1.0 Title Page

Protocol Number:	APR003-001
Title:	A Phase 1 dose escalation study to evaluate safety, tolerability, and pharmacokinetics/pharmacodynamics of APR003 in patients with advanced colorectal cancer (CRC) with malignant liver lesions
Sponsor:	Apros Therapeutics, Inc. 10210 Campus Point Drive, Suite 150 San Diego, CA 92121 USA
Investigational Product:	APR003
Phase:	1
Protocol Version and Date:	1.0, 03 August 2020 2.0, 16 November 2020 3.0, 28 January 2022
GCP Statement:	This study is to be performed in full compliance with the protocol, ICH E6 R(2) Guideline on Good Clinical Practice (GCP), and relevant regulatory authority guidance and regulations.
Confidentiality:	This document is confidential, it contains proprietary information of Apros Therapeutics, Inc. Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SPONSOR SIGNATURE

Protocol Title: A Phase 1 dose escalation study to evaluate safety, tolerability, and pharmacokinetics/pharmacodynamics of APR003 in patients with advanced colorectal cancer (CRC) with malignant liver lesions

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This protocol version 3.0 has been reviewed and approved by the Sponsor

Aaron Weitzman (Dec 14, 2023 17:38 PST)

28 January 2022

Ron Weitzman M.D.
Chief Medical Officer

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Protocol V3.0, Amendment 2	28 January 2022
Protocol V2.0, Amendment 1	16 November 2020
Original Protocol V1.0	03 August 2020

Amendment 3.0, 28 January 2022

Overall Rationale for the Amendment:

The Sponsor has introduced the following modifications to protocol V3.0 (Amendment 2); these changes are from V2.0 (Amendment 1) and are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 9.1.3 Direction for APR003 Administration Section 9.1.3.1 Premedications Appendix 1 Schedule of Evaluations	Add guidance on allowed premedication with acetaminophen and diphenhydramine	Safety Measure: such explicit guidance will ensure that all patients received appropriate premedication to minimize the risk of severe cytokine release syndrome (CRS) and provide clear instructions on dose modifications following such events
Section 5.4.3 Clinical Experience Section 5.4.3.1 Toxicity of TLR Therapies Section 5.4.3.2 Risk Assessment	Updated Clinical Experience with APR003 and other agents in the therapeutic class	Safety Measure: ensure greater understanding and knowledge of the risk associated with this class of therapeutