biliary atresia is mostly unknown. There have been several case reports that associate the development of biliary atresia with certain developmental genes (*cfc1*, *NPHP*, *Zic3*) (Davit-Spraul 2008, Garcia-Barceló 2010, Cheng 2013, Tsai 2015, Chen 2018), several pediatric syndromes (Simpson-Golabi, Meckel-Gruber, Jeune Syndromes), as well as viral (Hart 1991, Shivakumar 2004, Caton 2004) and environmental toxic etiologies (Harper 1990, Lorent 2015). The findings of laterality and splenic malformations suggest a developmental component to biliary atresia in some, but there are a few case reports of familial biliary atresia.

The clinical presentation is similar to all forms of neonatal cholestasis with prolonged jaundice, central features of hepatomegaly, and acholic stools. The infants are typically of normal gestation and essentially grow normally for the first few weeks of life. Upon examination at 8 weeks of life, the average age when most infants with biliary atresia are diagnosed, they appear essentially normal but are jaundiced with scleral icterus. A major diagnostic concern is the overlap between the high prevalence of unconjugated hyperbilirubinemia in newborns (>25%) and the inability to clinically distinguish between physiological hyperbilirubinemia (i.e., unconjugated) and cholestasis (conjugated hyperbilirubinemia) by parents or caregivers. The growth of infants with biliary atresia is generally slower than average, and if jaundice goes unnoticed, disease progression can lead to the development of firm hepatomegaly and splenomegaly (Harpavat 2011). Interestingly, there may be prominence of the left lobe of the liver, especially in those with laterality features.

The evaluation process includes assessment of hepatic function and rule out of metabolic diseases with etiologies other than biliary atresia. The blood tests reveal a modest degree of liver injury and cholestasis – usually alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values are approximately 80 U/L to 200 U/L, total bilirubin levels are approximately 5 mg/dL to 8 mg/dL, with direct (conjugated) levels approximately 2 mg/dL to 4 mg/dL. Alkaline phosphatase (ALP) levels are approximately 500 U/L to 1000 U/L or more while gamma-glutamyl transferase (GGT), an enzyme found in both hepatocytes and cholangiocytes, determination usually reveals values >300 IU. However, blood tests alone cannot distinguish biliary atresia from other forms of cholestasis. Abdominal ultrasonography usually reveals some degree of hepatomegaly and splenomegaly, and detailed examination of the porta hepatis and gall bladder region generally reveals either an absence of the gall bladder or an inability to properly visualize a lumen. Additionally, ultrasonography is used to exclude other anatomic causes of cholestasis such as cystic dilations, either for the entire common bile duct (choledochal cyst) or at the porta hepatis. The different types (Types 1 to 3) of biliary atresia are described

according to their anatomical abnormalities in the biliary tract. Features that are highly suggestive of biliary atresia are abnormal gallbladder size and shape, the "triangular cord" sign, gallbladder contractility, absence of the common bile duct, and an enlarged hepatic hilar lymph node (Humphrey 2007, Lee 2009, Takamizawa 2007, Mittal 2011, Zhou 2016).

Liver biopsy is performed to identify histological changes consistent with obstruction, and to differentiate biliary atresia from other causes of intrahepatic cholestasis such as Alagille syndrome, periodic acid-Schiff-positive disease granules (consistent with alpha-1 antitrypsin deficiency), loss of MDR3 staining (suggestive of PDFIC3), or giant cell hepatitis without proliferation of ducts. Characteristic histologic findings include bile duct plugs, bile ductular proliferation, portal tract edema, inflammation, and expansion—all hallmarks of distal bile duct obstruction. In addition, a proportion of patients clearly have developmental defects in bile duct morphogenesis, identified by ductal plate malformations (concentric sleeves of ductular profiles) along with extrahepatic duct dysgenesis (Azar 2002).

Once biliary atresia is confirmed by intraoperative cholangiogram, the Kasai hepatoportoenterostomy (HPE, also known as Kasai portoenterosomy) should be performed, as a timely diagnosis is important to optimize the response to this procedure aimed at re-establishing bile flow. Before the introduction of the HPE procedure, in the absence of a liver transplant, infants with biliary atresia died by age 2 to 3 years (Shneider 2007). If HPE is performed within the first 45 days of life, the procedure is associated with a 65.5% survival with native liver at 2 years of age (60% to 80% restoration of bile flow) and 40.5% at 15 years. If HPE is performed after 90 days of life, <25% of patients will have bile flow. Three months after HPE, there is a clear difference in 2-year transplant-free survival between children with total serum bilirubin <2mg/dL and those with total bilirubin >6 mg/dL (84% versus 16%; $p<0.001$) (Shneider 2006, Bezerra 2018).

In centers with much experience treating this disorder, up to 60% of children will achieve biliary drainage after Kasai HPE and will have serum bilirubin within the normal range within 6 months. About 80% of children who attain satisfactory biliary drainage will reach adolescence without undergoing liver transplantation (Hartley 2009). However, even in patients who exhibit a good response to the surgical HPE procedure, development of a progressive fibrotic disease over the ensuing years is inevitable. Thus, prevention of the progressive liver injury and fibrosis that occur even after successful HPE remains a major challenge (Bezerra 2018).

Children with poor bile drainage following HPE will uniformly develop significant malabsorption, growth failure, and developmental delay and require liver transplantation by 2 years of age (DeRusso 2007).

In France, if every patient with biliary atresia underwent the Kasai operation before 46 days of age, an estimated 5.7% of all liver transplantations performed annually in patients younger than 16 years old could be avoided, highlighting the importance of early detection of cholestasis.

Biliary tract occlusion with biliary atresia causes a rise in endogenous hepatocellular bile acids to cytotoxic levels, causing inflammatory damage, an increase in hepatocellular enzymes and apoptosis, which, over time, results in hepatic fibrosis and cirrhosis. Under non-cholestatic conditions, bile acid synthesis and excretion are tightly regulated processes. This regulation is essential since bile acids are natural detergents and can inflict significant cellular damage with sustained elevations in concentration. An essential regulator of bile acid homeostasis is the

farnesoid X receptor (FXR), which is a nuclear receptor expressed in multiple tissues, including the liver and intestine. FXR is activated by endogenous bile acids and regulates key response elements in both synthesis and release of bile acids by the liver. Cholestatic conditions, which impair delivery of bile acids to the intestine, greatly diminish the activation of intestinal FXR and, consequently, bile acid synthesis is no longer properly regulated, leading to sustained elevations in hepatic bile acids. Of particular interest is the possible role of fibroblast growth factor-19 (FGF-19), a circulating protein induced by bile acid activated FXR. Under normal circumstances, FGF-19 expressed in small intestine and gallbladder is an important intestinal negative feedback regulation to maintain bile acid homeostasis (Inagaki 2005, Song 2009, Angelin 2012). In human cholestasis conditions, FGF-19 expression is upregulated in the liver, and circulating FGF-19 levels are elevated to suppress bile acid synthesis (Schaap 2009, Wunsch 2015).

In a study in infants with biliary atresia undergoing HPE, circulating FGF-19 levels were elevated before HPE and correlated to hepatic gene expression. Following HPE, FGF-19 levels declined, coinciding with reduction in bilirubin and conjugated chenodeoxycholic acid (CDCA) and increased levels of bile acid synthesis marker 7-hydroxy-4-cholesten-3-one (C4) (Johansson 2020). Established bile flow after HPE may have led to decreased levels of intrahepatic bile acids. Consequently, the hepatic protective over-expression of FGF-19 was decreased, assuming the accumulation of bile acids in the cholestatic liver was the reason for upregulation of hepatic FGF-19 as a counterregulatory protective response (Johansson 2020).

In support of this concept, FXR activation in post (HPE) biliary atresia patients can serve as a rescue mechanism by targeting multiple aspects of bile acid homeostasis reducing toxic bile acid concentrations in hepatocytes and exerting its anti-apoptotic effects. As such, agonism of FXR represents an appealing therapeutic target for cholestasis.

CDCA is the most abundant endogenous bile acid and is the natural ligand of FXR. Understanding of the FXR binding conformation of CDCA and other bile acids led to the development of 6α-ethyl-chenodeoxycholic acid (6-ECDCA) or obeticholic acid (OCA), also formerly known as INT-747, a modified bile acid and FXR agonist with approximately 100x more potent FXR activation than CDCA (Pellicciari 2002). OCA is derived from CDCA, the natural human FXR ligand, and is also structurally similar to ursodeoxycholic acid (UDCA). However, UDCA has no significant FXR agonist properties (Pellicciari 2002).

Aside from HPE, there are no approved treatments for biliary atresia, although several medications are used based on local standards and with varying and sometimes contradictory results, as reported in the literature (Davenport 2007, Shneider 2006). These medications include UDCA, steroids, and antibiotics used to enhance choleresis, dampen bile duct inflammation (steroids), and treat or prevent cholangitis (antibiotics) resulting from cholestasis. There are few well-controlled studies of UDCA treatment in biliary atresia. One such study (Willot 2008), albeit small (N=16), describes sustained (>1 year) beneficial effects of UDCA therapy (mean dose of 25 mg/kg) in patients who have undergone a successful HPE procedure. Stopping treatment in these patients resulted in a deterioration of liver enzyme tests with subsequent improvement after restarting treatment. Moreover, no serious or harmful side effects were observed in this study or other studies evaluating UDCA in pediatric populations (Willot 2008, Al-Hathlol 2006). However, because UDCA lacks FXR activity, the use of an FXR agonist, such as OCA in the treatment of biliary atresia may be beneficial.

OCA has exhibited anti-cholestatic and hepatoprotective properties in in vitro and in vivo studies. Based on the pathologic mechanisms leading to cholestasis and fibrosis in chronic liver diseases, it is hypothesized that treatment with OCA will improve liver function and may be a potential therapeutic option for biliary atresia.

5.2. Mechanism of Action of OCA

Obeticholic acid has been shown to have choleretic effects and increase bile flow in cholestatic conditions. Obeticholic acid is believed to protect hepatocytes from toxic concentrations of endogenous bile acids and improve bile acid secretion from the hepatocytes by modulating the complex signal cascades involved in bile acid transport (Sanyal 2009, Marschall 2010).

OCA likely exerts its pharmacological effects by 2 routes:

- Intrinsic effects of a bile acid; however, these are likely relatively minor given the low concentration of OCA in humans.
- Potent FXR agonism that is an additive and/or synergistic, therapeutic benefit when added to UDCA. This effect is assumed to be the predominant driver for efficacy.

The key mechanisms of action of OCA are choleretic, anti-inflammatory, and antifibrotic properties as well as hepatoprotective effects, resulting in expected attenuation of injury and improved liver function in a cholestatic liver disease such as biliary atresia (Feldman 2020).

5.3. Nonclinical Experience with OCA

The hepatoprotective effects of OCA have been tested in in vivo rodent studies revealing the tolerability and dose-response characteristics of OCA, the ability of OCA to be absorbed and activate FXR in the liver, and the effectiveness of OCA as an anti-cholestatic and antifibrotic agent. The results indicate that OCA is effective in preventing or reducing cholestasis in rodents. Also, OCA significantly reduces fibrotic collagen synthesis in rodent models of chronic liver injury involving fibrosis and eventual cirrhosis. OCA administration in vivo not only prevents but also reverses liver fibrosis; in addition, in a thioacetamide (TAA) model, OCA reversed portal hypertension together with cirrhosis (Verbeke 2014, Verbeke 2016).

The nonclinical toxicology of OCA has been evaluated in a series of single-dose and repeat-dose general toxicity studies in mice, rats, and dogs as well as in a battery of genotoxicity studies, and juvenile, reproductive, and developmental studies in rats and rabbits. These studies examined administration of OCA as single doses and with daily dosing for up to 3, 6, and 9 months to mice, rats, and dogs, respectively. The target organs for OCA toxicity are the hepatobiliary system and gastrointestinal (GI) tract. Findings related to the liver and/or bile duct were observed in serum chemistries, organ weights, and macroscopic/microscopic evaluations in mice, rats, and dogs. Gastrointestinal effects included minimal to mild subacute inflammation in rats only. The toxicology findings with OCA are consistent with tissue (primarily hepatic) exposure to bile acids at high concentrations. Hepatobiliary toxicity seen in animals is similar to the hepatobiliary toxicity observed in humans at high doses and, therefore, the toxicology studies adequately reflect the dose-limiting toxicity of OCA and its conjugates.

Obeticholic acid was tested for carcinogenic potential in 2-year studies using rats and mice. Obeticholic acid was not carcinogenic at doses of up to 20 mg/kg/day and 25 mg/kg/day in rats

and mice, respectively. These results are consistent with the lack of genotoxicity for OCA and its conjugates in in vivo and in vitro tests.

Toxicity of OCA was evaluated in juvenile rats (PND 4 through PND 56), with dosing covering the period equivalent to a premature newborn baby through childhood, adolescence, and early adulthood. The target organs of toxicity in the juvenile study were the same as those in adults, namely the liver and bile duct. There was no increased sensitivity in juvenile animals for these target organs, and no new target organs were identified. Increased toxicity at a given dose was attributed to higher systemic exposure in the pre-weaning period and not to increased risk in juvenile animals.

Additional findings from nonclinical evaluations of OCA can be found in the current Investigator's Brochure (IB).

5.4. Clinical Experience with Obeticholic Acid

The safety and efficacy of OCA has been evaluated in healthy volunteers and multiple chronic liver diseases including those with cholestatic (primary biliary cholangitis [PBC], primary sclerosing cholangitis [PSC], and biliary atresia) and non-cholestatic (nonalcoholic fatty liver disease [NAFLD] with type 2 diabetes, nonalcoholic steatohepatitis [NASH], and portal hypertension due to alcohol cirrhosis) etiology. As of 26 May 2023, the majority of long-term OCA experience has been in subjects with NASH. Approximately 4616 subjects have received ≥1 dose of OCA.

Overall, the pharmacokinetic (PK) profile of OCA is consistent with that expected of a bile acid. Phase 1 studies demonstrated that OCA is rapidly absorbed and extensively conjugated with glycine and taurine to form glyco-OCA and tauro-OCA, respectively. OCA and its conjugates are primarily eliminated via biliary excretion, and plasma concentration time profiles demonstrated multiple peaking with prolonged exposure, indicative of enterohepatic circulation. Plasma concentrations of OCA and its conjugates spike shortly after meals, consistent with gall bladder emptying into the duodenum as expected of bile acid.

To date, the efficacy and safety of OCA in PBC has been evaluated in 2 placebo-controlled, double-blind (DB), Phase 2 studies (747-201 and 747-202), 1 placebo-controlled, DB, Phase 3 study (747-301), and 1 placebo-controlled, DB, Phase 3b/4 study (747-302). Following the DB phase, subjects in 3 of the studies were eligible to continue with treatment in a long-term safety extension (LTSE) phase for up to 5 years in Study 747-201, up to 1 year in Study 747-202, and up to 5 years in Study 747-301. Study 747-302 was a post-marketing study in PBC.

- Study 747-201 (59 subjects) evaluated 2 doses of OCA (10 and 50 mg) given as monotherapy versus placebo. Statistically significant and clinically relevant relative and absolute reductions from baseline in ALP were achieved with both doses of OCA versus placebo ($p<0.0001$). Mean relative ALP reductions were 44.5% (OCA 10 mg) and 37.6% (OCA 50 mg) compared to an increase of 0.4% with placebo. Further, significant improvements in GGT and in conjugated bilirubin were observed with both doses compared with placebo ($p<0.05$). OCA also resulted in decreased circulating ALT and AST levels.
- Study 747-202 (165 subjects) evaluated 3 doses of OCA (10, 25, and 50 mg) versus placebo in subjects on a stable therapeutic dose of UDCA. Overall, the data from

Study 747-202 were consistent with Study 747-201. Statistically significant and clinically meaningful relative and absolute reductions in ALP were achieved with all 3 doses of OCA versus placebo ($p<0.0001$). Mean ALP reductions from baseline ranged from 21% to 25% compared to 3% with placebo. Improvements were also seen in GGT and ALT levels and in conjugated bilirubin levels.

- Study 747-301 (216 subjects) was a Phase 3, DB, placebo-controlled, parallel group study followed by an LTSE phase using OCA in subjects with PBC. The primary endpoint for Study 747-301 was a composite endpoint based on the proportion of subjects reaching specific criteria for ALP and bilirubin (ALP <1.67x upper limit of normal [ULN] with a ≥15% reduction and bilirubin ≤ULN). Both OCA treatment groups met the primary endpoint of achieving a reduction in ALP to <1.67x ULN with a ≥15% reduction from baseline and a normal bilirubin level after 12 months of therapy. The placebo group experienced a mean decrease in ALP from baseline of 5%, compared to a significant mean decrease of 39% in the 10 mg OCA dose group and 33% in the OCA titration group (both OCA dose groups $p<0.0001$ versus placebo).
- Study 747-302 was a post-marketing requirement (PMR) study designed to confirm the clinical benefit of OCA treatment in subjects with PBC. The study was discontinued early due to subject recruiting challenges as OCA became commercially available during the study. This resulted in an underpowered study with significant crossover of subjects receiving placebo with active therapy. No treatment difference was seen between the placebo group and OCA for the primary composite endpoint.

The LTSE phases of both Phase 2 studies, Phase 3 study, and the Phase 3b/4 study are completed and demonstrate the long-term safety and durable therapeutic response of OCA.

Based on the updated company core data sheet [CCDS], which contraindicates OCA in patients with PBC with decompensated cirrhosis or a prior decompensation event, portal hypertension, or complete biliary obstruction, 1 post-marketing study in PBC was closed (Study 747-401).

- Study 747-401 was evaluating the PK and safety of OCA treatment in subjects with moderate to severe hepatic impairment defined as Child-Pugh B (CPB) (moderate) and Child-Pugh C (CPC) (severe)

Obeticholic acid was also evaluated in other indications including NASH.

Refer to the latest version of the Ocaliva® Summary of Product Characteristics (SmPC) for additional information regarding OCA safety.

5.5. Rationale for Study Design and Dose for Investigational Product

5.5.1. Rationale for Study Design

This study will utilize a placebo control to examine the effect of obeticholic acid on the clinical course of biliary atresia. Obeticholic acid will be titrated while PK parameters are measured. The effect of obeticholic acid on the progression of biliary atresia to require liver transplant or death will be estimated. Additional clinical outcomes will include the effect of treatment on

noninvasive measures of fibrosis as well as on key biomarkers of liver disease to include GGT, bilirubin, and bile acids.

5.5.2. Rationale for Obeticholic Acid Dose and Duration

Obeticholic acid doses for this study in children are based on PK measurements from adults and a modified, physiologic, PK model that incorporates body weight as a covariate to ensure exposures of obeticholic acid are equivalent to the 5-mg adult efficacious dose. Thus, doses are referred to as adult equivalent dose (AED) on a mg/kg basis. Doses will begin at levels achieved when adults are given 1.5 mg and will be titrated every 2 weeks based on safety and tolerability through a 3-mg AED before arriving at the 5-mg AED or the highest tolerated dose at Week 6. Treatment will then continue at the highest tolerable dose for at least 24 months.

5.5.3. Rationale for Placebo Control Group

The use of a randomized placebo control group added to established standard-of-care provides the best scientific evidence of efficacy and safety. The use of a placebo control provides a concurrent comparator group, accounting for not only a placebo effect but a standard-of-care effect. As there is no approved or proven pharmacologic therapy for disease state, using a placebo for comparative purposes is justified.

5.6. Summary of Known Potential Risks with Investigational Product

The primary adverse event (AE) shown to be related to OCA is pruritus. Pruritus has also been observed in clinical studies with OCA in other indications as well as in healthy subjects, with the highest frequency observed in subjects with PBC. There is no link established between pruritus severity and liver injury or progression of liver disease (dysfunction).

Recent safety findings in studies in adults with NASH clinical trials include 6 cases of hepatic decompensation reported as suspected unexpected serious adverse reactions (SUSARs), 1 of which resulted in death. The signs of hepatic decompensation included death due to a hepatic event; model of end-stage liver disease (MELD) score ≥15; liver transplant; ascites; or a serious adverse event (SAE) of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis.

Changes in lipid profiles have also been observed with OCA dosing in adult subjects with NASH and PBC, leading to an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. Based on the evaluation of the interim analysis results from the REGENERATE study, the cardiovascular signal was refuted for OCA in adult subjects with NASH. Studies demonstrate contradictory findings related to the effect of OCA on mean HDL cholesterol and LDL cholesterol. Both stability and a reduction in mean HDL cholesterol have been seen as well as stability and an increase in LDL cholesterol in adult subjects with PBC treated with OCA.

In adults with PBC, OCA is contraindicated in decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event, compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia), and complete biliary obstruction.

OCA has previously been dosed in 8 pediatric subjects in Study 747-206. The average exposure was approximately 7 months (range: 0-26 months). Overall, the most common AEs were nasopharyngitis (common cold symptoms) and headache, with 3 SAEs reported. While no conclusions can be drawn given the limited sample size, the adverse events reported were not dissimilar to those that would be expected in this population.

Refer to the current OCA Investigator's Brochure (Version 22, August 31, 2023) for additional information regarding the known potential risks with the investigational product.

6. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objectives

To evaluate the effect of OCA compared to placebo in conjunction with established local standard of care on clinical outcomes in subjects with biliary atresia who have had a successful Kasai procedure as measured by time to first occurrence of any of the following adjudicated events, derived as composite event endpoints:

- Death (all-cause)
- Liver transplant
- Pediatric end-stage liver disease (PELD) ≥17/MELD ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Clinically evident ascites related to portal hypertension (diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

6.2. Secondary Objectives

To evaluate the:

- PK of OCA as measured by unconjugated plasma OCA (parent), glyco-OCA, tauro-OCA, and total OCA (molar sum of OCA and its active conjugates).
- Pharmacodynamics (PD) of OCA as measured by biomarkers of FXR activation: FGF-19, C4, and endogenous bile acids, and
- Biomarkers of hepatobiliary function: GGT, total and direct (conjugated) bilirubin
- Effect of OCA on liver stiffness by transient elastography (if available at site)
- Disease progression as measured by plasma levels of fat-soluble vitamins (Vitamins D and K)
- Safety and tolerability of OCA

6.3. Exploratory Objectives

- To evaluate the acceptability and swallowability of the dosing regimen
- To evaluate the palatability of the dosing regimen

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a global, multicenter, DB, placebo-controlled Phase 2/3 study to evaluate the efficacy, safety, and tolerability as well as PK/PD of OCA in eligible pediatric subjects with biliary atresia with successful HPE (also known as a Kasai portoenterostomy).

Screening Phase: The Screening Visit assessments must be performed within 14 days before Day 1 to determine the eligibility for enrollment and allow for the analysis and reporting of the Screening hematology, serum chemistry, and urinalysis results. Subjects must be able to swallow the placebo tablets to be included in the study. Thus, subjects will receive placebo tablet(s) at the Screening Visit to evaluate acceptability and the ability to swallow. The number of placebo tablets will be determined based on the OCA 5-mg AED using individual subject weight. The study will initially enroll pediatric subjects aged 2 to <18 years to be randomized to receive OCA or placebo in a DB manner.

Double-Blind Phase

Dose Titration Phase: Subjects who satisfy the inclusion and exclusion criteria of the study will be randomized to receive placebo or OCA (starting at 1.5 mg AED) in a 1:1 ratio. Investigational product (OCA or placebo) will be taken orally, with water, once daily.

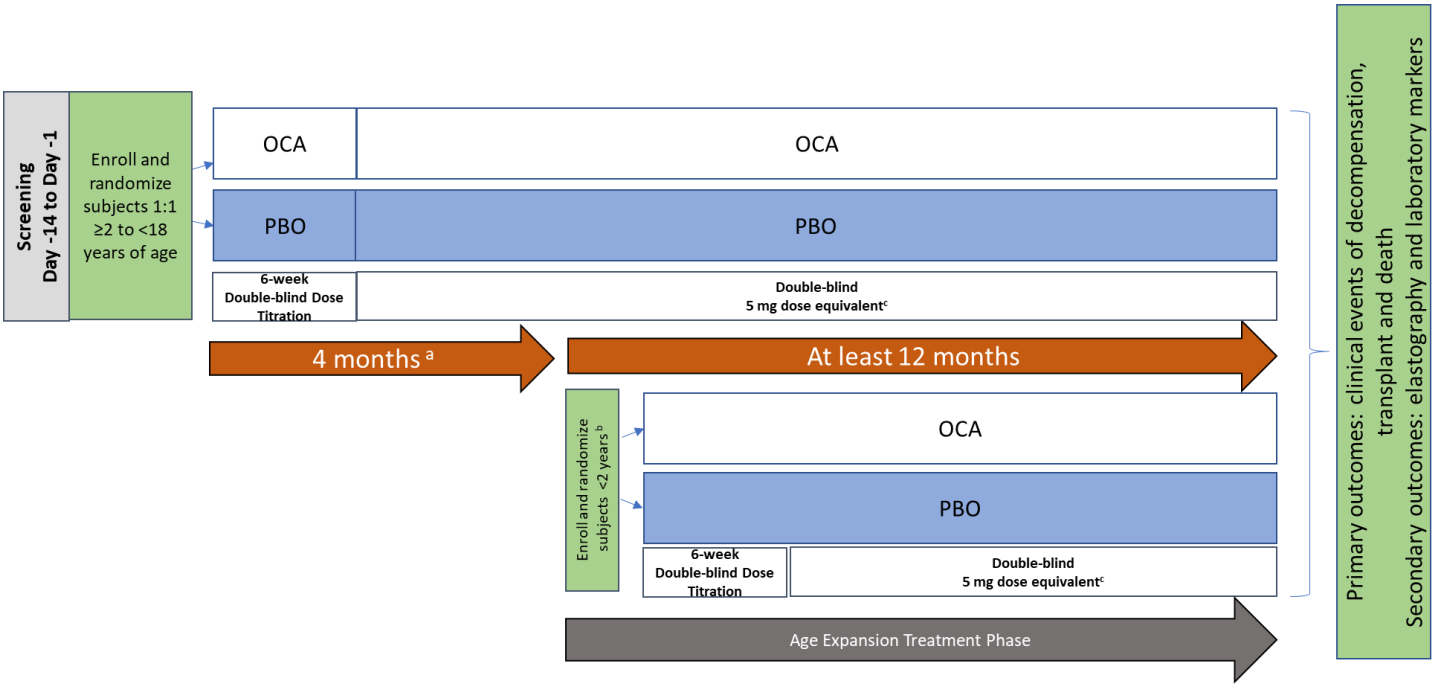
Doses of investigational product (i.e., OCA or placebo) will be titrated every 2 weeks in a stepwise manner for the first 6 weeks, starting at 1.5 mg AED and titrating through 3 mg AED to a maximum of 5 mg AED, as tolerated (refer to Section 7.2); a discussion with the Medical Monitor is encouraged when determining uptitration, if considerable signs or symptoms have arisen. Key PK parameters will be measured predose at Weeks 2, 4, and 6 (C_{trough}) (Section 11.1). Subjects who do not tolerate higher OCA doses may revert to their previous lower dose for the remainder of the study after discussion with the Medical Monitor.

Age Expansion Treatment Phase: Following the 6-week dose titration phase, subjects will continue at the tolerated dose. Blood samples will be collected predose at Weeks 10, 18, 30, end of treatment (EOT), and end of study (EOS)/early termination (ET) for PK characterization. The duration of dosing is expected to be approximately 24 months.

The first interim analysis will be conducted after approximately 25 to 30 subjects reach Month 4; assessments of GGT, total and direct (conjugated) bilirubin, and total plasma bile acids will be evaluated. An unblinded Data Safety Monitoring Board (DSMB) will assess these results, along with overall safety of the drug, and will advise on: 1) any safety concerns that would prohibit inclusion of subjects <2 years of age into the study, and 2) evidence of failure to sufficiently impact biomarkers, which would indicate futility of the study.

The timing of the second interim analysis will be at approximately 12 months and will be confirmed by the DSMB following the first interim analysis. The DSMB will continue to oversee the data throughout the study.

Figure 1: Study Design Schematic



AED=adult equivalent dose; DSMB=Data Safety Monitoring Board; OCA=obeticholic acid; PBO=placebo
Note: n=approximately 144 subjects
[a] Following the 6-week dose titration phase, subjects will continue on the tolerated dose for 12 months, inclusive of the titration phase. An interim analysis of safety and biochemical markers to determine potential study futility will be completed after approximately 25 to 30 subjects have been enrolled in the study for 4 months. The DSMB will be consulted for timing of a second interim analysis.
[b] Subjects aged <2 years will be enrolled only if supported by safety and efficacy data from the interim analysis.
[c] Subjects may be maintained at a lower, maximum, tolerated dose than OCA 5 mg AED, as deemed necessary.

7.1.1. Schedule of Study Procedures

The Schedule of Study Procedures is provided in Table 1.

Table 1: Schedule of Study Procedures

		Double-blind, Placebo-controlled Period																
	Screening[m]	Randomization	Dose Titration			Treatment												
Study Visit (Week)[a]	**-2 to -1**	**0**	**2**	**4**	**6**	**10**	**14**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**64/ EOT**	**EOS / ET[b]**	**Unscheduled Visit**
Study Visit (Day)	**-14 to -1**	**1**	**14**	**28**	**42**	**70**	**98**	**126**	**168**	**210**	**252**	**294**	**336**	**378**	**420**	**448**		
Visit Window (Days)		**0**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Informed Consent	X																	
Demographics (Race and Ethnicity)	X																	
Medical and Disease History	X	X																
Inclusion/Exclusion	X	X																
Randomization		X																
Physical Examination	X	X								X						X	X	X
Height	X	X								X							X	
Z-Score	X	X			X		X		X		X		X		X		X	
Triceps Skinfold Thickness and Mid-arm Circumference Measurement	X			X		X		X		X		X		X		X		
Vital Signs and body weight[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X	X								X								

		Double-blind, Placebo-controlled Period																
	Screening[m]	**Randomization**	**Dose Titration**			**Treatment**												
Study Visit (Week)[a]	**-2 to -1**	**0**	**2**	**4**	**6**	**10**	**14**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**64/ EOT**	**EOS / ET[b]**	**Unscheduled Visit**
Study Visit (Day)	**-14 to -1**	**1**	**14**	**28**	**42**	**70**	**98**	**126**	**168**	**210**	**252**	**294**	**336**	**378**	**420**	**448**		
Visit Window (Days)		**0**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Adverse Events[d]	X	X	X															
Prior and Concomitant Medications	X	X	X															
APRI	X	X								X								
Child-Pugh Score	X	X	X	X	X	X	X			X	X	X				X	X	
PELD/MELD[e]	X	X	X	X	X	X	X			X	X	X				X	X	
FIB4 score	X	X	X	X	X	X	X	X	X	X	X	X				X	X	
Ultrasound elastography of liver stiffness[f]		X						X			X			X		X	X	X
Ultrasound liver doppler[f]	X																	
PD (FGF-19, C4, Bile Acids) – predose[g]		X	X	X	X	X		X		X						X	X	
OCA PK Blood Samples – predose[h]			X	X	X	X		X		X						X	X	X
Chemistry, Hematology, Coagulation, lipoprotein and cholesterol analysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitamins D and K	X	X	X	X			X				X		X				X	

		Double-blind, Placebo-controlled Period																
	Screening[m]	**Randomization**	**Dose Titration**			**Treatment**												
Study Visit (Week)[a]	**-2 to -1**	**0**	**2**	**4**	**6**	**10**	**14**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**64/ EOT**	**EOS / ET[b]**	**Unscheduled Visit**
Study Visit (Day)	**-14 to -1**	**1**	**14**	**28**	**42**	**70**	**98**	**126**	**168**	**210**	**252**	**294**	**336**	**378**	**420**	**448**		
Visit Window (Days)		**0**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Thyroid function tests (T3, T4, and TSH)	X									X						X	X	
Virology (HIV/HCV/HBV)	X																	
SARs-CoV-2 Test as per Standard Site Operation Procedures	X	X																
Urine Drug Screen (amphetamines, barbiturates, benzodiazepines, phencyclidine, Cannabinoids, cocaine, and opiates)	X	X	X															
Urine Alcohol Test	X	X	X															
Urinalysis	X	X				X		X	X	X							X	X
Urine Pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quantitative Serum Pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Follicle-stimulating Hormone Test	X	X																
Investigational Product Acceptability/Swallowability Evaluation[j]	X																	

		Double-blind, Placebo-controlled Period																
	Screening[m]	**Randomization**	**Dose Titration**			**Treatment**												
Study Visit (Week)[a]	**-2 to -1**	**0**	**2**	**4**	**6**	**10**	**14**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**64/ EOT**	**EOS / ET[b]**	**Unscheduled Visit**
Study Visit (Day)	**-14 to -1**	**1**	**14**	**28**	**42**	**70**	**98**	**126**	**168**	**210**	**252**	**294**	**336**	**378**	**420**	**448**		
Visit Window (Days)		**0**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Investigational Product Palatability Evaluation					X													
Investigational Product Dispensing[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Investigational Product Accountability & Compliance[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		

AE=adverse event; APRI=aspartate aminotransferase to platelet ratio index; C4=7-hydroxy-4-cholesten-3-one; EOS=end of study; EOT=end of treatment; ET=early termination; FGF-19=fibroblast growth factor-19; FIB4=fibrosis 4; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IP=investigational product; IWRS=interactive web response system; MELD=model of end-stage liver disease; OCA=obeticholic acid; PELD=pediatric end-stage liver disease; PK=pharmacokinetics; PD=pharmacodynamics; SARs-CoV-2=severe acute respiratory syndrome coronavirus 2; TSH=thyroid-stimulating hormone

[a] All subjects will be contacted on a weekly basis during the intervals between clinic visits. Weekly safety calls will occur from Day 14.

[b] Subjects who terminate their participation early should have ET procedures performed as soon as possible following the decision to terminate and as close as possible to taking their last dose of OCA.

[c] Vital signs will be assessed immediately prior to collecting any blood samples.

[d] AEs will be collected from the time the signed informed consent is obtained.

[e] The PELD assessment is used in subjects <12 years of age and the MELD for pediatric subjects ≥12 years of age or older

[f] Ultrasound elastography of liver stiffness (e.g., FibroScan) and/or ultrasound liver doppler will be conducted at all study sites where available.

[g] Blood will be collected for FGF-19, C4, and endogenous bile acids. The PD schedule for subjects aged <2 years will be determined after interim analysis.

[h] Refer to Section 11.1 for PK schedule. The PK schedule for subjects aged <2 years will be determined after interim analysis. PK will be drawn at predose for the scheduled visits, after an overnight fast, for unscheduled visits, and as soon as feasible, preferably, within 7 days of an SAE.

[I] A urine pregnancy test will be conducted for females of childbearing potential. A quantitative serum pregnancy test will be conducted if the urine test is positive.

[j] At Screening Visit, subjects will be administered placebo tablets to evaluate acceptability and the ability to swallow prior to administering investigational product on Day 1.

[k] IWRS will be accessed on Day 1 to assign subjects to OCA or placebo groups and dispense investigational product. Investigational product will be dispensed to subjects on onsite clinic visits for onsite administration and to take home.

[l] Investigational product accountability and compliance assessment includes review of dosing diary. Dosing diary will be provided to the subject/parent/guardian on Day 1 Visit to document the dose taken daily and will be reviewed at all onsite clinic visits.

[m] During Screening, measure triceps skinfold thickness and mid-arm circumference using a Lange skinfold caliper for evaluation of nutritional status.

7.1.2. Study Duration

The total expected duration for each individual subject will be at least 24 months, including a screening period of 14 days, and at least 16 months of treatment. The total duration of the study (first subject consented to last subject completing the last study visit of the double-blind phase) will be approximately 4 years.

7.2. Number of Subjects

It is planned that approximately 144 male and female pediatric subjects with biliary atresia will be enrolled and randomized in a 1:1 ratio to OCA or matching placebo, to achieve approximately 66 evaluable, composite, primary endpoint events to fulfill the study objectives.

7.3. Treatment Assignment

Subjects aged 2 to < 18 years will be randomized in a 1:1 ratio to receive OCA (starting at 1.5-mg AED) or matching placebo. Additionally, subjects aged <2 years old may be considered for enrollment after the DSMB advises that there is sufficient safety data to enroll this age group. Tolerability will be assessed by the lack of a sign or symptom that will affect compliance or increase the risk of an adverse event. After investigational product is administered to the subject, if there are no signs or symptoms evident that are likely to affect the subject's overall health or quality of life in a clinically meaningful way (tolerated), then doses of the investigational product will be titrated every 2 weeks in a stepwise manner for 6 weeks according to the following sequence:

- 1.5-mg OCA AED or placebo tablet(s) for 2 weeks; if this dose is tolerated,
- Escalate dose to 3-mg OCA AED or placebo tablet(s) for 2 weeks; if this dose is tolerated,
- Escalate dose to 5-mg OCA AED or placebo tablet(s) for 2 weeks.

If the 5-mg OCA AED or placebo dose is tolerated for 2 weeks, the subject will be maintained on the 5-mg OCA AED or placebo for a total treatment duration of 24 months at the 5-mg OCA AED level.

7.4. Dose Adjustment Criteria

Refer to Section 7.1.

7.5. Stopping Criteria

At any point during the study, the occurrence of a single, definitely, investigational product-related SAE or 2 possibly or probably related SAEs will result in the suspension of the dosing of new subjects, pending a full assessment of the event(s) by the Principal Investigator and the Medical Monitor. If the nature, severity, and expectedness of the event(s), in the context of the dose and the subject's health status, exceed the threshold of reasonable concern defined by the aggregate safety experience and the reference safety information (RSI), the suspension will be upheld and reported to the European Medicines Agency (EMA)/local regulatory agency after review by the general safety committee (GSC). The study may be subsequently resumed

following submission to and acceptance of a substantial amendment by the EMA/local regulatory agency. If the event(s) does not exceed the threshold of concern, the discussion and decision will be recorded, and dosing may be resumed per protocol.

Furthermore, 2 analyses will be performed prior to the final analysis at study completion to monitor ongoing safety against the changes in primary and secondary outcomes. These analyses will be defined further in the statistical analytic plan and will be evaluated by the DSMB to determine the potential impact on study conduct.

7.6. Monitoring and Management of Potential Hepatic Injury and/or Disease Progression

Given the chronic nature of biliary atresia, it is important to monitor for potential hepatic injury, disease progression, and/or hepatic decompensation. AEs, signs and symptoms of potential hepatic injury or decompensation, will be reviewed with weekly calls.

Safety laboratory assessments will also be performed at each study visit (Section 7.1.1).

Based on the assessments of signs and symptoms of hepatic injury and liver biochemistry by the hepatic safety adjudication committee (HSAC), the investigational product may be interrupted, dose adjusted, or discontinued per criteria discussed in Section 7.6.2 and Section 7.6.4, and close monitoring procedures will be implemented (Section 7.8).

7.6.1. Signs and Symptoms of Hepatic Injury or Decompensation

Subjects and their parents/guardians should be instructed to contact study personnel if they notice any of the following signs and symptoms or have healthcare interactions outside of the study setting.

Signs and Symptoms of Hepatic Injury or Decompensation:

- Specific signs and symptoms of liver impairment: yellowing of the skin or the whites of eyes, pale-colored stools, urine color change from pale to deep amber [dark] (reflecting impaired bilirubin metabolism).
- More general signs and symptoms of ascites and encephalopathy: confusion, swelling of the legs or abdomen.
- Significant intercurrent illnesses such as (but not limited to) gastroenteritis, cholangitis with symptoms such as abdominal pain, vomiting, and persistent diarrhea >48 hours or resulting in volume depletion/ dehydration, weight loss, worsening or new fatigue, weakness, loss of appetite, fever and chills or other non-specific signs and symptoms of impaired health should be an indication for prompt investigational product interruption until the event is resolved and a complete subject evaluation to confirm cholangitis.

Other Symptoms:

- New onset or worsening pruritus
- Worsening of renal function (e.g., decreased urine output, urine color change, dizziness, lethargy) or likely dehydration

Healthcare Provider (HCP) Interactions:

- Visits to primary HCP or referral to any specialist for any new symptoms (other than ongoing care for stable comorbidities)
- New medications or changes to current medications prescribed from HCP or any new over the counter medications or herbal supplements
- Laboratory procedures or assessments performed by an HCP

Signs and symptoms for potential hepatic injury or decompensation should be followed by

1. Evaluation of liver biochemistry for suspected drug-induced liver injury (DILI) or potential hepatic decompensation (Section 7.6.2)
2. Assessment of clinical events for potential hepatic decompensation (Section 7.6.4)
3. Triggering of investigational product interruption or discontinuation per criteria (Section 7.7)
4. Documentation in the AE electronic case report form (eCRF) or the SAE eCRFs (Section 13.1.4.1) and (Section 13.1.4.2); and
5. Contact with the Medical Monitor.

7.6.2. Liver Biochemistry Assessments for Suspected Hepatic Injury or Potential Hepatic Decompensation

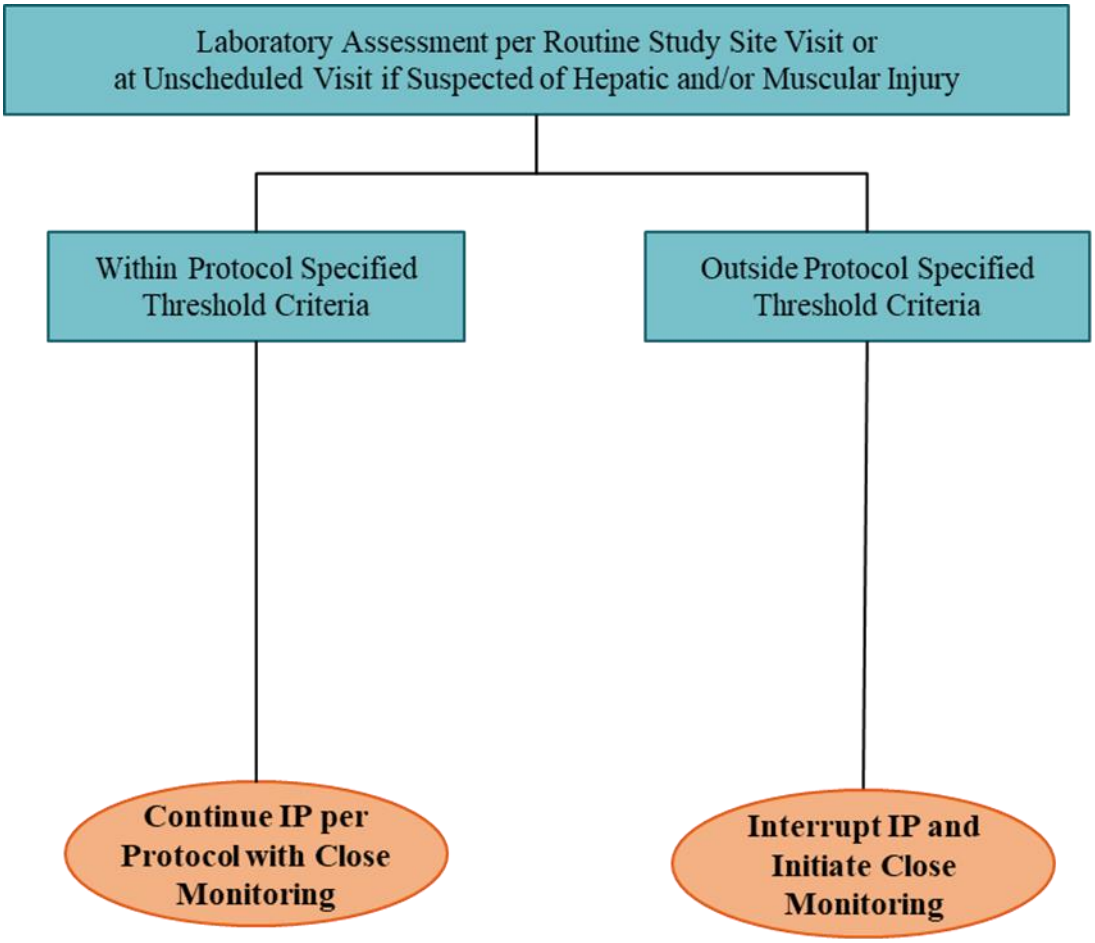
Liver biochemistries will be assessed to evaluate biochemical triggers that will prompt an immediate reevaluation of subjects for potential hepatic injury or hepatic decompensation. These assessments will be performed at:

- Each protocol-specified visit (Section 7.1.1)
- Unscheduled visits as needed in the event of signs or symptoms of potential hepatic injury or decompensation or if laboratory alerts have been triggered

It is important that the laboratory assessments be completed as required and that the central laboratory be used for assessments whenever possible. If a subject cannot return to the clinic for a scheduled or unscheduled visit, or there is an event that triggers a need for an immediate assessment, the use of a local laboratory is required. In these cases, the Investigator will obtain the laboratory results and the laboratory normal ranges. All local laboratory data, including the reference ranges, are to be collected and entered in the eCRF within 2 days of receiving the results. Local laboratory visits are specifically encouraged in lieu of remote (telemedicine) visits where subject's safety is of particular concern (e.g., adverse event monitoring).

The process for assessing criteria is presented in Figure 2, and the specific threshold(s) for each laboratory analyte to trigger mandatory repeat testing and, potentially a complete subject evaluation (depending on the repeat result) are summarized in Section 7.6.3.

Figure 2: DILI Management Algorithm



ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DILI=drug-induced liver injury; GGT=gamma-glutamyl transferase; INR=international normalized ratio; IP=Investigational Product
Laboratory assessments include: ALT, ALP, AST, GGT, direct and total bilirubin, and INR.
Note: Pharmacokinetic sampling should be conducted as soon as feasible, preferably, within 7 days of investigational product interruption; close monitoring, including physical exams and repeat biochemistry labs, should occur as deemed appropriate by the Investigator.

7.6.3. Summary of Safety Criteria for Mandatory Treatment Interruption or Discontinuation

Subjects who meet the following criteria will have investigational product interrupted and re-evaluated:

- If liver biochemistries (AST, ALT, or total bilirubin) indicative of potential hepatic injury exceed ULN:
  a. Increasing conjugated (direct) bilirubin ≥2x baseline and >ULN
  (If conjugated bilirubin is not available, then increasing total bilirubin ≥2x baseline and >ULN)
  b. ALT or AST >3x baseline that is >ULN, OR ALT or AST >300 U/L

c. GGT >3x baseline and >ULN

- Clinical events indicative of hepatic injury or decompensation

Subjects who meet any of the following criteria will be discontinued from investigational product permanently:

- INR >1.5
- 25% decrease in platelets from baseline value and <120,000/µL
- Pregnancy
- Organ failure requiring hospitalization

Subjects who are discontinued for a clinical or laboratory AE will be followed for as long as necessary to adequately evaluate the safety of the subject or until the event stabilizes, resolves, or is no longer of clinical concern. Subject may be considered to restart treatment pending:

- Full evaluation, provided labs and clinical status return to baseline and remain stable for 2 or more weeks,
- Lab abnormalities are determined not to be due to DILI and,
- Another etiology is identified and approved by the Medical Monitor and Investigator.

It should be noted that it is difficult to recognize every potential marker of hepatic or renal deterioration. There is no substitute for good medical judgment. Investigators will be reminded to be cautious and mindful in their evaluation of subjects' symptoms, signs, and laboratory results. However, for example, a single abnormal laboratory analyte result may be artefactual; accordingly, Investigators will be allowed to implement an alternate follow-up procedure if considered appropriate based on their medical judgment but only after documented agreement with the Sponsor's Medical Monitor.

7.6.4. Clinical Criteria for Monitoring of Potential Hepatic Decompensation Events

Subjects will be monitored for potential hepatic decompensation events throughout the study. Clinical criteria for the monitoring of these events and the interruption/discontinuation of investigational product are summarized in Section 7.6.3.

Investigational product should be discontinued permanently if the subject is listed for or receives a liver transplant or experiences clinical events listed in Table 2. Subjects should continue to return for scheduled study visits for safety follow-up.

Table 2: Clinical Criteria for Monitoring Potential Hepatic Decompensation Events and Discontinuation of Investigational Product

Clinical Criteria for Permanent Discontinuation of IP	
Events	**Actions Taken**
• Liver transplant (or actively listed for liver transplant) • Organ failure requiring hospitalization • Laboratory criteria consistent with disease progression: – Sodium <130 meq/L – Platelet decrease from baseline >25% and <120,000 – International normalized ratio (INR) >0.3 increase from baseline or >1.5 – Albumin <3.5 g/dL • Variceal bleeding documented by endoscopy or accompanied by anemia or melena with a hemoglobin drop of ≥2 g/dL • Onset of ascites or hepatic hydrothorax • Spontaneous Bacterial Peritonitis • Hepatic Encephalopathy Grade ≥2 • Any liver-related event requiring hospitalization and treatment • Hepatorenal syndrome Type 1 or Type 2 and acute kidney injury, hepatopulmonary syndrome, or portopulmonary syndrome • Intractable pruritus	Discontinue OCA permanently, Monitor and Follow- up with subjects for safety until normalization/stabilization.

7.6.5. Progression of Disease

Investigators will closely monitor subjects for potential progression or worsening of disease at every visit (or at unscheduled visits in the event of signs or symptoms of potential hepatic injury or decompensation). Child-Pugh, PELD, and MELD scores will be calculated and reported within the electronic data capture (EDC) system. Investigational product shall be discontinued in case of disease progression when a subject's Child-Pugh score increases in grade (e.g., from Child-Pugh A to Child-Pugh B, or from Child-Pugh B to Child-Pugh C). Any change in Child-Pugh, PELD, or MELD score should be discussed with the Medical Monitor.

7.6.5.1. Child-Pugh Score

Child-Pugh Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 3 and can range from 5 to 15. Although CP score calculation will automatically be computed in all subjects, it should only be applied to subjects who have suspected or confirmed cirrhosis. A total score of 5 to 6 is considered Grade A (mild, well-compensated disease); 7 to 9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease).

Calculation of the CP score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the AE review at the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time (PT), which will populate from the central laboratory.

Table 3: Child-Pugh Scoring System

Factor	Units	Points		
		1	2	3
Serum bilirubin	µmol/L	<34	34-50	>50
	mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	28-35	<28
	g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites		None	Mild	Moderate-Severe
Hepatic encephalopathy[a]		0	Grade 1 or 2	Grade 3 or 4

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
(Pugh 1973, Lucey 1997, Vilstrup 2014)

7.6.5.2. Pediatric End Stage Liver Disease and Model of End Stage Liver Disease Scores

The PELD Score and the MELD score are scoring systems assessing the severity of chronic liver disease. The PELD score is used in subjects younger than 12 years of age, and is calculated using total bilirubin, international normalized ratio (INR), albumin, age at listing, and growth failure (Barshes 2006, Weisner 2001). The MELD score is used in pediatric subjects 12 years of age and older and is derived from total bilirubin, serum creatinine, INR, and sodium (Kamath 2007). Higher scores indicate more severe disease.

PELD/MELD scores will be calculated using the Organ Procurement and Transplantation Network online calculators, which may be found at the following web addresses:

PELD

https://optn.transplant.hrsa.gov/resources/allocation-calculators/peld-calculator/

MELD

https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/

7.7. Dose Adjustment and Withdrawal from Investigational Product

Investigational product may be decreased in frequency or permanently stopped based on tolerability concerns, such as new onset or worsening pruritus or fatigue, per Investigator and Medical Monitor judgment. See Section 7.6.2, Section 7.6.4, and Section 8.4.

Subjects experiencing AEs that lead to discontinuation will be followed for as long as necessary to adequately evaluate the safety of the subject or until the event stabilizes, resolves, or is no longer of clinical concern, if possible, as described in Section 13.1.7.

7.8. Close Observation

If investigational product is interrupted or discontinued as described in Section 7.6.2 and Section 7.6.4, subjects should be closely monitored with a physical exam and thorough review of subject reported signs and symptoms and laboratory assessments (including liver biochemistry, prothrombin time/INR, serum electrolytes, platelets, and PELD/MELD scores) conducted at a minimum of every week.

In addition, a trough PK sample for assessment of OCA plasma drug levels and its major metabolites should be obtained in any subject who develops an AE that is indicative of or consistent with hepatic injury or decompensation as described in Section 7.6.1, Section 7.6.2, and Section 7.6.4, or based on Investigators and Medical Monitors clinical assessment. The date and time of the last OCA dose and fasting status of the subject at the time of sample collection must be recorded.

The following additional monitoring procedures should be performed for events of potential hepatic injury (per EMA [European Medicines Agency] Guidance for Industry on Drug-Induced Liver Injury) or potential hepatic decompensation based on criteria described in Section 7.6.1, Section 7.6.2, and Section 7.6.4.

These cases need to be discussed with the Sponsor's Medical Monitor:

- Repeating liver enzyme and serum bilirubin tests as described in Section 7.6.2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic, as clinically indicated.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use and special diets is important. Concomitant drugs with potential hepatotoxicity should be recorded and discontinued unless alternative therapies are not available. In the case of concomitant drugs potentially hepatotoxic, continued use of

investigational product should be discussed with the Sponsor's Medical Monitor. The subject may be discontinued from investigational product, if clinically appropriate.

- Obtaining a history of exposure to environmental chemical agents or herbal supplements that may be associated with liver toxicity.
- Ruling out acute viral hepatitis types A, B, C, D (in those thought to have acute hepatitis B virus [HBV] infection), and E, EBV, Schistosomiasis Parasites; autoimmune or alcoholic hepatitis; Wilson's disease, hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Seeking hepatology consultation if the Investigator is not a hepatologist.

7.9. Criteria for Study Termination

The study may be terminated or suspended at the request of the EMA/local regulatory agency, Institutional Review Board (IRB), Principal Investigator, or the Sponsor. The Sponsor reserves the right to terminate the study at any time for administrative reasons.

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the Sponsor without consultation with the EMA/local regulatory agency. The end of the study must be notified to the EMA/local regulatory agency and the IRB immediately and at the latest within 15 days after the study is halted, clearly explaining the reasons. A description of any follow-up measures taken for safety reasons, if applicable, should also be provided.

If the study is abandoned prior to commencement of any protocol activities, the Principal Investigator or Sponsor must notify the EMA/local regulatory agency by letter outlining the reasons for abandonment of the study.

Once dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require temporary suspension or ET of the study:

- The occurrence of SAE(s), as defined in Section 7.5, if considered to be definitely, possibly, or probably related to the investigational product, as defined in Section 8.4.1.1.
- New information regarding the safety of the investigational product that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Interim analysis concludes futility of the study.
- A significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety occurs.
- The Sponsor reserves the right to terminate the study at any time for administrative reasons.

If any of the above occurs, the study may be terminated if careful review of the overall risk/benefit analysis described in Section 8.4.2.1 demonstrates that the assumptions have

changed and that the overall balance of risk to the subject versus benefit to obtaining data is no longer acceptable. In these circumstances, termination can only take place with the agreement of the Sponsor. The EMA/local regulatory agency and IRB will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion with the Sponsor. Dosing may be suspended immediately on safety grounds.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Population

This study will be conducted globally in countries with experience in treating patients with biliary atresia.

8.2. Subject Inclusion Criteria

1. Male or female pediatric subjects from birth to <18 years old

   Note: Subjects aged <2 years old will not be enrolled until after review of safety data during the planned interim analysis and agreement from the DSMB that there is sufficient safety data to enroll this age group.

2. Diagnosis of non-syndromic biliary atresia
3. Demonstrated successful HPE as defined by total bilirubin <2 mg/dL (34.2 μmol/L) at least 3 months post-HPE procedure.
4. Female subjects of childbearing potential must use ≥1 highly effective method (≤1% failure rate) of contraception from the initiation of Screening and until at least 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product. Highly effective methods of contraception are considered to be those listed below:
   - Surgical sterilization (bilateral tubal occlusion, etc.)
   - Placement of an intrauterine device (IUD) or intrauterine system (e.g., intrauterine hormone-releasing system [IUS]).
   - Combined (estrogen and progesterone containing) hormonal contraceptive associated with inhibition of ovulation:
     – Oral
     – Intravaginal
     – Transdermal
   - Progesterone-only hormonal contraception associated with inhibition of ovulation:
     – Oral
     – Injectable
     – Implantable

- In the context of this study, the goal of using a highly effective contraception method is to avoid the potential embryofetal risks from exposure to investigational medicinal products. Sexual abstinence, as a form of highly effective contraception, is defined as avoiding all types of sexual activity that could result in pregnancy during the entire period of the study treatment until at least 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study.

5. Male subjects who are sexually active with female partners of childbearing potential must agree to use a condom with spermicide and to use one other approved method of highly effective contraception from the time of investigational product administration initiation of Screening and until at least 14 days or 5 half-lives, whichever is longer, after the dose of investigational product as listed in Inclusion Criteria #4.
6. Male subjects must refrain from sperm donation from Screening through at least 14 days or 5 half-lives, whichever is longer, following the last dose of investigational product.
7. Parent or guardian is willing to provide written informed consent and when appropriate, the subject is willing to assent and agree to comply with the study protocol.

8.3. Subject Exclusion Criteria

1. Prior liver transplant or active status on transplant list
2. Participants diagnosed with biliary atresia splenic malformation (BASM)
3. Conjugated (direct) bilirubin ≥ ULN of site-specific reference range. If conjugated bilirubin is not available: total bilirubin ≥2 mg/dL (34.2 mol/L)
4. Platelets <120,000/μL
5. INR ≥1.5
6. Current or history of complications of decompensated chronic liver disease including:
    a. gastroesophageal varices and/or variceal bleeding
    b. clinically evident ascites related to portal hypertension
    c. hepatic encephalopathy
    d. prior placement of portosystemic shunt
    e. hepatopulmonary syndrome or portopulmonary hypertension
    f. hepatorenal syndrome
    g. any evidence of portal hypertension based on imaging (e.g., cavernous transformation of portal vein, abdominal varices, etc.)
    h. Hepatocellular carcinoma
    i. Childs-Pugh B or C
7. Height and weight Z-score <-2 per site-specific reference ranges
8. Acholic (pale) stools
9. AST >4x ULN
10. Alanine aminotransferase >4x ULN

11. GGT >500 U/L
12. Anticoagulation therapy
13. Albumin <3.5 g/dL
14. Inability to swallow tablets (i.e., tablet or mini-tablet formulations)

8.4. Subject Withdrawal Criteria

Subjects can be discontinued from investigational product by the Investigator at any time for clinical safety concerns. Subjects who are discontinued from investigational product are expected to continue in the study and should follow the regular visit schedule for the duration of the study. See Section 8.4.1.1 for withdrawal criteria related to potential hepatic injury and/or decompensation including liver transplantation or multi-organ failure. Other reasons, including withdrawal of consent or lost to follow-up, are described in Section 8.4.2 below.

If a subject develops an exclusion criterion during participation in the study they will not be automatically withdrawn from study, but rather, their continued participation will be based on clinical judgment and discussed with the Medical Monitor, as necessary.

8.4.1. Reasons for Mandatory Discontinuation of Investigational Product

8.4.1.1. Severe and Related Adverse Events

If a subject experiences an AE that is Grade ≥3 in severity using criteria outlined in Section 13.1.3 and is considered possibly, probably, or definitely related to the investigational product, the investigational product must be discontinued and the subject should complete EOS procedures (i.e., Follow-Up Visit), including a PK sample

8.4.1.2. Pregnancy

When the site is notified of a possible pregnancy, the subject should be asked to come in for an unscheduled visit to perform a serum pregnancy test. If a female subject becomes pregnant, the subject must stop taking investigational product immediately and be withdrawn from the study. The subject must be followed by the Investigator through pregnancy outcome. The mother (and infant) will be followed as considered appropriate by the Investigator and the Sponsor. As described in Section 13.1.8 a pregnancy is not considered an AE for reporting purposes.

8.4.2. Other Reasons for Discontinuation of Investigational Product or Study Termination

8.4.2.1. Discontinuation of Investigational Product

Subjects who discontinue investigational product are expected to continue in the study until the end of the double-blind part of the study or at the discretion of the Sponsor. Subjects are expected to continue to follow the regular visit schedule through to end of the double-blind part of the study. In general, subjects should be strongly encouraged to both stay on investigational product and remain in the study until study termination. ET procedures will be conducted if the subject withdraws consent from the study during the double-blind part (see Section 9.8.5).

The following conditions are considered appropriate reasons for a subject to discontinue investigational product; however, these subjects are expected to continue in the study until study termination or at the discretion of the Sponsor.

- The Investigator or Sponsor considers that it is advisable or in the best interest of the subject
- The occurrence of safety concerns such as clinically important adverse events (e.g., clinical or laboratory AEs)
- There is a major violation of the clinical study protocol
- The development of any exclusion criteria that might jeopardize safety (see Section 8.3, Exclusion Criteria)

The Investigator is encouraged to contact the Sponsor prior to discontinuing a subject from treatment. The Investigator must notify the Sponsor study monitor by telephone or email as soon as possible if any subject prematurely withdraws from the study.

It is agreed that, for reasonable cause, either the Investigator or the Sponsor may terminate this study.

8.4.2.2. Withdrawal of Consent to Continue in the Study

If the subject decides that it is in his/her best interest to discontinue from the study, he or she may withdraw consent. It is fully understood that all subjects volunteer for the study and that they may withdraw their consent to continue in the study at any time.

A reasonable effort must be made to determine the reason(s) for subject discontinuation. This information and date of contact must be recorded in the appropriate eCRF.

8.4.2.3. Lost to Follow-Up

If a subject fails to return to the clinic for a study visit, and the Investigator ceases to have contact with the subject, he or she will be withdrawn from the study.

A reasonable effort must be made to contact the subject and determine the reason(s) why a subject fails to return for a study visit or is lost to follow-up. Subjects will be considered "lost to follow-up" only after reasonable, documented attempts to reach the subject prove unsuccessful. Reasonable attempts may be considered if at least 2 phone messages are unreturned and one certified mail is unanswered. This information and date of contact must be recorded in the appropriate eCRF.

8.4.3. Subject Discontinuation Notification

The Investigator must notify the Sponsor as soon as possible if any subject prematurely discontinues from the study. The date when the subject is withdrawn and the primary reason for discontinuation must be recorded in the eCRF; additional information may be requested by the Sponsor to complete a discontinuation narrative. In all cases, a reasonable effort must be made to determine the reason(s) that a subject fails to return for required study visits or discontinues from the study. This information must be documented in the eCRF.

If a subject is withdrawn from the study early (regardless of the cause), all of the EOS evaluations are to be performed at the time of withdrawal, to the extent possible.

9. TREATMENT OF SUBJECTS

9.1. Investigational Product Treatment Regimen

For this study, the term 'investigational product' refers to OCA or matching placebo tablets, provided as part of this clinical study.

Investigational product will be self (or by guardian)-administered orally with approximately 240 mL (8 oz) of water for the duration of the study. Subjects (or their guardian) will be instructed to begin dosing on Day 1 and are to take investigational product at approximately the same time each day. Subjects must be instructed to swallow the tablet or mini-tablet whole; they must not chew, divide, or crush the tablet.

At each study visit where the dose of investigational product is administered at the site, all assessments, except for the postdose collection of blood samples for PK assessments, must be completed before administration of the investigational product.

9.2. Concomitant Medications

Concomitant medications (other than prohibited concomitant medications listed in Section 9.2.3) will be used at the discretion of the usual care provider (or Investigator if also the usual care provider). Relevant information about all concomitant medications (including prescribed, over-the-counter, or herbal preparations) taken 30 days prior to Day -1 and during the study must be recorded in the source documents and eCRF, as should any dose or dose regimen changes that occur during the study.

9.2.1. Biliary Atresia Specific Therapy

Investigators are encouraged to follow guidelines for care based upon local and institutional practice patterns and any relevant published practice guidelines. Throughout the course of the study, Investigators are expected to monitor subjects' biliary atresia regimens and, if responsible for usual care, may adjust the regimen to achieve locally appropriate treatment goals. These goals will be individualized with the understanding that currently applicable guidelines may vary across different geographic regions.

Ideally, subjects should generally remain on the baseline therapies throughout the course of the study, unless the baseline therapy is no longer considered clinically appropriate by the Investigator.

9.2.2. Drug Interactions

Bile acid sequestrants (BAS, including cholestyramine and its derivatives, colestipol, colesevelam, or other sequestrants) or aluminum hydroxide- or smectite-containing antacids should be administered, at minimum, 4 hours before or 4 hours after investigational product administration.

OCA taken concomitantly with warfarin may result in decreased INR levels; therefore, INR should be monitored and the dosage of warfarin adjusted, as needed, during treatment with OCA and after cessation of OCA, to maintain the target INR range.

The effect of OCA on drug metabolizing enzymes has been evaluated in both in vitro and clinical studies. The PK profile of caffeine, a sensitive CYP1A2 substrate probe, showed weak effect of OCA on CYP1A2. Based on these results, OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, such as theophylline and tizanidine.

Information related to additional drug-drug interaction (DDI) studies is available in the current version of the IB. The aforementioned sections of the IB should be referred to during the course of the study and are accessible to Investigators to help facilitate the assessment of potential DDIs with OCA that may be observed in study subjects.

9.2.3. Prohibited Medications

Administration of the following medications is prohibited as specified below:

- Subjects who have received an investigational product within 30 days or 5 terminal half-lives ($t_{½}$), whichever is longer, before Day -1

9.2.4. Permitted Medications

Administration of other concomitant medications is permitted, as specified below:

- Standard-of-care medications used for the treatment of biliary atresia (e.g., UDCA) and prophylactic antibiotics to prevent infections, such as cholangitis, should be at a stable dose, per Investigator's clinical judgment, 30 days before Day -1. Investigators should endeavor to keep standard-of-care medications stable over the course of the study, where medically appropriate.
- Other concomitant medications should also be stable prior to Day -1, whenever possible. Investigators should endeavor to keep the doses of all concomitant medications the same during the course of the study, where medically appropriate.
- Subjects taking aluminum hydroxide- or smectite-containing antacids should be instructed to stagger their dosing of OCA (and UDCA, if it is part of their current standard of care treatment), ensuring at least 4 hours between doses of the antacids and OCA (and/or UDCA), if possible.
- If a subject develops pruritus during the study, concomitant medications for treatment may be allowed. Investigators may refer to the IB for guidance on treatment of pruritus. If treated with BAS (e.g., cholestyramine and colesevelam), subjects should stagger their dosing of OCA (and/or UDCA, if it is part of their current standard of care treatment), ensuring at least 4 hours between doses of the BAS and OCA (and/or UDCA).

9.2.5. COVID-19 VACCINE

Coronavirus disease 2019 (COVID-19) vaccination (with vaccines approved for emergency use in the country where you practice) is allowable for subjects enrolled in the Intercept-sponsored clinical trials. Of note, as the currently approved COVID-19 vaccines have not been specifically

tested in the biliary atresia patient population, there are no safety data available specific to use of COVID-19 vaccines in biliary atresia subjects.

If a subject receives a COVID-19 vaccination, the date(s) of vaccination(s), vaccine name, and manufacturer should be recorded as a concomitant medication for each dose.

9.3. Treatment Compliance

The Investigator should assess the subject's compliance with dosing of investigational product at each study visit after Day 1. Confirm compliance by conducting investigational product accountability by count of returned tablets (1.5-mg tablets) or by weight of the returned bottles (0.1-mg mini-tablets).

Subject and/or subject's parents/guardians should be instructed to retain all bottles of investigational product, even if empty, and to return them to the Investigator at the indicated visits in Table 1. The Investigator or designee should perform investigational product accountability (i.e., count of returned tablets) and, if applicable, follow-up with the subject to retrieve any investigational product bottles that have not been returned.

If the Investigator has concerns about a subject's dosing compliance, he or she should discuss this with the subject, assess the reasons for protocol- defined noncompliance (defined as under 80% or over 120% of expected remaining investigational product) and the likelihood that the subject will remain noncompliant, and notify the Sponsor accordingly.

9.4. Randomization and Blinding

9.4.1. Methods of Assigning Subjects to Treatment Groups

This study will be conducted in a DB, placebo-controlled manner. Enrolled subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (OCA or matching placebo) based on a pre-defined randomization code (generated by designee) using an interactive web response system (IWRS). The IWRS will serve as the investigational product inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the subject in the IWRS and may be prompted to provide subject data necessary to properly randomize and allocate the subject to treatment. A randomization number will be assigned and investigational product (OCA or placebo) dispensing information will be provided (e.g., bottle numbers allocated) while maintaining the study blind.

9.4.2. Blinding

The subjects, Investigator, and study site staff will be blinded to the subject's treatment allocation during the subject's participation in the study.

9.4.3. Emergency Unblinding Procedures

Treatment assignment for individual subjects in the study will be made available to the Investigator for medical emergency use only (e.g., in situations where knowledge of the blinded treatment assignment is necessary for the treatment of an SAE) through the IWRS system. When possible, the Medical Monitor should be consulted in the event that a medical emergency

necessitates unblinding. If it is not reasonable to inform the Medical Monitor in advance of unblinding, the Investigator must promptly document the case and the rationale for unblinding in the subject's source record and should subsequently contact the Medical Monitor to discuss any premature unblinding of treatment assignment. Procedures for unblinding a subject's treatment will be provided separately to the Investigator.

Similarly, if the Medical Monitor breaks the blind for the purpose of evaluating a medical emergency or emergent safety issue, the Medical Monitor will document within the study source documentation of the rationale, circumstances, and the person(s) being informed about the unblinding.

The DSMB (refer to Section 14.6) will have access to the IWRS and will be able to unblind individual subjects. The DSMB will document details about any unblinded subject data reviews in the closed session DSMB minutes, which will be made available to the Sponsor only after the double-blind database is locked, and the study is unblinded.

Access to randomization codes and corresponding treatment assignments will also be made available through the IWRS system to the designated Intercept staff responsible for unblinding SUSARs for reporting to the regulatory authorities.

9.5. Assignment of Site and Subject Numbers

9.5.1. Site Numbers

Each study site selected to participate in this study will be assigned a site number by the Sponsor. The site number will be used to categorize subject data and to identify the site and/or Investigator within study documents. This number will be recorded in the eCRF.

9.5.2. Subject Numbers

Subject numbers will be allocated on Day 1 following randomization. Subjects will be assigned a unique 6-character identifier independent of the randomization number. The first 3 digits represent the site number, and the last 3 digits represent a unique subject number that is assigned in sequential order (e.g., 001 to 110).

9.6. Restrictions

No additional restrictions.

9.7. Contraception

In the context of this study, the goal of using a highly effective contraception method is to avoid the potential embryofetal risks from exposure to investigational medicinal product. Female subjects who are sexually active and male subjects who are sexually active must use, with their partner, a method of highly effective contraception per Clinical Trial Facilitation Group guidelines (CTFG 2020) as listed in Inclusion Criterion #4 and Inclusion Criterion #5.

These guidelines recommend "highly effective" contraception measures for female subjects of childbearing potential for investigational products with limited or no human data available on pregnancies (CTFG 2020).

A woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Highly effective methods of contraception per the CTFG guidelines are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly.

9.7.1. Male Subjects

Subjects who are sexually active must use, with their partner, a method of highly effective contraception from the time of investigational product or study medication administration until 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product or study medication.

Highly effective methods of contraception include the following:

- IUD
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion (female partner)
- Vasectomy (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Combined (estrogen- and progestogen-containing) hormonal contraception (e.g., oral, intravaginal, or transdermal) associated with inhibition of ovulation (female partner).
- Progestogen-only hormonal contraception (e.g., oral, injectable, or implantable) associated with inhibition of ovulation (female partner).

Subjects who have been sterilized or have partners of nonchildbearing potential (including homosexual men) are required to use one barrier method of contraception (condom). This is to prevent unintended exposure of the partner to the investigational product via seminal fluid.

Subjects who have pregnant partners are required to use 1 barrier method of contraception (condom).

Alternatively, sexual abstinence is acceptable as a form of highly effective contraception and is defined as avoiding all types of sexual activity that could result in pregnancy during the entire period of the study treatment until at least 14 days or 5 half-lives, whichever is longer after the last dose of investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial.

9.7.2. Female Subjects

Subjects of childbearing potential who are sexually active and have a hormonal or nonhormonal IUD are required to have their heterosexual partner to use a condom during the study and until 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product or study medication.

If subjects of childbearing potential are sexually active and do not have a hormonal or nonhormonal IUD, 2 or more of the following options are acceptable during the study and until 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product or study medication, and must include at least 2 of the following methods:

- Bilateral tubal occlusion (subject)
- Vasectomy (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate of their partner)
- Combined (estrogen- and progestogen-containing) hormonal contraception (e.g., oral, intravaginal, or transdermal) associated with inhibition of ovulation.
- Progestogen-only hormonal contraception (e.g., oral, injectable, or implantable) associated with inhibition of ovulation.
- Barrier methods (condom or use of an occlusive cap [diaphragm or cervical/vault caps]; with spermicidal foam/gel/film/cream/suppository/pessary).

Alternatively, sexual abstinence is acceptable as a form of highly effective contraception and is defined as avoiding all types of sexual activity that could result in pregnancy during the entire period of the study treatment until at least 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial.

If a subject is not sexually active but becomes active, the subject, along with their partner, must comply with the contraceptive requirements detailed above.

9.7.3. Exposure to Partners of Male Subjects During the Study

As there is a potential risk of investigational product exposure through the ejaculate (which also applies to vasectomized males) that might be harmful to the sexual partners, including pregnant partners of male subjects, barrier contraception should be used throughout the study and for 14 days or 5 half-lives, whichever is longer, after the last dose of investigational product.

9.7.4. Sperm Donation

Male subjects should not donate sperm for the duration of the study and for at least 14 days or 5 half-lives, whichever is longer, after the last dose of study medication.

9.8. Visit Procedures

9.8.1. Visit Windows

Visits should be based on Day 1 (not on the prior visit) unless stated otherwise. For example, Week 2 should ideally occur 2 calendar weeks (±2 days) following Day 1. Visit procedures are provided in Table 1 and the visit windows are as follows:

Visit or Procedure	Visit Window and/or Interval
Screening	Visit(s) are to occur ≤14 days before Day 1.
Day 1	This is the day of randomization and day of the first dose of investigational product. On-treatment visit scheduling should be calculated from this point going forward unless stated otherwise.
Week 2	±2 days
Week 4 through Week 18	±5 days
Week 24 through EOS	±7 days
EOT	As soon as possible upon study discontinuation and as near as possible to last dose taken

EOS=end of study; EOT=end of treatment

9.8.2. Informed Consent Procedures

The parent or guardian of the subject will be provided with a written explanation of the study during the Screening Visit. A physician/nurse will explain to each subject and parent or guardian the nature of the study, its purpose, expected duration, and the benefits and risks involved in study participation, and will be provided with a copy of the informed consent form (ICF). The subject and parent or guardian will be given sufficient time to consider the study before deciding whether or not to participate. The subject and parent/guardian will be informed that participation is voluntary, that future medical treatment will not be compromised by participation in the study, and that they can withdraw from the study at any time.

The parent or guardian must be willing and able to provide written informed consent and when appropriate and mandated by law, the subject must be willing to assent with the study protocol before entering the study. The Principal Investigator or a medically qualified designee is responsible for administering and documenting the written informed consent of the parent or guardian and, when appropriate, the subject's assent. All parents or guardians will receive a copy of their signed and dated ICF.

If changes are made to the ICF during the study, which are considered relevant to subjects still participating in the study, they should be re-consented at the earliest opportunity. If a visit is not due within 3 weeks of the new ICF being approved, the subject should be contacted via phone and informed of the new safety information. The updated ICF may be provided via post/email.

Confirmation that the subject wishes to continue the study should be appropriately documented in the medical records. The ICF should be appropriately signed and dated at the following visit that the subject attends, whether it is scheduled or unscheduled.

9.8.3. Screening Procedures

The Screening Visit assessments must be performed within ≤2 weeks prior to Day 1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study. Subjects may be

rescreened after 2 months; however, all screening procedures should be repeated and a new 3-digit screening number assigned.

Screening Visit procedures are as follows:

- Obtain informed assent/consent before performing any study-related procedures, including screening procedures.
- Obtain Demographics including Race and Ethnicity
- Collect medical and disease history, including history of growth failure (for calculation of PELD score in subjects aged <12 years).
- Verify inclusion and exclusion criteria for eligibility.
- Perform a physical examination.
- Record height and body weight.
- FIB4 score and PELD/MELD score
- Record Z-Score (height and weight).
- Measure triceps skinfold thickness and mid-arm circumference using a Lange skinfold caliper for evaluation of nutritional status.
- Record vital signs immediately prior to collecting any blood samples.
- Perform a standard 12-lead electrocardiogram (ECG).
- Assess and record any pretreatment AEs.
- Record prior (within 30 days of Day -1) and current concomitant medications.
- To assess eligibility criteria: ability to swallow tablets, administer 5 mg AED using site supplies of placebo (Access IWRS to obtain [1] screening number and [2] dose regimen based on subject's weight [Appendix B]. Refer to Section 10.1.4 for study dose administration techniques.)
  - Evaluate acceptability and swallowability of dosing regimen (refer to Section 11.4).
  - Document the dose administration start/end time on the eCRF.
- Ultrasound elastography of liver stiffness and ultrasound liver doppler will be conducted at all study sites where available.
- Obtain blood samples for hematology, serum chemistry (including Vitamins A, D, and K), coagulation factors, and virology, per standard site operating procedures.
- Obtain urine sample for urinalysis (if possible).
- Perform a urine-based β-human chorionic gonadotropin (β-hCG) pregnancy test in females of childbearing potential. A quantitative serum pregnancy test will be performed if the urine test is positive.
- Obtain Follicle-stimulating Hormone (FSH) Test

9.8.4. Study Day Procedures

9.8.4.1. Timing of Procedures

Where the protocol requires more than one procedure to be completed at the same timepoint, the following rules will apply:

- Blood sample collection will take precedence over other procedures and will therefore be collected at the nominal time
- Vital signs will be recorded prior to the nominal time
- ECG recordings will be taken prior to the nominal time

All safety assessments will be timed and performed relative to the start of dosing.

9.8.4.2. Blood Volume

The estimated blood volume to be drawn for each subject is less than 200 mL. The blood volume is approximately that which is taken during a blood donation and is not anticipated to cause any ill effects in healthy volunteers. Furthermore, the risk is minimized by ensuring the hemoglobin is at or above the lower limit of normal at Screening and Admission, and subjects will be instructed not to donate blood for 3 months after discharge from the study. The volume drawn will be sufficient to fulfill the study objectives.

9.8.5. Early Discontinuation and/or Early Termination

If a subject is withdrawn from the study early (regardless of the cause), all the EOS discharge evaluations should be performed at the time of withdrawal, to the extent possible.

9.8.6. Unscheduled Visit

A member of the medical or nursing staff will ask about the subject's well-being at the time of discharge following their final PK sample collection.

If a subject reports any AEs that can present a cause for concern, they will be required to attend the clinic for a further follow-up assessment and PK sampling (as an unscheduled visit).

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product: Obeticholic Acid

The term investigational product refers to either OCA or placebo (provided as part of this clinical study). Investigational product for this study will be provided as 0.1-mg OCA mini-tablets and 1.5-mg OCA tablets as well as matching placebo tablets.

The 0.1-mg OCA mini-tablets are small, white, round tablets, approximately 2 mm in diameter with no markings, and weighing 6.5-mg per mini-tablet. The 0.1-mg OCA mini-tablets contain the following inactive ingredients: [redacted] The matching

placebo mini-tablet (0.1 mg) contains the same inactive ingredients as the active OCA 0.1-mg mini-tablets.

The 1.5-mg OCA tablets are small, white, round tablets, approximately 5 mm in diameter with no markings, and weighing 60 mg per tablet. The OCA 1.5-mg tablets contain the following inactive ingredients: [redacted] The matching placebo (1.5 mg) contains the same inactive ingredients as the active OCA 1.5-mg tablets.

All investigational product will be manufactured according to Good Manufacturing Practices (GMP).

10.1.1. Investigational Product Packaging and Labeling

The packaging and labeling of investigational product supplies will be performed according to GMP standards by a designated, qualified vendor. A designated investigational product distribution vendor will also be responsible for the distribution of the investigational product to the Investigator.

OCA and placebo tablets are for oral administration and are provided in high-density polyethylene bottles with an induction seal and child-resistant closures. The 0.1-mg mini-tablets (OCA or placebo) will be provided in 40-cc bottles containing 3 g ± 65 mg (approximately 461 mini-tablets). The 1.5-mg (OCA or placebo) tablets will be provided in 40-cc bottles containing 100 tablets. All bottles also contain a desiccant sachet.

10.1.2. Investigational Product Storage

The investigational product should be stored in the containers in which they are received from the Sponsor's supplier at 15°C to 25°C (59°F to 77°F).

10.1.3. Investigational Product Preparation

Dispensing aids, such as counting trays and tweezers, may be used to assist subjects and their parents/guardians in the counting and dispensing of the 0.1 mg OCA and placebo mini-tablets. No other preparation of investigational product is necessary.

10.1.4. Investigational Product Administration

Refer to Section 7.1 for details of the treatment regimens in the Dose Titration and Age Expansion Treatment phases of the study.

10.1.4.1. Administration of 0.1 mg Mini-Tablets (OCA and Placebo)

The 0.1 mg mini-tablets (OCA and placebo) may be placed in the mouth followed by a drink of water or any other liquid (e.g., milk or juice) to aid oral administration. If it is not possible to swallow the dose regimen of mini-tablets with water or liquid, the mini-tablets may be placed on a spoonful of soft food (e.g., apple sauce, pudding, or yogurt) for administration. If multiple 0.1 mg mini-tablets are required, the parent/guardian should try to administer mini-tablets all at once (preferred method, if possible) or in divided doses administered simultaneously. If the dose is divided, the time it takes to complete the dose must not exceed 30 minutes. The parent/guardian may not mix 0.1 mg mini-tablets in a bottle or cup of liquid to attempt dissolution

or add to a bowl or container of food for administration. Subjects should be instructed to swallow tablets whole and must not crush or chew tablets. Parent/guardian will be instructed to administer investigational product to subjects at approximately the same time each dosing day.

10.1.4.2. Administration of 1.5 mg (OCA and Placebo)

OCA 1.5 mg and matching placebo tablets may be placed in the mouth followed by water or any other liquid (e.g., milk or juice) required to aid administration. If it is not possible to swallow the tablets with water or liquid, the tablets may be placed on a spoonful of soft food (e.g., apple sauce, pudding, or yogurt) for administration. Subjects will be instructed to take OCA at approximately the same time each dosing day. Subjects should be instructed to swallow tablets whole and must not crush or chew tablets.

10.1.4.3. Administration of Combinations of Tablets

If a subject is to receive a combination of 2 tablet formulations (e.g., 0.1 mg mini-tablets and 1.5 mg tablet), each tablet formulation should be taken separately, ensuring proper techniques are followed for each tablet formulation.

10.1.5. Investigational Product Accountability and Disposal

The Sponsor's representative will send investigational product to the study site under appropriate storage conditions. All shipments of investigational product should be unpacked, and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored under the appropriate storage conditions until verification of the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the investigational product against the shipment documentation. The pharmacist or designee should contact the Sponsor immediately to report any concerns regarding the shipment.

All investigational product will be provided for use only in this study and is not to be used for any other purpose. The Principal Investigator or designee will maintain a full record of investigational product accountability, including records of individual subject dispensing and final return or disposition (as directed by the Sponsor).

The study monitor, also known as the "Clinical Research Associate" (CRA), will review accountability records against investigational product dispensed and that remaining in stock, during on-site monitoring visits and when the study is completed, or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return or destruction of the investigational product.

11. PHARMACOKINETIC ASSESSMENTS

11.1. Blood Sample Collection

Predose sample at steady state (C_{trough}) has been established as an effective exposure parameter for total OCA in adult patients with PBC. Blood samples for the measurement of plasma concentrations of OCA and its conjugates will thus be collected predose on Weeks 2 (to support dose uptitration), 4, 6, 10, 18, 30, 64/EOT, EOS/ET, unscheduled visits, and as soon as feasible, preferably, within 7 days of an SAE.

11.2. Processing and Handling of PK Samples

Whole blood will be collected at each scheduled sample timepoint. Detailed procedures for the collection of blood samples, including further processing into plasma, will be provided in a separate laboratory manual. The storage and shipment procedures for subsequent bioanalysis will be provided to the investigational site in a separate document before the study is initiated.

11.3. Bioanalysis

Plasma concentrations of OCA and its conjugates (glyco-OCA and tauro-OCA) will be determined using validated liquid-chromatography mass spectrometry/mass spectrometry methods. A detailed description of validation information and results from the bioanalytical assay will be provided in separate reports.

11.4. Exploratory Measures

11.4.1. Acceptability and Swallowability Evaluation

Acceptability and swallowability of dose regimen will be evaluated in all subjects at the Screening Visit (Table 1). The subjects will receive a 5 mg AED of placebo-matched tablet(s) at Screening.

The subject's ability to swallow the dose regimen and acceptance of the dose regimen will be evaluated via a five-point criteria evaluation as an exploratory measure following a mouth check. Since there is not an accepted or validated tool for the evaluation of acceptability and swallowability in children, this five-point criteria evaluation was adapted from other studies that evaluated the acceptability and swallowability of other mini-tablet formulations (Klingmann 2013, Spomer 2012) and revised to meet the needs for all OCA tablet formulations that are being used in this study.

1. Swallowed and/or consumed (i.e., dissolved in mouth) the entire dose regimen
2. Partially swallowed and/or consumed (i.e., dissolved in mouth) the majority of the required dose regimen
3. Spat out the majority of the dose regimen
4. Inhaled or coughed during deglutition (no tablets were swallowed or consumed)
5. Refused to take: did not allow any tablets or the majority of the dose regimen to be put in mouth

Acceptability and swallowability will be considered for the different tablet regimens as follows:

Table 4: Acceptability and Swallowability Evaluation Chart

Evaluation	1.5-mg Tablets	0.1-mg Mini-Tablets	Combination of 1.5-mg and Mini-Tablets
Swallowed	Criteria 1	Criteria 1	Criteria 1
Acceptable	Criteria 1	Criteria 1 and 2	Criteria 1 and 2

In addition, the subject's and/or parents'/guardians' ability to dispense the required dose regimen will be assessed.

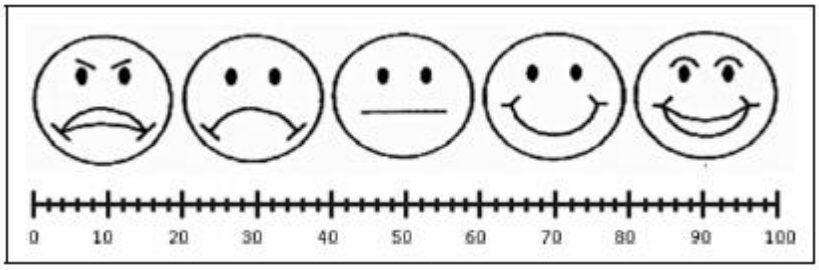
11.4.2. Palatability Evaluation

Palatability will be evaluated at the Week 6 visit. Palatability will be evaluated for each tablet formulation (i.e., 0.1-mg mini-tablet[s] and 1.5-mg tablet[s]) of a subject's dose regimen by evaluating their regular scheduled dose. If a subject is taking a combination of tablets (e.g., 0.1-mg mini-tablet[s] and 1.5-mg tablet[s]), both the 0.1-mg mini-tablet(s) and 1.5-mg tablet will be assessed separately.

Dose administration may only be performed with water. No other liquids or soft food may be used for palatability evaluations.

Children 4 years and older will assess palatability via a five-point facial hedonic scale (FHS; very bad, bad, neutral, good, and very good) with a correlated 100-point visual analog scale (FHS/VAS-5) (Thompson 2015) as shown in Figure 3.

Figure 3: Five-Point FHS/VAS-5 Scale



In children <4 years of age, palatability will be assessed by the parents'/guardians' observation of the subject's dosing experience as follows: 1) swallowed; 2) partially swallowed; 3) spat out; or 4) refused to take. Palatability will be assumed if a subject swallowed or partially swallowed.

12. EFFICACY ASSESSMENTS

12.1. Primary Assessments

The following primary efficacy assessments will be measured:

- Death (all-cause)
- Liver transplant

- PELD score ≥17/MELD ≥15
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
  - Variceal bleed
  - Hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Uncontrolled ascites (diuretic-resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

12.2. Secondary Assessments

The following secondary efficacy assessments will be measured:

- PK of OCA as measured by unconjugated plasma OCA (parent), glyco-OCA, tauro-OCA, and total OCA (molar sum of OCA and its active conjugates).
- PD of OCA as measured by:
  - Biomarkers of FXR activation: FGF-19, C4, and endogenous bile acids, and
- Biomarkers of hepatobiliary function: GGT, total and direct (conjugated) bilirubin
- Effect of OCA on liver stiffness by transient elastography (if available at site)
- Disease progression as measured by plasma levels of fat-soluble vitamins (Vitamins D and K)

12.3. Exploratory Assessments

The following exploratory efficacy assessments will be measured:

- To evaluate the acceptability and swallowability of the dosing regimen
- To evaluate the palatability of the dosing regimen

12.4. Efficacy Laboratory Assessments

12.4.1. Blood Samples for Pharmacokinetics Analyses

Refer to Section 11.1 for instructions regarding sample collection and Section 13.2.10 for a full list of analytes to be tested. Table 1 provides a detailed schedule for collection.

12.4.2. Blood Samples for Pharmacodynamics Analyses

Blood samples will also be collected in all subjects to measure C4, FGF-19, and bile acids, according to the schedule provided in Table 1.

12.5. Anthropometric Measures

Anthropometric measures include Z-score for body weight, height and, body mass index (BMI). Anthropometric measures will be performed during the visits indicated in Table 1.

BMI will be calculated by the Sponsor as (Weight in Kilograms / [Height in Meters × Height in Meters]). Instructions for measuring body weight are described below. Body weight measures are to be obtained after the subject has fasted for at least 8 hours.

Body weight: Body weight is collected at each visit that vital signs are assessed and should be obtained with the subject wearing a hospital gown or similar light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study. The floor surface on which the scale rests must be hard rather than carpeted or covered with other soft material. The subject should stand in the center of the platform. The weight is to be read and recorded to the first decimal point (e.g., 97.1 kg) by study staff.

13. ASSESSMENT OF SAFETY

13.1. Adverse Events and Serious Adverse Events

13.1.1. Definitions of Adverse Events

13.1.1.1. Adverse Event

AEs are defined as any untoward medical occurrence associated with the use of an investigational product in humans, whether or not considered related to the investigational product. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational products, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose. For the purpose of this study, 'investigational product' refers to OCA or placebo tablets.

AEs include but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

AEs should be elicited in a general way, without leading the subject or asking about the occurrence of any specific symptom.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms "sudden numbness, dizziness, and difficulty speaking." The AE medical term of "stroke or cerebrovascular accident" should be recorded as it more accurately describes the AE.

Subjects should be instructed to contact the site promptly upon awareness if they develop signs and symptoms of potential hepatic decompensation such as pale-colored stools, urine color from pale to deep amber (dark), nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, fatigue, weakness, loss of appetite, confusion, swelling of the legs or abdomen, yellowing of the skin or whites of eyes, and bruising easily.

13.1.1.2. Treatment-Emergent Adverse Event

A treatment-emergent AE (TEAE) is any event not present before the initiation of the investigational product or any event already present that worsens in either intensity or frequency following exposure to the investigational product.

13.1.1.3. Adverse Events of Special Interest

The following are considered AEs of special interest (AESI):

- Pruritus
- Drug-induced liver injury

13.1.1.4. Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Any malignancy is to be reported as a serious AE.

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE;
- Elective treatment for a pre-existing condition that did not worsen such as elective cosmetic surgery or medical procedure;
- Respite care or observation when there is no AE associated with the hospitalization.

13.1.1.5. Suspected Unexpected Serious Adverse Reactions

A SUSAR is defined as a suspected adverse reaction (SAR) which is assessed as serious, causally related to the investigational medicinal product, and unexpected per the RSI in the IB.

SUSARs are subject to expedited reporting. The Sponsor shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the relevant competent authorities, and to the IRB/Independent Ethics Committee (IEC), no later than 7 days after knowledge by the Sponsor of such a case.

Relevant follow-up information is subsequently communicated within an additional 8 days, unless required differently by local laws and regulations.

All other SUSARs shall be reported to the competent authorities concerned and to the Ethics Committees concerned, within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor shall also inform all participating Investigators, as applicable, to the local regulations.

13.1.2. Relationship to Investigational Product

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 5. An AE for which there is a "reasonable possibility" that the investigational product caused the AE is otherwise referred to as SAR. "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "definite," "probable," or "possible" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 5: Relationship of Adverse Events to Investigational Product

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; that is confirmed by stopping or reducing the dosage of the investigational product; and that could not be reasonably explained by the known characteristics of the subject's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the investigational product; that does not follow a known or suspected response pattern to the suspected investigational product; and that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

13.1.3. Recording Adverse Event Severity

AEs must be graded for severity (i.e., intensity). A severity category of mild, moderate, severe, life-threatening, or death as defined in Table 6, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE.

Table 6: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	• Asymptomatic or mild symptoms; clinical or diagnostic observations only • Intervention not indicated • ADLs minimally or not affected • No or minimal intervention/therapy may be required
2 = Moderate	• Symptom(s) cause moderate discomfort • Local or noninvasive intervention indicated • More than minimal interference with ADLs but able to carry out daily social and functional activities. • Drug therapy may be required
3 = Severe (could be non-serious or serious)	• Symptoms causing severe discomfort/pain • Symptoms requiring medical/surgical attention/intervention • Interference with ADLs including inability to perform daily social and functional activities (e.g., absenteeism and/or bed rest) • Drug therapy is required
4 = Potentially Life-Threatening	• Symptoms requiring transport to the emergency room or hospitalization for medical/surgical attention/intervention, or, in the opinion of the Investigator, the subject is at immediate risk of death from the AE

ADLs=Activities of daily living; AE=adverse event.

13.1.3.1. Severity of Pruritus (as an Adverse Event)

Pruritus was the most common AE observed in the Phase 2 PBC studies of OCA and thus may occur in this study.

To ensure consistency in reporting, the following guidelines for assessing severity of pruritus should be used for AE reporting. As pruritus is a subjective symptom, clinical judgment should be used to determine its severity and management, as shown in Table 7.

Table 7: Severity of Pruritus

Pruritus Grade	Clinical Description of Severity for Pruritus and Medical Intervention
1 = Mild	Generally localized; causing no limitation of usual activities or minimal sleep disturbance; the subject may experience slight discomfort. Medicinal intervention is not indicated.
2 = Moderate	Intense or widespread; causing some limitation of usual activities or sleep disturbance; the subject may experience annoying discomfort. Medicinal intervention may be indicated.
3 = Severe	Intense or widespread and interfering with activities of daily living (ADL), i.e., causing inability to carry out usual activities, or severe sleep disturbance; the subject may experience intolerable discomfort. Medicinal intervention is typically indicated.

Since pruritus is a subjective symptom and the occurrence and magnitude of which are not readily measured by objective tools, clinical judgment needs to be applied in the management of each subject. Managing OCA-related pruritus may help improve tolerance in those subjects who experience clinically significant pruritus and may otherwise discontinue from the study prematurely. General guidance for the management of subjects experiencing significant pruritus includes the following:

- Drug holiday: A drug holiday is defined as an Investigator's "prescribed" complete interruption of dosing for 1 or more consecutive days (i.e., nondaily dosing does not constitute a drug holiday). Details of drug holidays and/or nondaily dosing regimens should be recorded in the eCRF. Subjects with pruritus ≥Grade 3 in severity (Table 7) and possibly, probably, or definitely related to the investigational product must discontinue investigational product but are encouraged to continue study visits. If the drug holiday lasts more than 30 days in the DB or LTSE Phase, the subject should be withdrawn from the study.
- Prescribing BAS (see Section 9.2.2): Subjects taking BAS (including cholestyramine and its derivatives, colestipol, colesevelam, or other BAS) should be instructed to not take these medicines during conduct of the study.
- Other therapies may be tried as deemed clinically appropriate.
- Less frequent dosing of investigational product (e.g., on alternate days) may be administered, after which, subjects may return to their original daily dose as soon as tolerated.

13.1.4. Reporting of Adverse Events and Serious Adverse Events

13.1.4.1. Reporting of Adverse Events

AE data will be collected from the time the signed informed consent is obtained until the subject fully completes her/his study participation of the study (i.e., discharge from the clinical unit).

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, severity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

In addition, the Investigator should contact the study Medical Monitor upon awareness of signs or symptoms of hepatic decompensation in any subject.

13.1.4.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Medical Monitor.

All SAEs must be immediately reported (i.e., within 24 hours of awareness) to the Sponsor.

SAEs are reported by entering the SAE data into the study-specific EDC system. Entering the SAE data into the EDC system will automatically notify the Sponsor of the SAE. In the event that the EDC system is inaccessible, an SAE may be reported by:

- Email to the SAE email address: sae@interceptpharma.com
- Fax using a paper SAE report form: + 1-800-497-8521

If an SAE is initially reported by email or fax, SAEs must also be entered in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Subject number
- Event term
- At least 1 criterion classifying the event as serious
- Name and title of the reporting individual
- Causal relationship to the investigational product

The Investigator will assess whether the event is causally related to investigational product. The Sponsor will also assess whether the event is causally related to investigational product, in addition to assessing the overall safety profile of the investigational product. The Sponsor will notify the appropriate regulatory agencies as well as all participating Investigators (where required) of Expedited Safety Reports that occur during the study within the time frames required by each regulatory agency.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to the Sponsor in the same manner as described above for the initial SAE report. Any supporting source documentation should be faxed to +1-800-497-8521 or emailed to sae@interceptpharma.com as soon as possible. Redacted medical record source documentation will be requested for all SAEs.

The Investigator is responsible for submitting information on Expedited Safety Reports received from the Sponsor to her/his local IRB/IEC, as directed by the local-country requirements. Documentation of the applicable submissions to IECs/IRBs must be retained in the appropriate

study file(s). As instructed by the Sponsor, Expedited Safety Reports should be retained in the appropriate investigative site study files, or with the IB.

13.1.4.3. Additional Investigator Responsibilities for SAEs

The safety data recorded in the eCRF represent the official record of all AEs and SAEs reported in the study. The Investigator should comply with requests by the Medical Monitor or other Sponsor personnel to record the SAE on the AE page of the subject's eCRF. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by the Medical Monitor, the Investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The Investigator and supporting personnel responsible for subject care should discuss any need for supplemental investigations of SAEs with the Medical Monitor. The results of these additional assessments must be reported to the Medical Monitor and to the SAE email address (sae@interceptpharma.com) or SAE fax number (+1 800-497-8521).

13.1.5. Notification of Post-Treatment SAEs for Subjects Who Continue in the Study

Post-treatment SAEs that occur in subjects who remain in the study after investigational product has been discontinued must be reported to the Sponsor within 24 hours by following the instructions provided in Section 13.1.4.2.

13.1.6. Notification of Post-Study SAEs

All SAEs that occur within 30 days following discontinuation from the study, whether or not they are related to the investigational product, must be reported to the Sponsor within 24 hours.

If an Investigator becomes aware of an SAE that may be attributable to the investigational product or study medication at any time after the end of the study, the Sponsor should be notified immediately (i.e., within 24 hours).

13.1.7. Follow-Up of Adverse Events and Serious Adverse Events

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the subject is lost to follow-up.

AEs ongoing at the final visit that are deemed to be "possibly, probably, or definitely" related or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the subject or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented on the eCRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

13.1.8. Pregnancy and Follow-Up

Pregnancies are not considered AEs in and of themselves; however, if a female study participant becomes pregnant while she is enrolled in the clinical study or within 14 days or 5 half-lives

after the last dose of investigational product, she must discontinue treatment with investigational product or study medication immediately and the Sponsor must be notified within 24 hours of the Investigator's awareness of the pregnancy by completing the Pregnancy CRF in EDC system and completing the Pregnancy Report Form.

In the event that a subject's partner is subsequently found to have become pregnant during the study or within 14 days or 5 half-lives after the last dose of investigational product or study medication, consent will be sought from the partner and, if granted, the partner (and infant) will be followed as considered appropriate by the Investigator and the Medical Monitor; at a minimum, the subject's partner must be followed by the Investigator through pregnancy outcome.

The Pregnancy Report Form must be emailed to sae@interceptpharma.com or faxed to +1 800-497-8521. The subject and neonate must be followed for outcome information and/or as considered appropriate by the Investigator and the Sponsor.

Completing the Pregnancy Report Form is not a substitute for reporting an AE/SAE when an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures must also be followed (Section 13.1.4).

13.2. Other Safety Parameters

13.2.1. Medical History/Demographics

A complete medical history will be obtained from the subject at Screening. Demographic characteristics (age, sex, race, and ethnicity) will be recorded.

13.2.2. Physical Examination

To assess for clinical findings, the Investigator or designee will perform a physical examination at the timepoints specified in the Schedule of Study Procedures (Table 1). This includes height and body weight only at Screening. The physical examination must include the following:

- General appearance
- Height (Screening Visit only)
- Body weight (and BMI at Screening Visit only)
- Skin
- Head, eyes, ears, nose, and throat
- Neck
- Lymph nodes
- Chest/Respiratory system
- Cardiovascular system
- Abdominal region
- Extremities

- Musculoskeletal system
- Mental status
- Neurological system

13.2.3. Height and Weight

Weight will be measured using a scale that has been calibrated per the manufacturer's manual before the start of the study.

Depending on the subject's age and ability to stand, height may be measured lying down (recumbent) or standing upright. If possible, measure the subject in the same position (i.e., recumbent or upright) throughout the study.

13.2.4. Z-Score

Z-scores will be calculated using guidance provided by WHO or other site-specific reference standards.

13.2.5. Child-Pugh

The Child-Pugh score will be calculated as described in Section 7.6.5.1.

13.2.6. PELD/MELD

The PELD or MELD scores will be calculated as described in Section 7.6.5.2.

13.2.7. Vital Signs

Vital signs will be assessed at the timepoints specified in the Schedule of Study Procedures (Table 1). Vital signs include oral temperature, sitting heart rate, respiratory rate, and sitting blood pressure (BP), as per site's standard for the subject's age. When taking heart rate, respiratory rate, and BP readings, subjects should be seated quietly for a minimum of 3 minutes before the readings are taken.

Since drinking hot or cold beverages (including water) has a significant impact on recorded oral body temperature, no beverages should be ingested within 15 minutes prior to all oral body temperature measurements. If the scheduled time for vital signs coincides with a blood collection, the blood draw should be performed as scheduled, with vital signs being performed prior to the blood collection. The same timing for obtaining vital signs (e.g., prior to blood collection) should be used for all vital sign measurements.

Acceptable deviations from the nominal vital sign measurement timepoints are:

- Predose vital signs measurements should be taken within ≤2 hours before dosing.
- Postdose vital signs measurements may be taken ±15 minutes from the nominal postdose timepoints.
- Discharge vital signs measurements may be taken ±1 hour from the nominal timepoint.

If a subject shows an abnormal assessment at any stage, repeat measurements may be requested by the Investigator and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the Investigator.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

13.2.8. Nutritional Status

Nutritional status will be evaluated using a combination of BMI and triceps skinfold thickness and mid-arm circumference using a Lange skinfold caliper per WHO or other site-specific reference standards.

https://www.who.int/tools/child-growth-standards/standards/triceps-skinfold-for-age

13.2.9. Electrocardiograms

Standard 12-lead ECGs will be collected. The Investigator or designee will review the 12-lead ECG and findings will be recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. Any clinically significant abnormalities on ECGs recorded after Day -1 will also be documented as AEs and entered on the AE page of the eCRF.

Investigative sites must retain a copy of all 12-lead ECGs evaluated by the Investigator or designee. These ECGs must be clearly labeled with the Subject ID number, date, and time.

13.2.10. Laboratory Assessments

Blood and urine samples will be collected and analyzed or tested for the following (all of these samples will be collected while the subject is fasting):

- Hematology (hemoglobin, hematocrit, white blood count with differential, platelets, red blood count)
- Serum chemistry (albumin, blood urea nitrogen, creatine phosphokinase, creatinine, direct bilirubin, total bilirubin, AST, ALT, ALP, GGT, electrolytes [calcium, chloride, potassium, and sodium], glucose, total protein, and blood lipids [total cholesterol, LDL, HDL, and very low-density lipoprotein fractions and triglycerides], FSH).
- Coagulation (prothrombin time, activated partial prothrombin time, and INR).
- Virology screen (human immunodeficiency virus [HIV], hepatitis B surface antigen, and hepatitis C virus antibody)
- Urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, blood, microscopic exam)
- Drug screen (amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and cannabinoids)
- Urine alcohol test
- Urine-based β-hCG pregnancy test

All subjects with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product-related AE, is identified; or until further follow-up is deemed medically unnecessary. Subjects who test positive for urine drug screen will be excluded from the study.

Serum-based human chorionic gonadotropin pregnancy tests will be performed on all female subjects per protocol-specified visits. If positive, the Sponsor must be notified, and the subject will be followed as outlined in Section 13.1.8 until pregnancy outcome. FSH tests will also be performed for females of nonchildbearing potential and postmenopausal subjects per protocol-specified visits (Table 1).

All additional biomarkers of disease severity and blood samples (including lipid panel) collected for additional biomarker analysis will be stored for up to 1 year after the end of the study and destroyed if not analyzed.

The list of laboratory analytes to be tested is shown in Table 8.

Table 8: List of Laboratory Analytes to be Tested

Laboratory Assessment	Analyte
All Subjects	
Serum chemistry	Albumin, BUN, creatinine, conjugated (direct) bilirubin, total bilirubin, AST, ALT, ALP, GGT, creatinine phosphokinase, electrolytes (calcium, chloride, magnesium, phosphorus, potassium, sodium), total protein, bicarbonate, free fatty acids; and blood lipids (total cholesterol, LDL, HDL, and VLDL fractions and triglycerides)
Hematology	Hemoglobin, hematocrit, white blood count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets, red blood cell count (including MCV, MCH, MCHC)
Urinalysis	pH, specific gravity, protein, glucose, ketones, bilirubin, blood, microscopic exam
Urine Drug Screen	Amphetamines, barbiturates, benzodiazepines, phencyclidine, Cannabinoids, cocaine, and opiates
Coagulation	PT, PTT, INR
Glycemic control measures	Fasting plasma glucose, insulin, C-peptide, HbA1c, HOMA-β, and HOMA-IR
Lipoprotein analysis[a]	LDL, HDL, VLDL, total cholesterol, triglycerides, ApoA1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a), PCSK9
Reverse Cholesterol Transport	Pre-β HDL, macrophage cholesterol efflux, LCAT and CEPT
Markers of Inflammation	IL-6, hs-CRP, and TNF-α

Markers of fibrosis and apoptosis	CK-18-M30
Vitamin D and K levels	Vitamin Dand K
Thyroid function tests	T3, T4, TSH
Virology	HIV, HCV, HBV
SARs-CoV-2 Test	SARs-CoV-2
PD Assessment	C4 and FGF-19; analysis of conjugated and unconjugated bile acids
Blood sample for future analysis, including markers of cardiovascular risk	adiponectin, PAI-1, BNP
Pregnancy Test (female subjects of childbearing potential)	β-hCG
PK analytes	OCA, tauro-OCA, glyco-OCA

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; ApoCI=apolipoprotein CI; ApoCII=apolipoprotein CII; ApoE=apolipoprotein E; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; BUN=blood urea nitrogen; C4=7α-hydroxy-4-cholesten-3-one; CK-18-M30=cytokeratin-18 neoepitope M30; GGT=gamma-glutamyl transferase; HbA1c=hemoglobin-specific A1c fraction; HBV=hepatitis B virus; HCV=hepatitis C virus; HDL=high-density lipoprotein; HIV=human immunodeficiency virus; HOMA-β=homeostatic model assessment–beta-cell function; HOMA-IR=homeostatic model assessment – insulin resistance; hs-CRP=high-sensitivity C-reactive protein; IL-6=interleukin-6; INR=international normalized ratio; LCAT=lecithin cholesterol acyltransferase; LDL=low-density lipoprotein; Lp(a)=lipoprotein(a); MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PAI-1=plasminogen activator inhibitor-1; PCSK9=proprotein convertase subtilisin/kexin type 9; PK=pharmacokinetic; PT=prothrombin time; PTT=partial thromboplastin time; T3=triiodothyronine; T4=thyroxine; TNF-α=tumor necrosis factor-α; TSH=thyroid-stimulating hormone; VLDL=very low-density lipoprotein

[a] NMR-based panel will be used for (a) LDL, HDL, and VLDL cholesterol concentrations, particle sizes, and particle concentrations, and (b) ApoA1, ApoB, ApoE, ApoCII, ApoCIII and Lp(a) concentrations. Serum chemistry panel will be used for LDL, HDL, VLDL, triglycerides, and total cholesterol concentration.

All subjects with laboratory tests containing clinically significant abnormal values are to be followed regularly until the values return to normal ranges; until a valid reason, other than investigational product-related AE, is identified; or until further follow-up is deemed medically unnecessary.

Urine-based β-hCG pregnancy tests will be performed in female subjects of childbearing potential per protocol-specified visits (Table 1). If a urine pregnancy test is positive, a quantitative serum pregnancy test must be performed to confirm the result. If positive, the Sponsor must be notified, and the subject will be followed as outlined in Section 13.1.8 until pregnancy outcome.

All blood samples for future analysis and blood samples collected after Month 18 for enhanced liver fibrosis (ELF) and FibroTest/FibroSure will be stored for up to 1 year after the end of the study and destroyed if not analyzed.

INR will be calculated based on prothrombin time value by the central laboratory. MELD scores will be calculated based on creatinine, bilirubin, and INR values, with modification by United Network for Organ Sharing. Homeostatic model assessment – insulin resistance (HOMA-IR) values will be calculated based on glucose and insulin concentrations. Total OCA will be calculated based on OCA, tauro-OCA, and glyco-OCA concentrations. Laboratory analyte results may be used to calculate various cardiovascular risk and fibrosis measurement scores.

14. STATISTICAL METHODS

A Statistical Analysis Plan (SAP) providing details about the specific planned analyses (interim and final), which include efficacy, safety, and PK/PD analyses, will be prepared and approved by the Sponsor or its designees prior to study database lock. The PK modeling will be included in a separate clinical pharmacology analysis plan (CPAP).

In general, data will be presented by treatment group. Data for all subjects combined will also be reported when appropriate.

The following descriptive statistics will be used to summarize the data where applicable or otherwise specified:

- Categorical variables: number and percentage of subjects within each category, including a category for missing data, will be presented.
- Continuous variables: summary statistics will include the number of subjects, number of non-missing counts, the mean, standard deviation (SD), median, interquartile range, minimum, and maximum values.

The demographic variables and baseline disease characteristics, the exposure to treatment, the prior and concomitant medications/therapies, as well as the efficacy, safety, and PK/PD variables will be summarized by the treatment group. In addition to the summary statistics, the inferential statistics involving estimation and hypothesis testing will be conducted for the efficacy variables. All tests will be two-tailed using a 0.05 level of significance and all confidence intervals (CIs) two-sided 95% CIs.

14.1. Analysis Populations

The following analysis populations will be used:

Intent-to-Treat (ITT) Population

The ITT Population will include all randomized subjects. The treatment assignment will be based on randomized treatment. The ITT Population will be the primary population used for all interim and final efficacy analyses and PD analyses, if applicable.

Modified ITT (mITT) Population

The mITT Population will include all subjects from the ITT Population, who took at least one dose of investigational product (OCA or placebo) and who received treatment for at least 4 months. The mITT population will serve as the secondary analysis population for the efficacy and PD analyses.

Pharmacokinetic Population

The PK Population will consist of all subjects who receive OCA, have at least one confirmed analyzable sample, and have no major protocol deviations that may potentially affect the PK analysis.

Safety Population

The Safety Population will include all subjects who receive at least one dose of investigational product (OCA or placebo). Treatment assignment will be based on the actual treatment that is received.

14.2. Determination of Sample Size

The overall study sample size is estimated based on the clinical outcome composite endpoint analysis at the end of the study; time to the first occurrence of any component of the adjudicated clinical outcome (death, liver transplant, and markers of decompensated liver damage).

A total of 66 composite events will be required in the OCA and placebo groups in a 1:1 ratio, to provide about 80% power via two-sided log-rank test at the 0.05 significance level, assuming a hazard ratio of 0.50 between the OCA and placebo groups. Approximately 144 subjects for the 2 groups will be required to obtain the 66 events based on the additional assumptions:

- Total study duration of 4 years, allowing 1.5 years accrual and up to approximately 24 months of follow-up
- Placebo event rate of 52% over 1.5 years
- 20% discontinuation rate

14.3. Efficacy and PD Analyses

14.3.1. Primary Efficacy Analyses

The primary efficacy variable is time to the first occurrence of any component of the composite clinical outcome (adjudicated death, liver transplant, and markers of decompensated liver damage).

The OCA and placebo treatment groups will be compared using the log-rank test stratified by age group (using median as the cutoff value). A Cox regression model, including the treatment group and the age group, will be used to estimate the hazard ratio, along with a 95% CI. Kaplan-Meier estimates of the distribution of the time to event will be tabulated and presented by treatment group. The number and percentage of subjects censored and with events will be presented.

The primary analysis will be based on the ITT Population including all data, regardless of the intercurrent events (i.e., the use of prohibited medication and treatment discontinuation).

The same analysis will be repeated for mITT population as a sensitivity analysis.

Another sensitivity analysis will be performed based on the ITT Population, excluding data following the intercurrent events (prohibited medication and treatment discontinuation) by censoring the time to event at the time of any intercurrent event.

14.3.2. Secondary Efficacy Analyses

The secondary efficacy endpoints include:

- Composite endpoint of biomarkers – proportion of subjects with improvement in GGT and direct (conjugated) bilirubin. A subject is a responder if:
    - Percent change from baseline in GGT is ≤ -40%
    - Percent change from baseline in bilirubin is ≤ -25%
    - The month-4 assessments will be used for the first interim analysis, and final assessments used for the EOS analysis
- Change and percent change in GGT
- Change and percent change in total and direct (conjugated) bilirubin
- Change and percent change in total plasma bile acids
- Change in Plasma FGF-19, C4, transient elastography
- Change in plasma levels of fat-soluble vitamins (D and K)

All secondary efficacy endpoints will be analyzed based on the ITT Population including all data, regardless of intercurrent events (i.e., the use of prohibited medication and treatment discontinuation).

The composite endpoint of biomarkers and other responder endpoints will be analyzed by using Cochran Mantel Haenszel (CMH) test, stratifying by age group (using median as the cutoff value). Subjects with missing values will be considered as non-responders.

Continuous variables (e.g., percent change in GGT, bilirubin, total plasma bile acids, and change in GGT from baseline) will be carried out using a mixed model for repeated measures (MMRM) to evaluate the effect of treatment groups over time. The model will include the terms of treatment group, visit, and treatment by visit interaction as factors, and age and the corresponding baseline value as covariates.

The least-squares means (LSM) (95% CI) of change will be presented for each treatment group. The LSM (95% CI) for the treatment difference will also be presented.

14.3.3. Exploratory Analyses

Acceptability and swallowability of a subject's dose regimen will be determined using the five-point criteria evaluation and will be summarized by the treatment group. A by-age subgroup summary will also be presented. Palatability will be assessed at the Week 6 visit using a five-point FHS/VAS-5 scale in children ≥4 years of age. Children <4 years will have palatability assessed using a four-point criteria evaluation.

14.3.4. Interim Analyses

The first interim analysis will be conducted after approximately 25 to 30 subjects reach Month 4; assessments of GGT, total and direct (conjugated) bilirubin, and total plasma bile acids will be evaluated. Responders are defined as having a ≥40% reduction from baseline in GGT and ≥25% reduction from baseline in direct bilirubin at Month 4.

Assuming a 10% and 55% response rate for the placebo and OCA groups, respectively, and a total sample size of 30, the mean (95% CI) for the treatment difference is 45% (16% to 74%). The treatment difference of at least 15% is considered to be a clinically important difference.

The study will be terminated for futility if the futility boundary of 15% is crossed (i.e., if the treatment difference falls outside of the lower bound of the 95% CI).

Safety data will be evaluated by the DSMB at the time of the interim analysis. The study may be terminated for safety reasons (see Section 7.5).

Subjects <2 years of age will be recruited into the study following advice of the DSMB after the interim analysis.

The second interim analysis will be performed based on the primary endpoint (time to first occurrence of clinical outcomes). The timing of the second interim analysis will be at approximately 12 months and will be confirmed by the DSMB following the first interim analysis. A group sequential design and conditional power approach will be utilized (EMA 2007). At the time of the interim analysis, the interim data will be analyzed to determine the conditional power. If the power is not acceptable, the trial will be terminated for futility.

The interim analyses will be detailed in the SAP.

14.3.5. Examination of Subgroups

The primary and secondary efficacy endpoints will be analyzed for subject subgroups based on the ITT Population. Subgroups will be assessed at baseline.

Baseline subgroups of interest are as follows: age group, years since diagnosis of biliary atresia, sex, race, GGT, total and direct bilirubin, and total plasma bile acids.

14.3.6. Handling of Missing Data

Subjects who discontinue the treatment are expected to continue in the study until study termination. Missing data will be assumed to be missing at random in general. No data will be imputed unless otherwise specified. Missing data handling will be detailed in SAP.

14.3.7. Multiplicity

The 2-sided alpha allocated to all testing for the final data analyses will be 0.05.

In addition to the final data analyses, the IA based on the biochemical endpoints will be tested at month 4 data cut to detect early signs of efficacy. The second IA will be performed based on the primary endpoint, the composite score of the clinical outcomes. The trial will be terminated for futility for either IA. The IAs will be detailed in SAP.

14.4. Pharmacokinetic (PK), Pharmacodynamic (PD), and PK/PD Analysis

Plasma concentrations of OCA (parent), glyco-OCA, tauro-OCA, and total OCA will be quantified and summed for total OCA. The predose plasma concentrations at steady state (C_{trough}) will be the only PK exposure parameter to be summarized for the OCA final dose groups and utilized in exposure-response analyses. For this pediatric study, the body weight-adjusted concentrations may be presented in addition to the un-adjusted values.

For further modeling and simulation efforts to support eventual efficacious dose in pediatric patient population, the PK data obtained from this study may also be integrated with the PK data from other studies including in adult patients.

PD data will be summarized as the change from baseline, which will then be correlated with PK exposure (C_{trough}) for PK/PD analyses. The clinical response (efficacy and safety) data will also be attempted to examine their associations with PK exposure.

14.5. Safety Analysis

Safety data will be summarized using descriptive statistics. The safety analysis will include the incidence of TEAEs. The incidence will be tabulated by system organ class (SOC) and preferred term, and similarly by severity and relationship to treatment.

Laboratory parameters, vital signs, and ECGs will be summarized using descriptive statistics at baseline and at each scheduled postbaseline visit. The change from baseline will also be summarized.

14.5.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables of TEAEs will be provided.

The incidence of TEAEs will be tabulated by system organ class (SOC) and preferred term for each treatment group and by severity and relationship to treatment. Summaries of TEAEs leading to treatment discontinuation and SAEs will be provided.

In addition, the following AESI will be summarized: pruritus, hepatic disorders, cholecystitis/cholelithiasis, renal, cardiovascular, dyslipidemia.

14.5.2. Clinical Laboratory Evaluations

Laboratory parameters will be summarized using descriptive statistics at baseline and at each scheduled postbaseline visit. The change from baseline will also be summarized.

In addition, shift tables from baseline based on normal ranges will be provided for hematology, coagulation, and serum chemistry to assess changes in laboratory values from baseline to each postbaseline evaluation.

14.5.3. Additional Safety Analysis

14.5.3.1. Vital Signs

Vital signs will be summarized using descriptive statistics at baseline and at each scheduled postbaseline visit. The change from baseline will also be summarized.

14.5.3.2. Electrocardiograms

ECGs will be summarized using descriptive statistics at baseline and at each scheduled postbaseline visit. The change from baseline will also be summarized.

14.5.3.3. Physical Examination

The abnormal findings observed during physical examinations will be summarized for each study visit.

14.6. Data Management

To ensure the quality of clinical data across all subjects and sites, Intercept's Data Management or its designee will perform data review on a regular basis throughout the conduct of a study in accordance to the study's Data Management Plan (DMP). Data Management Review is performed on an ongoing basis throughout the project. Queries are posted accordingly and resolved/closed in a timely manner. Special focus to critical safety and efficacy variables is given prior to any milestone being completed. Reconciliation of SAEs between the clinical and safety databases will be performed by Intercept's Data Management or designee.

A start-up training presentation is conducted at the Investigator kick-off meeting wherein Investigators and site coordinators are trained on different aspects of the web-based EDC system and completion of the electronic case report forms (eCRF). Data Management also creates instructional material (such as eCRF Completion Guidelines) which is made available to the study sites.

Access to the EDC system will be granted once the system-specific user role training has been successfully completed. eCRF data will be encoded and stored in a clinical trial database. Edit checks, which are part of the data validation process, and safety alerts will be programmed in the EDC application to detect data errors and safety signals. Corrections to data collected in eCRFs will be automatically documented through the audit trail of the EDC system which is 21 CFR Part 11 compliant.

14.7. Data Safety Monitoring Board

The DSMB is an independent committee that includes individuals who will not be involved in the study. The independent DSMB will review safety data periodically during the conduct of the trial. The safety review will be detailed in the DSMB Charter.

14.8. Adjudication Committees

All suspected liver-related clinical outcomes that occur after administration of the first dose of investigational product will be reviewed by a blinded GSC, Hepatic Outcomes Committee (HOC), and HSAC before inclusion in any final analysis.

Each adjudication committee will have a charter that documents the reporting of events by the study site, definition of the suspected events to be adjudicated, supply of source documentation to the committee, entire data flow and process from committee membership, review of the events by the committee, reporting of the final assessment, and the working procedures of the committee.

The adjudication committee members will include experts with relevant adjudication experience; they will not be involved in the study as Investigators, DSMB members, or consultants. Any candidate found to have a conflict or whose name is listed on the EMA/local regulatory agency debarment list is not offered membership. Conflicts of interest are assessed regularly, and if members are found to have a new conflict of interest they will be replaced.

The adjudication of suspected events will be based on available source documentation, including but not limited to individual clinical study data, hospital records, histology, discharge summaries, and/or death certificates. The adjudication committees will not receive any individual subject

treatment or site-specific information. The assessment of events will be conducted in compliance with study-specific procedures, manuals, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Study records at each site will be monitored at regular intervals by a representative of the Sponsor, the CRA. The role of the CRA is to aid the Investigator in the maintenance and documentation of complete, accurate, legible, well-organized, and easily retrievable data. In addition, the CRA will ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential documentation is available.

In order to perform this role, the CRA must perform source data verification and as such must be given access to the subject's primary source documentation (e.g., paper or electronic medical records such as consent to participate in the study, visit dates, screening and randomization numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs, concomitant medications, dates of dispensing investigational product, ECGs, etc.) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the Medical Monitor.

The Investigator may exercise judgment in allowing the CRA access to particular sections of the subject's medical records if these are deemed irrelevant to the performance, observations or conduct of this study.

15.2. Audits and Inspections

The Investigator should understand that it may be necessary for the Sponsor, the IEC/IRB and/or regulatory agencies to conduct one or more site audits during or after the study and agrees to allow access to all study-related documentation and information and be available for discussion about the study.

16. QUALITY CONTROL AND QUALITY ASSURANCE

Logic and consistency checks will be performed on all data entered into the eCRF or ultimately transferred into the database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the Sponsor or designated personnel (e.g., CRA), instruction manuals, data verification, cross checking and data audits will be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate collection of study data.

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 15.2 for more details regarding the audit process.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF and/or other subject information, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written IRB/IEC approval to Intercept before he or she can enroll any subject into the study. The Investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to study subjects to the IRB/IEC for review.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. A favorable opinion on amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, according to local regulations and guidelines. The Sponsor will provide this information to the Investigator. Progress reports and notifications of SARs will be provided to the IRB/IEC according to local regulations and guidelines. Investigators or the Sponsor or its designee will provide reports to the IRB/IEC as requested, at a minimum annually, and after the study is complete.

17.2. Declaration of the End of the Study

The definition of the end of the study is defined as the last visit of the last subject (e.g., follow-up assessment; discharge from the clinical unit, follow-up assessment). Any changes to this definition will be notified as a substantial amendment (see Section 18.2).

The Principal Investigator or the Sponsor or its designee will provide reports to the IRB as requested, at a minimum annually, and after the study is complete.

17.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor's policies.

17.4. Written Informed Consent

The Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects

must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated consent form must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed Patient Information Sheet and Consent Form (PIS-IC). A copy of the PIS-IC must be given to the subject.

17.5. Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (e.g., CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification, but the subject's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access.

The Investigator will maintain a list of subject's names and identifying information (e.g., subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by the Sponsor or designee will be identified by unique subject number/randomization code/site number, only.

When personal data on subjects are stored or processed by computer, the data must be protected to prevent disclosure to unauthorized third parties. The pertinent sections of the data protection laws in the country in which the protocol is being conducted will be complied with in full.

The ICF will explain that, for data verification purposes, authorized representatives of the Sponsor, regulatory authorities, or IEC/IRBs may require direct access to parts of the hospital or study site records relevant to the study, including subject's medical history.

18. INVESTIGATOR OBLIGATIONS

The Investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects for the duration of the study. If the Investigator is not present in the study site during the assessment, he or she will leave instructions for the study site staff and a telephone number where he or she can be reached.

Named physician(s) will be responsible for the medical follow-up of subjects, as applicable.

18.1. Adverse Event Reporting

The Investigator is responsible for recording AEs reported by the subject or discovered by any other means during the study. In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediate reporting of SAEs to the Sponsor.

18.2. Protocol Amendments and Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee) unless the Investigator and/or IRB/IEC considers a subject's safety to be compromised if immediate action is not taken. Only the Sponsor may amend the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval, as necessary.

18.3. Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained:

- Approved ICFs (all versions)
- IRB/IEC approvals (of protocol/amendments, subject questionnaires, etc.)
- ICH-GCP agreement/non-USA 1572 alternate form
- Current medical license of Investigators,
- Curriculum vitae of Investigators,
- Laboratory certification and reference ranges,
- Financial disclosure forms.

In addition, a copy of the IRB approval will be available at the clinical and Sponsor sites.

18.4. Ethics Review (IRB/IEC)

Please see Section 17.1 for the Investigator's responsibilities regarding ethics review.

18.5. Archiving and Record Retention

The Investigator should retain all essential documents and correspondence relating to this study in the investigator site file (ISF). Any study documents stored elsewhere should have their location referenced in the ISF table of contents or in a note to file.

All documents relating to the study including the ISF itself, source documents and subject medical files (retained per country specific regulations), completed study subject log and confidential subject identification list will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an International Conference for Harmonisation (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. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by

the Sponsor. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the Investigator should obtain written authorization from the Sponsor before the destruction of any records. The Investigator will notify the Sponsor if ownership of documents or responsibility for the study site is transferred. The Sponsor will inform Investigators should it become aware of any changes in storage requirements.

19. PUBLICATION POLICY

The Sponsor intends to publish the results of all of the clinical studies that it Sponsors consistent with the Declaration of Helsinki. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Intercept-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study (http://www.icmje.org). Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, the Sponsor has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include the following:

- Clinical Trial Registries (e.g., www.clinicaltrials.gov, www.clinicaltrialsregister.eu): A description of the study and relevant design elements (e.g., basic design, objectives and endpoints, sample size, study population, and key inclusion/exclusion criteria) and results will be published online in a manner consistent with applicable regulatory guidelines.
- Overview: Investigators, reviewers and editors will have the right to audit the data to verify its accuracy.
- Responsibility: Each Investigator is responsible for the accuracy and completeness of all data from her/his site. The Sponsor (or its representatives) is responsible for the accuracy of the data entered into the study databases and the analyses conducted.
- Data Management: The Sponsor will establish data management and SAP. The Investigators will have the opportunity to provide input into the plans. The Investigators will have the right to review the audit reports and data resolution decisions prior to the establishment of a clean file. The Investigators will have the right to appoint appropriately qualified auditors, with GCP experience, to audit the Sponsor's data prior to the establishment of a clean file. The Investigators must provide adequate notice (at least 2 months) to the Sponsor of their intention to audit a study. The audit should be conducted in a timely manner to allow the resolution of discrepancies before a clean file is established. The Investigators will bear all the costs for the conduct of audits that they initiate, except those related to the resolution of data queries which the Sponsor will bear. Such audits must be conducted in such a manner as to minimize the time to create the clean file.
- Authorship: Intercept, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance

with the principles of the ICMJE. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.

- Single Center Publication and Additional Publications: This is a multicenter study and is designed to be published with complete data from all the study sites. Single center publications are therefore not considered appropriate. Any such publications should clearly state that the data are "extracted" from a multicenter study and that the study was not intended, or statistically powered, for data presentation by a single study site.
- Intercept Review of External Manuscripts: Consistent with this, Investigators must submit any drafts of any publications or presentations that may arise from this study to the Sponsor for review and approval and to ensure consistency with the policy in this protocol at least 30 days prior to submission for publication or presentation. The Sponsor will have the right to request appropriate modification to correct facts and to represent its, or the Publication Committee's, opinion if these differ with the proposed publication.
- Confidentiality: Investigators will conduct all interactions with the company and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of preclinical studies or chemical formulae) may still need to remain confidential.
- Medical Journal Review: Upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, e.g., protocol and amendments, data tabulations, etc. Arrangements will be made to maintain the confidentiality of such supplemental information. Arrangements will also be made to maintain the confidentiality of the identity of journal reviewers. Records will be maintained of which documents and datasets were reviewed.

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APPENDIX A. WEIGHT-BASED DOSING CHARTS

Table 9: Target Dose of 1.5 mg Adult-Equivalent

Target Dose of 1.5 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
9	2	0
10	2	0
11	2	0
12	3	0
13	3	0
14	3	0
15	3	0
16	3	0
17	4	0
18	4	0
19	4	0
20	4	0
21	5	0
22	5	0
23	5	0
24	5	0
25	5	0
26	6	0
27	6	0
28	6	0
29	6	0
30	6	0
31	7	0
32	7	0
33	7	0
34	7	0
35	8	0
36	8	0
37	8	0
38	8	0
39	8	0

Target Dose of 1.5 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
40	9	0
41	9	0
42	9	0
43	9	0
44	9	0
45	10	0
46	10	0
47	10	0
48	10	0
49	11	0
50	11	0
51	11	0
52	11	0
53	11	0
54	12	0
55	12	0
56	12	0
57	12	0
58	12	0
59	0	1
60	0	1
61	0	1
62	0	1
63	0	1
64	0	1
65	0	1
66	0	1
67	0	1
68	0	1
69	0	1
70	0	1
71	0	1

Target Dose of 1.5 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
72	0	1
73	0	1
74	0	1
75	0	1
76	0	1
77	0	1
78	0	1
79	0	1
80	0	1
81	0	1
82	0	1
83	0	1
84	0	1
85	0	1
86	0	1
87	0	1
88	0	1
89	0	1
≥ 90	0	1

Table 10: Target Dose of 3 mg Adult-Equivalent

Target Dose of 3 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
9	4	0
10	4	0
11	5	0
12	5	0
13	6	0
14	6	0
15	6	0
16	7	0
17	7	0
18	8	0
19	8	0
20	9	0
21	9	0
22	9	0
23	10	0
24	10	0
25	11	0
26	11	0
27	12	0
28	12	0
29	12	0
30	0	1
31	0	1
32	0	1
33	0	1
34	0	1
35	0	1
36	0	1
37	0	1
38	0	1

Target Dose of 3 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
39	0	1
40	0	1
41	0	1
42	0	1
43	0	1
44	0	1
45	0	1
46	0	1
47	0	1
48	0	1
49	0	1
50	0	1
51	0	1
52	0	1
53	0	2
54	0	2
55	0	2
56	0	2
57	0	2
58	0	2
59	0	2
60	0	2
61	0	2
62	0	2
63	0	2
64	0	2
65	0	2
66	0	2
67	0	2
68	0	2

Target Dose of 3 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
69	0	2
70	0	2
71	0	2
72	0	2
73	0	2
74	0	2
75	0	2
76	0	2
77	0	2
78	0	2
79	0	2
80	0	2
81	0	2
82	0	2
83	0	2
84	0	2
85	0	2
86	0	2
87	0	2
88	0	2
89	0	2
≥ 90	0	2

Table 11: Target Dose of 5 mg Adult-Equivalent

Target Dose of 5 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
9	6	0
10	7	0
11	8	0
12	9	0
13	9	0
14	10	0
15	11	0
16	11	0
17	12	0
18	0	1
19	0	1
20	0	1
21	0	1
22	0	1
23	0	1
24	0	1
25	0	1
26	0	1
27	0	1
28	0	1
29	0	1
30	0	1
31	0	1
32	0	2
33	0	2
34	0	2
35	0	2
36	0	2
37	0	2
38	0	2

Target Dose of 5 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
39	0	2
40	0	2
41	0	2
42	0	2
43	0	2
44	0	2
45	0	2
46	0	2
47	0	2
48	0	2
49	0	2
50	0	2
51	0	2
52	0	2
53	0	3
54	0	3
55	0	3
56	0	3
57	0	3
58	0	3
59	0	3
60	0	3
61	0	3
62	0	3
63	0	3
64	0	3
65	0	3
66	0	3
67	0	3
68	0	3

Target Dose of 5 mg Adult-Equivalent		
Subject Weight (kg)	**0.1 mg OCA Mini-tablet (Number of Mini-tablets)**	**1.5 mg OCA Tablet (Number of Tablets)**
69	0	3
70	5	3
71	5	3
72	5	3
73	5	3
74	5	3
75	5	3
76	5	3
77	5	3
78	5	3
79	5	3
80	5	3
81	5	3
82	5	3
83	5	3
84	5	3
85	5	3
86	5	3
87	5	3
88	5	3
89	5	3
≥ 90	5	3

APPENDIX B. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Publish Date: November 27, 2017

Introduction
The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms
An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

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 ADL*.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5
Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

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Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements. **Navigational Note:** -					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors. **Navigational Note:** -					
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood. **Navigational Note:** -					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. **Navigational Note:** -					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 g decrease in hemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction. **Navigational Note:** -					

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemolytic uremic syndrome	-	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. **Navigational Note:** -					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood. **Navigational Note:** -					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node. **Navigational Note:** -					
Methemoglobinemia	-	>ULN	Requiring urgent intervention	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate increased methemoglobin in the blood. **Navigational Note:** -					
Thrombotic thrombocytopenic purpura	-	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition. **Navigational Note:** -					
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in aortic valve function or structure. **Navigational Note:** -					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the pumping function of the heart. **Navigational Note:** -					
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation; new onset	Life-threatening consequences; embolus requiring urgent intervention	Death
Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles. **Navigational Note:** -					
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation	Life-threatening consequences; embolus requiring urgent intervention	Death
Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria. **Navigational Note:** -					
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles. **Navigational Note:** -					
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart. **Navigational Note:** -					
Chest pain - cardiac	Mild pain	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable	Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation e.g., angina pectoris. **Navigational Note:** Also consider Cardiac disorders: Myocardial infarction.					
Conduction disorder	Mild symptoms; intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences	Death
Definition: A disorder characterized by pathological irregularities in the cardiac conduction system. **Navigational Note:** -					
Cyanosis	-	Present	-	-	-
Definition: A disorder characterized by a bluish discoloration of the skin and/or mucous membranes. **Navigational Note:** -					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure. **Navigational Note:** If left sided use Cardiac disorders: Left ventricular systolic dysfunction; also consider Cardiac disorders: Restrictive cardiomyopathy, Investigations: Ejection fraction decreased.					
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output. **Navigational Note:** Also consider Investigations: Ejection fraction decreased.					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in mitral valve function or structure. **Navigational Note:** -					
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles. **Navigational Note:** -					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles. **Navigational Note:** -					
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area. **Navigational Note:** -					
Myocarditis	-	Symptoms with moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart. **Navigational Note:** -					
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; ablation	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria. **Navigational Note:** -					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation. **Navigational Note:** -					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium. **Navigational Note:** -					
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart). **Navigational Note:** -					
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in pulmonary valve function or structure. **Navigational Note:** -					
Restrictive cardiomyopathy	Imaging findings only	Symptomatic without signs of heart failure	Symptomatic heart failure or other cardiac symptoms, responsive to intervention; new onset of symptoms	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
Definition: A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall. **Navigational Note:** -					
Sick sinus syndrome	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness. **Navigational Note:** -					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node. **Navigational Note:** -					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node. **Navigational Note:** -					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles. **Navigational Note:** -					
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in tricuspid valve function or structure. **Navigational Note:** -					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles. **Navigational Note:** -					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His. **Navigational Note:** -					
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Congenital, familial and genetic disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Congenital, familial and genetic disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear. **Navigational Note:** -					
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the external ear region. **Navigational Note:** -					
Hearing impaired	**Adults** enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6, and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Subjective change in hearing in the absence of documented hearing loss; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB hearing loss (HL) (i.e., 25 dB HL or greater); sensorineural hearing loss (SNHL) above 4 kHz (i.e., 6 or 8 kHz) in at least one ear	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention not indicated; limiting instrumental ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz in at least one ear	**Adults** enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated; **Adults** not enrolled on a Monitoring Program: Hearing loss with hearing aid or intervention indicated; limiting self care ADL; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 2 to < 4 kHz in at least one ear	**Adults:** Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); nonservicable hearing **Pediatric:** Audiologic indication for cochlear implant; > 40 dB HL (i.e., 45 dB HL or more); SNHL at 2 kHz and above	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. **Navigational Note:** -					
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear. **Navigational Note:** -					

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking. **Navigational Note:** -					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). **Navigational Note:** -					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, and vision problems. **Navigational Note:** -					
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the adrenal cortex not producing enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency. **Navigational Note:** -					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids. **Navigational Note:** -					
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder characterized by unusually late sexual maturity. **Navigational Note:** -					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age. **Navigational Note:** -					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood). **Navigational Note:** -					
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose. **Navigational Note:** -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands. **Navigational Note:** -					
Hypophysitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation and cellular infiltration of the pituitary gland. **Navigational Note:** -					
Hypopituitarism	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of hormones from the pituitary gland. **Navigational Note:** -					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland. **Navigational Note:** -					
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys. **Navigational Note:** -					
Testosterone deficiency	Asymptomatic; mild symptoms with no intervention indicated	Replacement therapy initiated	-	-	-
Definition: A disorder characterized by low testosterone. **Navigational Note:** -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal male. **Navigational Note:** -					
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images. **Navigational Note:** -					
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); glare symptoms affecting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated. **Navigational Note:** -					
Corneal ulcer	-	-	Corneal ulcer without perforation in the affected eye	Perforation in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber. **Navigational Note:** -					
Dry eye	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva. **Navigational Note:** If corneal ulcer is present, grade under Eye disorders: Corneal ulcer.					
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Unilateral paresis without double vision	Bilateral paresis or unilateral paresis causing double vision in peripheral gaze, but not in central gaze	Bilateral paresis requiring head turning to see beyond central 60 degrees or double vision in central gaze	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the eye. **Navigational Note:** -					
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by impaired eyelid function. **Navigational Note:** -					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Glaucoma	Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit	EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit	EIOP causing visual field deficits	Visual field deficit within the central 10 degrees of the visual field in the affected eye	-
Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. **Navigational Note:** -					
Keratitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self care ADL	Perforation; best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the cornea of the eye. **Navigational Note:** Also consider Eye disorders: Corneal ulcer					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Night blindness	Symptomatic but not limiting ADL	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an inability to see clearly in dim light. **Navigational Note:** -					
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve). **Navigational Note:** -					
Papilledema	Asymptomatic; no visual field deficit	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by swelling around the optic disc. **Navigational Note:** -					
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face. **Navigational Note:** -					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of light. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Retinal detachment	-	-	Macular sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment	-
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium. **Navigational Note:** -					
Retinal tear	No retinal detachment and treatment not indicated	No retinal detachment and treatment indicated	-	-	-
Definition: A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters. **Navigational Note:** If retinal detachment is present, grade under Eye disorders: Retinal detachment					
Retinal vascular disorder	-	Retinal vascular disorder without neovascularization	Retinal vascular disorder with neovascularization	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects vision. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder involving the retina. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					
Scleral disorder	No change in vision from baseline	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the sclera of the eye. **Navigational Note:** -					
Uveitis	Anterior uveitis with trace cells	Anterior uveitis with 1+ or 2+ cells	Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vision decreased	-	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by a decrease in visual acuity. **Navigational Note:** If etiology is known, use a more specific CTCAE term.					
Vitreous hemorrhage	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL; vitrectomy indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by bleeding into the vitreous humor. **Navigational Note:** -					
Watering eyes	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct. **Navigational Note:** -					
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; no change in vision	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL; best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline	Severe or medically significant but not immediately sight-threatening; limiting self care ADL; decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: - **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterized by swelling of the abdomen. **Navigational Note:** -					
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region. **Navigational Note:** -					
Anal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
Definition: A disorder characterized by a tear in the lining of the anus. **Navigational Note:** -					
Anal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin. **Navigational Note:** -					
Anal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region. **Navigational Note:** -					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the anus. **Navigational Note:** Report Grade 4 and 5 as Gastrointestinal disorders: Anal ulcer					
Anal necrosis	-	-	TPN or hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the anal region. **Navigational Note:** -					
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the anal region. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the anal canal. **Navigational Note:** -					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the anal canal. **Navigational Note:** -					
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity. **Navigational Note:** -					
Belching	Increase from baseline	Intervention initiated (including over the counter medications)	-	-	-
Definition: To expel gas noisily from the mouth. **Navigational Note:** Synonym: Burping					
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen. **Navigational Note:** -					
Cecal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cecum. **Navigational Note:** -					
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
Definition: A disorder characterized by inflammation of the lip. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chylous ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., fat-restricted diet); paracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of milky fluid in the peritoneal cavity. **Navigational Note:** -					
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon. **Navigational Note:** -					
Colonic fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site. **Navigational Note:** -					
Colonic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon. **Navigational Note:** -					
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon. **Navigational Note:** -					
Colonic perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall. **Navigational Note:** -					
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the colon. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the colon. **Navigational Note:** -					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels. **Navigational Note:** -					
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-
Definition: A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous. **Navigational Note:** -					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements. **Navigational Note:** -					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity. **Navigational Note:** -					
Duodenal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Duodenal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the duodenum. **Navigational Note:** -					
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum. **Navigational Note:** -					
Duodenal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall. **Navigational Note:** -					
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the duodenum. **Navigational Note:** -					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the duodenal wall. **Navigational Note:** -					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing. **Navigational Note:** -					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines. **Navigational Note:** If reporting a known abnormality of the colon, use Gastrointestinal disorders: Colitis. If reporting a documented infection, use Infections and infestations: Enterocolitis infectious.					
Enterovesical fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. **Navigational Note:** -					
Esophageal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. **Navigational Note:** -					
Esophageal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus. **Navigational Note:** -					
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the esophageal wall. **Navigational Note:** -					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the esophagus. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region. **Navigational Note:** -					
Esophageal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus. **Navigational Note:** -					
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the esophagus. **Navigational Note:** -					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the esophageal wall. **Navigational Note:** -					
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from esophageal varices. **Navigational Note:** -					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall. **Navigational Note:** -					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a discharge of excessive gas from the lower GI tract. **Navigational Note:** -					
Gastric fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site. **Navigational Note:** -					
Gastric hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the gastric wall. **Navigational Note:** -					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastric wall. **Navigational Note:** -					
Gastric perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall. **Navigational Note:** -					
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the stomach. **Navigational Note:** -					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the stomach. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach. **Navigational Note:** -					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion. **Navigational Note:** -					
Gastrointestinal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site. **Navigational Note:** -					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region. **Navigational Note:** -					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss >=20% from baseline; tube feeding or TPN indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine. **Navigational Note:** -					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region. **Navigational Note:** -					
Hemorrhoidal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the hemorrhoids. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area. **Navigational Note:** -					
Ileal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the ileum and another organ or anatomic site. **Navigational Note:** -					
Ileal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ileal wall. **Navigational Note:** -					
Ileal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL; naso-gastric tube indicated	Hospitalization indicated; invasive intervention indicated; limiting self care ADL; long intestinal tube indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the ileum. **Navigational Note:** -					
Ileal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall. **Navigational Note:** -					
Ileal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the ileum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ileal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the ileum. **Navigational Note:** -					
Ileus	Asymptomatic and radiologic observations only	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated; tube placement indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents. **Navigational Note:** -					
Intra-abdominal hemorrhage	-	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity. **Navigational Note:** -					
Jejunal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site. **Navigational Note:** -					
Jejunal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the jejunal wall. **Navigational Note:** -					
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum. **Navigational Note:** -					
Jejunal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the jejunal wall. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the jejunum. **Navigational Note:** -					
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the jejunum. **Navigational Note:** -					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip. **Navigational Note:** -					
Lower gastrointestinal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus). **Navigational Note:** -					
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea. **Navigational Note:** -					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the stomach. **Navigational Note:** -					
Oral cavity fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site. **Navigational Note:** -					
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth. **Navigational Note:** -					
Oral hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mouth. **Navigational Note:** -					
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips. **Navigational Note:** -					
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the pancreatic duct. **Navigational Note:** -					
Pancreatic fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pancreas and another organ or anatomic site. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pancreatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pancreas. **Navigational Note:** -					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pancreas. **Navigational Note:** -					
Pancreatitis	-	Enzyme elevation; radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the pancreas with no documented pancreas infection. **Navigational Note:** -					
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
Definition: A disorder in the gingival tissue around the teeth. **Navigational Note:** -					
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the peritoneum. **Navigational Note:** -					
Proctitis	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum. **Navigational Note:** -					
Rectal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
Definition: A disorder characterized by a tear in the lining of the rectum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rectal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site. **Navigational Note:** -					
Rectal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus. **Navigational Note:** -					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the rectum. **Navigational Note:** -					
Rectal necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the rectal wall. **Navigational Note:** -					
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum. **Navigational Note:** -					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region. **Navigational Note:** -					
Rectal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum. **Navigational Note:** -					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the rectum. **Navigational Note:** -					
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the retroperitoneal area. **Navigational Note:** -					
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the salivary duct. **Navigational Note:** -					
Salivary gland fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site. **Navigational Note:** -					
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the small intestine. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents of the small intestine. **Navigational Note:** -					
Small intestinal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the small intestine wall. **Navigational Note:** -					
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the small intestine. **Navigational Note:** -					
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the small intestine. **Navigational Note:** -					
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the stomach. **Navigational Note:** -					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; limiting self care ADL	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development. **Navigational Note:** -					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the tooth. **Navigational Note:** -					
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by necrotizing enterocolitis in neutropenic patients. **Navigational Note:** Also report Investigations: Neutrophil count decreased					
Upper gastrointestinal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach). **Navigational Note:** -					
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by a decrease in blood supply due to narrowing or blockage of a visceral (mesenteric) artery. **Navigational Note:** -					
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth. **Navigational Note:** -					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever. **Navigational Note:** -					
Death neonatal	-	-	-	Neonatal loss of life	-
Definition: Newborn death occurring during the first 28 days after birth. **Navigational Note:** -					
Death NOS	-	-	-	-	Death
Definition: Death that cannot be attributed to a CTCAE term associated with Grade 5. **Navigational Note:** If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Disease progression	-	-	-	-	Death
Definition: Death due to disease progression that cannot be attributed to a CTCAE term associated with Grade 5. **Navigational Note:** If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues. **Navigational Note:** -					
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area. **Navigational Note:** -					
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face. **Navigational Note:** -					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities. **Navigational Note:** -					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal. **Navigational Note:** -					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough. **Navigational Note:** Synonym: Flu, Influenza					
Gait disturbance	Mild change in gait (e.g., wide-based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by walking difficulties. **Navigational Note:** -					
Generalized edema	Noted on exam; 1+ pitting edema	Interfering with instrumental ADLs; oral therapy initiated	Interferes with self care ADL; intravenous therapy indicated; skin breakdown	Life-threatening consequences	-
Definition: A disorder characterized by fluid accumulation in the tissues of the body including the skin. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below. **Navigational Note:** -					
Infusion site extravasation	Painless edema	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of the infusion into the surrounding tissue. Signs and symptoms may include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site. **Navigational Note:** -					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection. **Navigational Note:** -					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site. **Navigational Note:** Prior to using this term consider specific edema areas: General disorders and administration site conditions: Edema face, Edema limbs, Edema trunk, or Edema neck; Nervous system disorders: Edema cerebral; Reproductive system and breast disorders: Genital edema; Respiratory, thoracic and mediastinal disorders: Laryngeal edema or Pulmonary edema; Skin and subcutaneous tissue disorders: Periorbital edema; Vascular disorders: Lymphedema					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being limiting instrumental ADL	Uneasiness or lack of well being limiting self-care ADL	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling. **Navigational Note:** -					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Neck edema	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	Vascular or respiratory impairment requiring urgent intervention	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck. **Navigational Note:** -					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the chest unrelated to a heart disorder. **Navigational Note:** -					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony. **Navigational Note:** Prior to using this term consider using a specific body part pain term found throughout the CTCAE (over 40 different pain terms).					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected death that cannot be attributed to a CTCAE term associated with Grade 5. **Navigational Note:** If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Vaccination site lymphadenopathy	Local lymph node enlargement	Localized ulceration; generalized lymph node enlargement	-	-	-
Definition: A disorder characterized by lymph node enlargement after vaccination. **Navigational Note:** -					
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct. **Navigational Note:** -					
Biliary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site. **Navigational Note:** -					
Budd-Chiari syndrome	-	Medical management indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; asterixis; mild encephalopathy	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by occlusion of the hepatic veins and typically presents with abdominal pain, ascites and hepatomegaly. **Navigational Note:** -					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones. **Navigational Note:** -					
Gallbladder fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site. **Navigational Note:** -					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder. **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder. **Navigational Note:** -					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region. **Navigational Note:** -					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall. **Navigational Note:** -					
Hepatic failure	-	-	Asterixis; mild encephalopathy; drug-induced liver injury (DILI); limiting self care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time (INR.) Drug-induced liever injury (DILI) as defined by Hy's Law. **Navigational Note:** -					
Hepatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver. **Navigational Note:** -					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. **Navigational Note:** -					
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region. **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Perforation bile duct	-	-	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct. **Navigational Note:** -					
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system. **Navigational Note:** -					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein. **Navigational Note:** -					
Sinusoidal obstruction syndrome	-	Blood bilirubin 2-5 mg/dL; minor interventions required (i.e., blood product, diuretic, oxygen)	Blood bilirubin >5 mg/dL; coagulation modifier indicated (e.g., defibrotide); reversal of flow on ultrasound	Life-threatening consequences (e.g., ventilatory support, dialysis, plasmapheresis, peritoneal drainage)	Death
Definition: A disorder characterized by severe hepatic injury as a result of the blood vessels of the liver becoming inflamed and/or blocked. **Navigational Note:** -					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. **Navigational Note:** If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death. **Navigational Note:** -					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents. **Navigational Note:** Prior to using this term consider specific autoimmune AEs					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. **Navigational Note:** Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea. **Navigational Note:** -					

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the abdominal cavity. **Navigational Note:** -					
Anorectal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the anal area and the rectum. **Navigational Note:** -					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent. **Navigational Note:** -					
Appendicitis perforated	-	-	Medical intervention indicated; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity. **Navigational Note:** -					
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving an artery. **Navigational Note:** -					
Bacteremia	-	Blood culture positive with no signs or symptoms	-	-	-
Definition: A disorder characterized by the presence of bacteria in the blood stream. **Navigational Note:** Consider Infections and infestations: Sepsis (Grades 3, 4 & 5)					
Biliary tract infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the biliary tract. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bladder. **Navigational Note:** -					
Bone infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bones. **Navigational Note:** -					
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; severe infection; axillary adenitis	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the breast. **Navigational Note:** -					
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bronchi. **Navigational Note:** -					
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process that arises secondary to catheter use. **Navigational Note:** -					
Cecal infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cecum. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the uterine cervix. **Navigational Note:** -					
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye. **Navigational Note:** Consider Infections and infestations: Conjunctivitis infective if caused by infection					
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by an infectious process involving the conjunctiva. Clinical manifestations include pink or red color in the eyes. **Navigational Note:** -					
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cornea. **Navigational Note:** -					
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a cranial nerve. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cytomegalovirus infection reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated; blindness	Death
Definition: A disorder characterized by the reactivation of cytomegalovirus (CMV). **Navigational Note:** Synonym: CMV					
Device related infection	-	Oral intervention indicated (e.g., antibiotic, antifungal)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the use of a medical device. **Navigational Note:** -					
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the duodenum. **Navigational Note:** -					
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain tissue. **Navigational Note:** -					
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain and spinal cord tissues. **Navigational Note:** -					
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endocardial layer of the heart. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Endophthalmitis	-	Local intervention indicated	Systemic intervention; hospitalization indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye. **Navigational Note:** -					
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines. **Navigational Note:** Includes Clostridium difficile (c. diff, c. difficile).					
Epstein-Barr virus infection reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of Epstein-Barr virus (EBV). **Navigational Note:** Synonym: EBV					
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the esophagus. **Navigational Note:** -					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Folliculitis	Covering <10% of the body surface area; no intervention indicated	Covering 10-30% of the body surface area; topical intervention initiated	>30% BSA; systemic intervention indicated	-	-
Definition: A disorder characterized by inflammation or infection of the hair follicles. **Navigational Note:** -					
Fungemia	-	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	-	-
Definition: A disorder characterized by the presence of fungus in the blood stream. **Navigational Note:** -					
Gallbladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gallbladder. **Navigational Note:** -					
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gums. **Navigational Note:** -					
Hepatic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the liver. **Navigational Note:** -					
Hepatitis B reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated; severe decompensated liver function (e.g., coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by the reactivation of hepatitis B virus. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hepatitis viral	Asymptomatic, intervention not indicated	Moderate symptoms; medical intervention indicated	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; severe decompensated liver function (e.g., coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma. **Navigational Note:** -					
Herpes simplex reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of Herpes simplex virus. **Navigational Note:** -					
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skeletal muscles. **Navigational Note:** -					
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a joint. **Navigational Note:** -					
Kidney infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammatory process involving the larynx. **Navigational Note:** For symptoms and no intervention, consider Respiratory, thoracic and mediastinal disorders: Sore throat or Hoarseness.					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the lips. **Navigational Note:** -					
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lungs, including pneumonia. **Navigational Note:** If infection is due to aspiration, consider reporting Respiratory, thoracic and mediastinal disorders: Apiration					
Lymph gland infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lymph nodes. **Navigational Note:** -					
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mediastinum. **Navigational Note:** -					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a mucosal surface. **Navigational Note:** -					
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence. **Navigational Note:** -					
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the nail. **Navigational Note:** -					
Otitis externa	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage. **Navigational Note:** Changes associated with radiation to external ear (pinnae) are graded under Injury, poisoning and procedural complications: Dermatitis radiation					
Otitis media	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the middle ear. **Navigational Note:** -					
Ovarian infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pancreas. **Navigational Note:** -					
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; IV antibiotics indicated	Life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions. **Navigational Note:** -					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Operative intervention indicated; IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail. **Navigational Note:** -					
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pelvic cavity. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Penile infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the penis. **Navigational Note:** -					
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the orbit of the eye. **Navigational Note:** -					
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peripheral nerves. **Navigational Note:** -					
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peritoneum. **Navigational Note:** -					
Pharyngitis	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the throat. **Navigational Note:** For Grade 1 Consider Respiratory, thoracic and mediastinal disorders: Sore throat					
Phlebitis infective	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pleural infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pleura. **Navigational Note:** -					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the prostate gland. **Navigational Note:** -					
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus. **Navigational Note:** Synonym: Boil					
Rhinitis infective	-	Localized; local intervention indicated	-	-	-
Definition: A disorder characterized by an infectious process involving the nasal mucosal. **Navigational Note:** -					
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the salivary gland. **Navigational Note:** -					
Scrotal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the scrotum. **Navigational Note:** -					
Sepsis	-	-	Blood culture positive with signs or symptoms; treatment indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock. **Navigational Note:** Includes SIRS. Also consider Infections and infestations: Bacteremia (Grade 2)					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Shingles	Localized, local intervention indicated	Local infection with moderate symptoms; oral intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of herpes zoster virus. **Navigational Note:** Synonym: Herpes zoster					
Sinusitis	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. **Navigational Note:** -					
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skin such as cellulitis. **Navigational Note:** -					
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine. **Navigational Note:** -					
Soft tissue infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving soft tissues. **Navigational Note:** -					
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the spleen. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a stoma (surgically created opening on the surface of the body). **Navigational Note:** -					
Thrush	Asymptomatic; local symptomatic management	Oral intervention indicated (e.g., antifungal)	IV antifungal intervention indicated	-	-
Definition: A disorder characterized by a suspected candidal infection involving an oral mucosal surface. **Navigational Note:** -					
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a tooth. **Navigational Note:** -					
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the trachea. **Navigational Note:** -					
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea). **Navigational Note:** -					
Urethral infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urethra. **Navigational Note:** -					
Urinary tract infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial tissues. **Navigational Note:** -					
Vaginal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vagina. **Navigational Note:** -					
Viremia	-	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	-	-
Definition: A disorder characterized by the presence of a virus in the blood stream. **Navigational Note:** -					
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vulva. **Navigational Note:** -					
Wound infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the wound. **Navigational Note:** -					
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ankle fracture	Mild; non-operative intervention indicated	Limiting instrumental ADL; outpatient operative intervention indicated	Limiting self care ADL; elective operative intervention indicated requiring hospitalization	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot. **Navigational Note:** -					
Aortic injury	-	Operative intervention not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta. **Navigational Note:** -					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery. **Navigational Note:** -					
Biliary anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Bladder anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment. **Navigational Note:** -					
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation. **Navigational Note:** Synonym: Radiation induced skin toxicities (CTCAE v3.0)					
Esophageal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated; invasive intervention indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury. **Navigational Note:** -					
Fallopian tube anastomotic leak	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Fallopian tube perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A disorder characterized by a rupture of the fallopian tube wall. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; limiting self care ADL; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken. **Navigational Note:** Prior to using this term consider specific fracture areas: Injury, poisoning and procedural complications: Ankle fracture, Hip fracture, Spinal fracture, or Wrist fracture					
Gastric anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Gastrointestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastrointestinal tract stoma. **Navigational Note:** -					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-operative intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances. **Navigational Note:** -					
Injury to carotid artery	-	Repair or revision not indicated	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery. **Navigational Note:** -					
Injury to inferior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava. **Navigational Note:** -					
Injury to jugular vein	-	Repair or revision not indicated	Symptomatic limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein. **Navigational Note:** -					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the superior vena cava. **Navigational Note:** -					
Intestinal stoma leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from an intestinal stoma (surgically created opening on the surface of the body). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the intestinal stoma. **Navigational Note:** -					
Intestinal stoma site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the intestinal stoma. **Navigational Note:** -					
Intraoperative arterial injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to an artery during a surgical procedure. **Navigational Note:** -					
Intraoperative breast injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the breast parenchyma during a surgical procedure. **Navigational Note:** -					
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the heart during a surgical procedure. **Navigational Note:** -					
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the ear during a surgical procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the endocrine gland during a surgical procedure. **Navigational Note:** -					
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the gastrointestinal system during a surgical procedure. **Navigational Note:** -					
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the head and neck during a surgical procedure. **Navigational Note:** -					
Intraoperative hemorrhage	-	-	Postoperative invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure. **Navigational Note:** -					
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the hepatic parenchyma and/or biliary tract during a surgical procedure. **Navigational Note:** -					
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the musculoskeletal system during a surgical procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intraoperative neurological injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the nervous system during a surgical procedure. **Navigational Note:** -					
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the eye during a surgical procedure. **Navigational Note:** -					
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the kidney during a surgical procedure. **Navigational Note:** -					
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the reproductive organs during a surgical procedure. **Navigational Note:** -					
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the respiratory system during a surgical procedure. **Navigational Note:** -					
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the spleen during a surgical procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the urinary system during a surgical procedure. **Navigational Note:** -					
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to a vein during a surgical procedure. **Navigational Note:** -					
Kidney anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a kidney anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Large intestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large intestine. **Navigational Note:** -					
Pancreatic anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Pharyngeal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Postoperative hemorrhage	Mild symptoms; intervention not indicated	Moderate bleeding requiring transfusion < 2 units (10 cc/kg for pediatrics) of pRBCs	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding occurring after a surgical procedure. **Navigational Note:** -					
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of a previously undocumented problem that occurs after a thoracic procedure. **Navigational Note:** -					
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of protrusion of the intestinal stoma (surgically created opening on the surface of the body) above the abdominal surface. **Navigational Note:** -					
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of displacement of the urostomy. **Navigational Note:** -					
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent. **Navigational Note:** -					
Rectal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a rectal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective invasive intervention indicated	-	-
Definition: A finding of tumor-like collection of serum in the tissues. **Navigational Note:** -					
Small intestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small bowel. **Navigational Note:** -					
Spermatic cord anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Definition: A finding of traumatic injury to the spine in which the continuity of a vertebral bone is broken. **Navigational Note:** -					
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the gastrointestinal stoma (surgically created opening on the surface of the body). **Navigational Note:** -					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Tracheal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the trachea. **Navigational Note:** -					
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor or respiratory distress limiting self care ADL; invasive intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by blockage of the lumen of the trachea. **Navigational Note:** -					
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the tracheostomy site. **Navigational Note:** -					
Ureteric anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Urethral anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a urethral anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Urostomy leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from a urostomy. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Urostomy obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the urostomy. **Navigational Note:** -					
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the urostomy site. **Navigational Note:** -					
Urostomy stenosis	-	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the opening of a urostomy. **Navigational Note:** -					
Uterine anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a uterine anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Uterine perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the uterine wall. **Navigational Note:** -					
Vaccination complication	Mild pain; erythema 2.5-5cm; induration/swelling 2.5-5cm; does not interfere with activity	Moderate pain; Erythema 5.1-10 cm; Induration/swelling 5.1-10 cm; lipodystrophy; limiting instrumental ADL	Severe pain; Erythema > 10 cm; Induration/swelling > 10 cm; necrosis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder that occurs after the injection of a substance with antigenic properties, administered to activate the immune system. **Navigational Note:** For systemic vaccination complications, consider Immune system disorders: Allergic reaction or Anaphylaxis.					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vaginal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Vas deferens anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Vascular access complication	TPA administration into line with no intent for systemic therapy indicated	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Pulmonary embolism, deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Definition: A finding of a previously undocumented problem related to the vascular access site. **Navigational Note:** -					
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to a vein. **Navigational Note:** -					
Wound complication	Observation only; topical intervention indicated	Bedside local care indicated	Operative intervention indicated	Life-threatening consequences	Death
Definition: A finding of development of a new problem at the site of an existing wound. **Navigational Note:** Prior to using this term consider Injury, poisoning and procedural complications: Wound dehiscence or Infections and infestations: Wound infection					
Wound dehiscence	Incisional separation, intervention not indicated	Incisional separation, local care (e.g., suturing) or medical intervention indicated (e.g., analgesic)	Fascial disruption or dehiscence without evisceration; revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation of the approximated margins of a surgical wound. **Navigational Note:** Also consider Infections and infestations: Wound infection					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Wrist fracture	Mild; non-operative intervention indicated	Limiting instrumental ADL; outpatient operative intervention indicated	Limiting self care ADL; elective operative intervention indicated requiring hospitalization	-	-
Definition: A finding of traumatic injury to the wrist joint in which the continuity of a wrist bone is broken. **Navigational Note:** -					
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-
Definition: A finding based on laboratory test results in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment. **Navigational Note:** -					
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen. **Navigational Note:** Also consider Hepatobiliary disorders: Hepatic failure					
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen. **Navigational Note:** -					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen. **Navigational Note:** Also consider Hepatobiliary disorders: Hepatic failure					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen. **Navigational Note:** -					
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-
Definition: A finding based on laboratory test results that indicate a decrease in levels of bicarbonate in a venous blood specimen. **Navigational Note:** Also consider Metabolism and nutrition disorders: Acidosis or Alkalosis					
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice. **Navigational Note:** Also consider Hepatobiliary disorders: Hepatic failure					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen. **Navigational Note:** -					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen. **Navigational Note:** -					
Blood lactate dehydrogenase increased	>ULN	-	-	-	-
Definition: A finding based on laboratory test results that indicate increased levels of lactate dehydrogenase in the blood specimen. **Navigational Note:** -					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen. **Navigational Note:** -					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value; asymptomatic and intervention not indicated	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value; symptomatic and intervention not indicated	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 dyspnea); intervention indicated	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide. **Navigational Note:** Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A finding based on laboratory test results that indicate increased levels of cardiac troponin I in a biological specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A finding based on laboratory test results that indicate increased levels of cardiac troponin T in a biological specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen. **Navigational Note:** -					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen. **Navigational Note:** -					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen. **Navigational Note:** Also consider Renal and urinary disorders: Acute kidney injury					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >=20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction. **Navigational Note:** Also consider Cardiac disorders: Left ventricular systolic dysfunction. Report Cardiac disorders: Left ventricular systolic dysfunction if same grade event.					
Electrocardiogram QT corrected interval prolonged	Average QTc 450 - 480 ms	Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval. **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Electrocardiogram T wave abnormal	T wave flattening	Nonspecific ST segment change	-	-	-
Definition: A disorder characterized by Electrocardiogram T wave amplitude changes. **Navigational Note:** -					
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen. **Navigational Note:** -					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds. **Navigational Note:** Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water. **Navigational Note:** -					
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen. **Navigational Note:** -					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen. **Navigational Note:** -					
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal. **Navigational Note:** -					
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood. **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen. **Navigational Note:** -					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen. **Navigational Note:** -					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow. **Navigational Note:** -					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen. **Navigational Note:** -					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen. **Navigational Note:** -					
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen. **Navigational Note:** -					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen. **Navigational Note:** -					
Thyroid stimulating hormone increased	TSH increased and no intervention initiated	-	-	-	-
Definition: A disorder characterized by an increase in thyroid stimulating hormone. **Navigational Note:** If intervention initiated or symptomatic, report as Endocrine disorders: Hypothyroidism.					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Urine output decreased	-	-	**Adult:** Oliguria (<80 ml in 8 hr); **Infants:** < 0.5 mL/kg per hour for 24 hours; **Children:** < 500 mL/1.73 m2 body surface area per day	**Adult:** Anuria (<240 ml in 24 hr); **Pediatric:** No urine output over 12 hours	-
Definition: A finding based on test results that indicate urine production is less relative to previous output. **Navigational Note:** -					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value. **Navigational Note:** Also consider Investigations: Forced Expiratory Volume; Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an unexpected or abnormal increase in overall body weight; for pediatrics, greater than the baseline growth curve. **Navigational Note:** Do not use Metabolism and nutrition disorders: Obesity, this term is being retired.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve. **Navigational Note:** -					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen. **Navigational Note:** -					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues. **Navigational Note:** -					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches. **Navigational Note:** -					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues. **Navigational Note:** -					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite. **Navigational Note:** -					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated	Hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis. **Navigational Note:** -					
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inability to properly metabolize glucose. **Navigational Note:** -					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance. **Navigational Note:** -					
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs. **Navigational Note:** -					
Hyperlipidemia	Requiring diet changes	Requiring pharmaceutical intervention	Hospitalization; pancreatitis	Life-threatening consequences	-
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of lipids in blood. **Navigational Note:** -					
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood. **Navigational Note:** -					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood. **Navigational Note:** -					
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of phosphate in a blood. **Navigational Note:** -					
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood. **Navigational Note:** -					
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood. **Navigational Note:** -					
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood. **Navigational Note:** -					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood. **Navigational Note:** -					
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood. **Navigational Note:** -					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood. **Navigational Note:** -					
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood. **Navigational Note:** -					
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues. **Navigational Note:** -					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat. **Navigational Note:** Use term Investigations: Weight gain					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells. **Navigational Note:** -					
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the abdominal wall. **Navigational Note:** -					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint. **Navigational Note:** -					
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving a joint. **Navigational Note:** -					
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure. **Navigational Note:** Use new term: Musculoskeletal and connective tissue disorders: Osteonecrosis					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the back region. **Navigational Note:** -					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the bones. **Navigational Note:** -					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the buttocks. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chest wall necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the chest wall including breast. **Navigational Note:** -					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the chest wall. **Navigational Note:** -					
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-
Definition: A disorder characterized by non-neoplastic overgrowth of bone. **Navigational Note:** -					
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the deep connective tissues. **Navigational Note:** -					
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort on the lateral side of the body in the region below the ribs and above the hip. **Navigational Note:** -					
Generalized muscle weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-
Definition: A disorder characterized by stature that is smaller than normal as expected for age. **Navigational Note:** -					
Head soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the head. **Navigational Note:** -					
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; invasive intervention indicated	-	-
Definition: A disorder characterized by excessive fluid in a joint, usually as a result of joint inflammation. **Navigational Note:** -					
Joint range of motion decreased	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self care ADL	-	-
Definition: A disorder characterized by a decrease in joint flexibility of any joint. **Navigational Note:** -					
Joint range of motion decreased cervical spine	Mild restriction of rotation or flexion between 60 - 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	-	-
Definition: A disorder characterized by a decrease in flexibility of a cervical spine joint. **Navigational Note:** -					
Joint range of motion decreased lumbar spine	Stiffness; difficulty bending to the floor to pick up a very light object but able to do athletic activity	Pain with range of motion (ROM) in lumbar spine; requires a reaching aid to pick up a very light object from the floor	<50% lumbar spine flexion; associated with symptoms of ankylosis or fused over multiple segments with no L-spine flexion (e.g., unable to reach to floor to pick up a very light object)	-	-
Definition: A disorder characterized by a decrease in flexibility of a lumbar spine joint. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Kyphosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine. **Navigational Note:** -					
Lordosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the lumbar portion of the spine. **Navigational Note:** -					
Muscle cramp	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked cramping sensation originating from a muscle or group of muscles. **Navigational Note:** Synonym: Muscle spasm					
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the lower limb muscles. **Navigational Note:** -					
Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles. **Navigational Note:** -					
Muscle weakness upper limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the upper limb muscles. **Navigational Note:** -					
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; limiting self care ADL	-	-
Definition: A disorder characterized by a malformation of the musculoskeletal system. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles. **Navigational Note:** -					
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by inflammation involving the skeletal muscles. **Navigational Note:** -					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the neck area. **Navigational Note:** -					
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the neck. **Navigational Note:** -					
Osteonecrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., analgesics or bisphosphonates); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure. **Navigational Note:** -					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Osteoporosis	**Adult:** Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); **Pediatric:** Radiologic evidence of low BMD with z score of <= -2.0 and no history of significant fractures	**Adult:** BMD t-score < -2.5; loss of height <2 cm; therapy to improve BMD indicated; limiting instrumental ADL; **Pediatric:** Low BMD (z-score <= -2.0) and significant fracture history (defined as a long bone fracture of the lower extremity, vertebral compression, 2 or more long bone fractures of the upper extremities); therapy to improve BMD indicated	**Adult:** Loss of height >=2 cm; hospitalization indicated; limiting self care ADL; **Pediatric:** Limiting self care ADL	-	-
Definition: A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence. **Navigational Note:** -					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the upper or lower extremities. **Navigational Note:** -					
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis. **Navigational Note:** -					
Rhabdomyolysis	Asymptomatic, intervention not indicated; laboratory findings only	Non-urgent intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; dialysis	Death
Definition: A disorder characterized by the breakdown of muscle tissue resulting in the release of muscle fiber contents into the bloodstream. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rotator cuff injury	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an injury of the rotator cuff. **Navigational Note:** -					
Scoliosis	<20 degrees; clinically undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by a malformed, lateral curvature of the spine. **Navigational Note:** -					
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the lower extremity. **Navigational Note:** -					
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity. **Navigational Note:** -					
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the superficial soft tissues. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-
Definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication. **Navigational Note:** -					
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	Severe length discrepancy >5 cm; limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by a discrepancy between the lengths of the lower or upper extremities. **Navigational Note:** -					
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents. **Navigational Note:** -					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow. **Navigational Note:** -					
Skin papilloma	Asymptomatic; intervention not indicated	Intervention initiated	-	-	-
Definition: A disorder characterized by the presence of one or more warts. **Navigational Note:** -					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy. **Navigational Note:** -					
Tumor hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in a tumor. **Navigational Note:** -					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis. **Navigational Note:** -					
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the abducens nerve (sixth cranial nerve). **Navigational Note:** -					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the accessory nerve (eleventh cranial nerve). **Navigational Note:** -					
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the acoustic nerve (eighth cranial nerve). **Navigational Note:** -					
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs. **Navigational Note:** -					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory. **Navigational Note:** -					
Anosmia	Present	-	-	-	-
Definition: A disorder characterized by a change in the sense of smell. **Navigational Note:** Also consider Olfactory nerve disorder					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic). **Navigational Note:** -					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities. **Navigational Note:** -					
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand. **Navigational Note:** -					
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the brain and/or spinal cord. **Navigational Note:** -					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues. **Navigational Note:** -					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function. **Navigational Note:** -					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond. **Navigational Note:** -					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking. **Navigational Note:** -					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech. **Navigational Note:** -					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation. **Navigational Note:** -					
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell. **Navigational Note:** -					
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Definition: A disorder characterized by impairment of verbal communication skills, often resulting from brain damage. **Navigational Note:** -					
Edema cerebral	-	-	New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain. **Navigational Note:** -					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness. **Navigational Note:** Synonym: Restless legs					
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the facial muscles. **Navigational Note:** -					
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the facial nerve (seventh cranial nerve). **Navigational Note:** -					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the glossopharyngeal nerve (ninth cranial nerve). **Navigational Note:** -					
Guillain-Barre syndrome	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated; intubation	Death
Definition: A disorder characterized by the body's immune system attacking the peripheral nervous system causing ascending paralysis. **Navigational Note:** -					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve. **Navigational Note:** -					
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain. **Navigational Note:** -					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized by characterized by excessive sleepiness during the daytime. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the hypoglossal nerve (twelfth cranial nerve). **Navigational Note:** -					
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cranium. **Navigational Note:** -					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage. **Navigational Note:** Prior to using this term consider Nervous system disorder: TIA or Stroke					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness. **Navigational Note:** -					
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation. **Navigational Note:** -					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges. **Navigational Note:** -					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements. **Navigational Note:** -					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body. **Navigational Note:** -					
Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body. **Navigational Note:** -					
Myasthenia gravis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by weakness and rapid fatigue of any of the skeletal muscles. **Navigational Note:** -					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves. **Navigational Note:** -					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs. **Navigational Note:** -					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the oculomotor nerve (third cranial nerve). **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the olfactory nerve (first cranial nerve). **Navigational Note:** -					
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth. **Navigational Note:** -					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by damage or dysfunction of the peripheral motor nerves. **Navigational Note:** Also consider Nervous system disroders: Peripheral sensory neuropathy					
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by damage or dysfunction of the peripheral sensory nerves. **Navigational Note:** -					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort related to a limb or an organ that is removed from or is not physically part of the body. **Navigational Note:** -					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope. **Navigational Note:** -					
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination. **Navigational Note:** -					
Radiculitis	Mild symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by paralysis of the recurrent laryngeal nerve. **Navigational Note:** -					
Reversible posterior leukoencephalopathy syndrome	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization	Life-threatening consequences	Death
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and/or seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition. Also known as posterior reversible encephalopathy syndrome (PRES). **Navigational Note:** -					
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences; prolonged repetitive seizures	Death
Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin. **Navigational Note:** -					
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness. **Navigational Note:** -					
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening consequences; unable to move active or passive range of motion	Death
Definition: A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances. **Navigational Note:** -					
Spinal cord compression	-	-	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by pressure on the spinal cord. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stroke	Incidental radiographic findings only	Mild to moderate neurologic deficit; limiting instrumental ADL	Severe neurologic deficit; limiting self care ADL; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage. **Navigational Note:** -					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain. **Navigational Note:** -					
Tendon reflex decreased	Ankle reflex reduced	Ankle reflex absent; other reflexes reduced	Absence of all reflexes	-	-
Definition: A disorder characterized by less than normal deep tendon reflexes. **Navigational Note:** Also consider Nervous system disorders: Peripheral motor neuropathy or Peripheral sensory neuropathy					
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit. **Navigational Note:** If >24 hours, Consider Nervous system disorders: Stroke					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts. **Navigational Note:** -					
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trigeminal nerve (fifth cranial nerve). **Navigational Note:** -					
Trochlear nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trochlear nerve (fourth cranial nerve). **Navigational Note:** -					
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the vagus nerve (tenth cranial nerve). **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve. **Navigational Note:** -					
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Pregnancy, puerperium and perinatal conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Fetal growth retardation	-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-
Definition: A disorder characterized by inhibition of fetal growth resulting in the inability of the fetus to achieve its potential weight. **Navigational Note:** -					
Pregnancy loss	-	-	-	Fetal loss at any gestational age	-
Definition: Death in utero. **Navigational Note:** -					
Premature delivery	Delivery of a liveborn infant at >34 to 37 weeks gestation	Delivery of a liveborn infant at >28 to 34 weeks gestation	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-
Definition: A disorder characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation. **Navigational Note:** -					
Pregnancy, puerperium and perinatal conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension. **Navigational Note:** -					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm. **Navigational Note:** -					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus. **Navigational Note:** -					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a lack of clear and orderly thought and behavior. **Navigational Note:** -					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax. **Navigational Note:** -					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; urgent intervention indicated; new onset	Life-threatening consequences, threats of harm to self or others; urgent intervention indicated	Death
Definition: A disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition. **Navigational Note:** -					
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness. **Navigational Note:** -					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-being which is disproportionate to events and stimuli. **Navigational Note:** -					
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by a false sensory perception in the absence of an external stimulus. **Navigational Note:** -					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characterized by difficulty in falling asleep and/or remaining asleep. **Navigational Note:** -					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable; medical or psychiatric intervention indicated	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition. **Navigational Note:** -					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized by a decrease in sexual desire. **Navigational Note:** -					
Libido increased	Present	-	-	-	-
Definition: A disorder characterized by an increase in sexual desire. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behavior and elevation of mood. **Navigational Note:** -					
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	-
Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking. **Navigational Note:** -					
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid, extreme disorganization); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor. **Navigational Note:** -					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be still. **Navigational Note:** -					
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own life. **Navigational Note:** -					
Suicide attempt	-	-	Suicide attempt or gesture without intent to die	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own life. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Acute kidney injury	-	-	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction). **Navigational Note:** Also consider Investigations: Creatinine increased					
Bladder perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall. **Navigational Note:** -					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall. **Navigational Note:** -					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure. **Navigational Note:** -					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract. **Navigational Note:** -					
Dysuria	Present	-	-	-	-
Definition: A disorder characterized by painful urination. **Navigational Note:** If associated with an infection, report the infection. For grades higher than Grade 1, consider Renal and urinary disorders: Bladder spasm or Cystitis noninfective; Infections and infestations: Urinary tract infection.					
Glucosuria	Present	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate glucose in the urine. **Navigational Note:** -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine. **Navigational Note:** -					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine. **Navigational Note:** Report underlying AE if > Grade 1					
Nephrotic syndrome	-	-	Not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by symptoms that include severe edema, proteinuria, and hypoalbuminemia; it is indicative of renal dysfunction. **Navigational Note:** -					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	**Adult:** Urinary protein >=3.5 g/24 hrs; 4+ proteinuria; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin. **Navigational Note:** 24-hour urine collection takes precedence over dipstick					
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by the formation of crystals/kidney stones in the pelvis of the kidney. **Navigational Note:** -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of crystals/kidney stones. **Navigational Note:** -					
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the kidney. **Navigational Note:** -					
Urinary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site. **Navigational Note:** -					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals. **Navigational Note:** -					
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by inability to control the flow of urine from the bladder. **Navigational Note:** -					
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate. **Navigational Note:** -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Altered organ function (e.g., hydronephrosis or renal dysfunction); invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract. **Navigational Note:** -					
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract. **Navigational Note:** -					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate. **Navigational Note:** -					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized by a change in the color of the urine. **Navigational Note:** -					
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Amenorrhea	-	Present	-	-	-
Definition: A disorder characterized by the abnormal absence of menses for at least three consecutive menstrual cycles. **Navigational Note:** -					
Azoospermia	-	Absence of sperm in ejaculate	-	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen. **Navigational Note:** -					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast. **Navigational Note:** -					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the breast region. **Navigational Note:** -					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses. **Navigational Note:** -					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus. **Navigational Note:** -					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity. **Navigational Note:** -					
Fallopian tube obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube. **Navigational Note:** -					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors. **Navigational Note:** -					
Genital edema	Mild swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals. **Navigational Note:** -					
Gynecomastia	Asymptomatic	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males. **Navigational Note:** -					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by the presence of blood in a fallopian tube. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Irregular menstruation	Intermittent/irregular menses for no more than 3 consecutive menstrual cycles	Intermittent/irregular menses for more than 3 consecutive menstrual cycles	-	-	-
Definition: A disorder characterized by a change in cycle or duration of menses from baseline. **Navigational Note:** Also consider Reproductive system and breast disorders: Premature menopause, Amenorrhea.					
Lactation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-
Definition: A disorder characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males. **Navigational Note:** -					
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; operative intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormally heavy vaginal bleeding during menses. **Navigational Note:** -					
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-
Definition: A disorder characterized by a malformation of the nipple. **Navigational Note:** -					
Oligospermia	Sperm concentration > 0 to < 15 million/ml	-	-	-	-
Definition: A disorder characterized by a decrease in the number of spermatozoa in the semen. **Navigational Note:** -					
Ovarian hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ovary. **Navigational Note:** -					
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by tearing or disruption of the ovarian tissue. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ovulation pain	-	Present	-	-	-
Definition: A disorder characterized by a sensation of marked discomfort in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle. **Navigational Note:** -					
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles of the pelvic floor. **Navigational Note:** -					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pelvis. **Navigational Note:** -					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the penis. **Navigational Note:** -					
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the area between the genital organs and the anus. **Navigational Note:** -					
Premature menopause	-	Present	-	-	-
Definition: A disorder characterized by premature ovarian failure. Symptoms may include hot flashes, night sweats, mood swings, and a decrease in sex drive. Laboratory findings include elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH.) **Navigational Note:** -					
Prostatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the prostate gland. **Navigational Note:** -					
Prostatic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder). **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the prostate gland. **Navigational Note:** -					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the scrotal area. **Navigational Note:** -					
Spermatic cord hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the spermatic cord. **Navigational Note:** -					
Spermatic cord obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents of the spermatic cord. **Navigational Note:** -					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with sexual function; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by abnormal function or appearance of the testis. **Navigational Note:** Also consider Reproductive system and breast disorders: Genital edema or other AE terms in the Renal and urinary disorders SOC or Reproductive system and breast disorders SOC.					
Testicular hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the testis. **Navigational Note:** -					
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the testis. **Navigational Note:** -					
Uterine fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the uterus and another organ or anatomic site. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Uterine hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the uterus. **Navigational Note:** -					
Uterine obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the uterine outlet. **Navigational Note:** -					
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the uterus. **Navigational Note:** -					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years. **Navigational Note:** -					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina. **Navigational Note:** -					
Vaginal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the vagina and another organ or anatomic site. **Navigational Note:** -					
Vaginal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the vagina. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Life-threatening consequences; widespread areas of mucosal ulceration; urgent intervention indicated	-
Definition: A disorder characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge. **Navigational Note:** -					
Vaginal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal. **Navigational Note:** -					
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the vagina. **Navigational Note:** -					
Vaginal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the vaginal wall. **Navigational Note:** -					
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterized by a narrowing of the vaginal canal. **Navigational Note:** -					
Reproductive system and breast disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery. **Navigational Note:** -					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching. **Navigational Note:** -					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing. **Navigational Note:** -					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by inhalation of solids or liquids into the lungs. **Navigational Note:** -					
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Supplemental oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by the collapse of part or the entire lung. **Navigational Note:** -					
Bronchial fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates. **Navigational Note:** -					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube. **Navigational Note:** -					
Bronchopleural fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Hospitalization; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity. **Navigational Note:** -					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; invasive intervention not indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma. **Navigational Note:** -					
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; supplemental oxygen indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall. **Navigational Note:** -					
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., fat-restricted diet); thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by milky pleural effusion (abnormal collection of fluid) resulting from accumulation of lymph fluid in the pleural cavity. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound. **Navigational Note:** -					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing. **Navigational Note:** -					
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion; invasive intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the nose. **Navigational Note:** -					
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm. **Navigational Note:** -					
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder characterized by harsh and raspy voice arising from or spreading to the larynx. **Navigational Note:** -					
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx. **Navigational Note:** -					
Laryngeal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the larynx and another organ or anatomic site. **Navigational Note:** -					
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by bleeding from the larynx. **Navigational Note:** -					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx. **Navigational Note:** -					
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate pain, analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by ulceration or inflammation involving the mucous membrane of the larynx. **Navigational Note:** -					
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the laryngeal airway. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway. **Navigational Note:** -					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and/or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx. **Navigational Note:** -					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords. **Navigational Note:** -					
Mediastinal hemorrhage	Mild symptoms; intervention not indicated; radiologic evidence only	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mediastinum. **Navigational Note:** -					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema. **Navigational Note:** -					
Oropharyngeal pain	Mild pain	Moderate pain; altered oral intake; non-narcotics initiated; topical analgesics initiated	Severe pain; severely altered eating/swallowing; narcotics initiated; requires parenteral nutrition	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the oropharynx. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pharyngeal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site. **Navigational Note:** -					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx. **Navigational Note:** -					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain, analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation involving the mucous membrane of the pharynx. **Navigational Note:** -					
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated; tube feeding or TPN indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pharynx. **Navigational Note:** -					
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the pharyngeal airway. **Navigational Note:** -					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pharyngolaryngeal region. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; operative intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort. **Navigational Note:** -					
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity. **Navigational Note:** -					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pleura. **Navigational Note:** -					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma. **Navigational Note:** -					
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung. **Navigational Note:** -					
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing. **Navigational Note:** -					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure. **Navigational Note:** -					
Pulmonary fibrosis	Radiologic pulmonary fibrosis <25% of lung volume associated with hypoxia	Evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50% associated with hypoxia	Severe hypoxia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure. **Navigational Note:** -					
Pulmonary fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site. **Navigational Note:** -					
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder. **Navigational Note:** -					
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid. **Navigational Note:** -					
Rhinorrhea	Present	-	-	-	-
Definition: A disorder characterized by excessive mucous secretions draining from the nose. **Navigational Note:** -					
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characterized by involvement of the paranasal sinuses. **Navigational Note:** -					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses. **Navigational Note:** -					
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with pulmonary hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characterized by cessation of breathing for short periods during sleep. **Navigational Note:** -					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the involuntary expulsion of air from the nose. **Navigational Note:** -					
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characterized by marked discomfort in the throat. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a high pitched breathing sound due to laryngeal or upper airway obstruction. **Navigational Note:** -					
Tracheal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site. **Navigational Note:** -					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation or ulceration involving the mucous membrane of the trachea. **Navigational Note:** -					
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor or respiratory distress limiting self care ADL; invasive intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea. **Navigational Note:** -					
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-
Definition: A disorder characterized by a change in the sound and/or speed of the voice. **Navigational Note:** -					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location. **Navigational Note:** -					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body. **Navigational Note:** -					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid. **Navigational Note:** If infectious, consider Infections and infestations: Rash pustular or other site-specific Infections and infestations term.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture. **Navigational Note:** -					
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	-	-
Definition: A disorder characterized by skin which becomes itchy, red, inflamed, crusty, thick, scaly, and/or forms blisters. **Navigational Note:** -					
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center). **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area. **Navigational Note:** -					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-
Definition: A disorder characterized by shrinking of adipose tissue. **Navigational Note:** -					
Hair color changes	Present	-	-	-	-
Definition: A disorder characterized by change in hair color or loss of normal pigmentation. **Navigational Note:** -					
Hair texture abnormal	Present	-	-	-	-
Definition: A disorder characterized by a change in the way the hair feels. **Navigational Note:** -					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen). **Navigational Note:** -					
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Associated with electrolyte/hemodynamic imbalance	-	-
Definition: A disorder characterized by excessive sweating. **Navigational Note:** Synonym: Night sweats, diaphoresis					
Hyperkeratosis	Present	-	Limiting self-care ADLs	-	-
Definition: A disorder characterized by a thickening of the outer layer of the skin. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race. **Navigational Note:** -					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating. **Navigational Note:** -					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin. **Navigational Note:** -					
Nail changes	Present	-	-	-	-
Definition: A disorder characterized by a change in the nails. **Navigational Note:** -					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate. **Navigational Note:** -					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails. **Navigational Note:** -					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin. **Navigational Note:** -					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet. Also known as Hand-Foot Syndrome. **Navigational Note:** -					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light. **Navigational Note:** -					
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color. **Navigational Note:** -					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back. **Navigational Note:** -					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis. **Navigational Note:** -					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin covering the top and the back of the head. **Navigational Note:** -					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition. **Navigational Note:** -					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment (e.g., vitiligo). **Navigational Note:** -					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin. **Navigational Note:** -					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the skin. **Navigational Note:** -					
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Subcutaneous emphysema	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by air in the subcutaneous tissue. **Navigational Note:** -					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >=10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes. **Navigational Note:** -					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. **Navigational Note:** -					
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins. **Navigational Note:** -					
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Social circumstances					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Surgical and medical procedures					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Surgical and medical procedures - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Arterial thromboembolism	-	-	Urgent intervention indicated	Life-threatening consequences; hemodynamic or neurologic instability; organ damage; loss of extremity(ies)	Death
Definition: A disorder characterized by occlusion of an arterial vessel by a blood clot that develops in an artery. **Navigational Note:** Consider Nervous system disorders: TIA or Stroke for CNS-related events or Cardiac disorders: Myocardial infarction					
Capillary leak syndrome	Asymptomatic	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure. **Navigational Note:** -					
Flushing	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characterized by episodic reddening of the skin, especially face, neck, or chest. **Navigational Note:** -					
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel. **Navigational Note:** -					
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling. **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypertension	**Adult:** Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg; **Pediatric:** Systolic/diastolic BP >90th percentile but< 95th percentile; **Adolescent:** BP ≥120/80 even if < 95th percentile	**Adult:** Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated; **Pediatric and adolescent:** Recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated; systolic and /or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; A**dolescent:** Systolic between 130-139 or diastolic between 80-89 even if < 95th percentile	**Adult:** Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated; **Pediatric and adolescent:** Systolic and/or diastolic > 5 mmHg above the 99th percentile	**Adult and Pediatric:** Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Definition: A disorder characterized by a pathological increase in blood pressure. **Navigational Note:** -					
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated; hospitalization indicated	Life-threatening consequences and urgent intervention indicated	Death
Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment. **Navigational Note:** -					
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity. **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by excessive fluid collection in tissues that causes swelling. **Navigational Note:** -					
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by a cystic lesion containing lymph. **Navigational Note:** -					
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by impaired circulation to an extremity. **Navigational Note:** -					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein. **Navigational Note:** -					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities. **Navigational Note:** -					
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi-modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characterized by obstruction of the blood flow in the superior vena cava. Signs and symptoms include swelling and cyanosis of the face, neck, and upper arms, cough, orthopnea and headache. **Navigational Note:** -					
Thromboembolic event	Medical intervention not indicated (e.g., superficial thrombosis)	Medical intervention indicated	Urgent medical intervention indicated (e.g., pulmonary embolism or intracardiac thrombus)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. **Navigational Note:** Consider Nervous system disorders: TIA or Stroke for CNS-related events. Use Vascular disorders: Arterial thromboembolism for arterial thrombi.					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening consequences; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel. **Navigational Note:** -					
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					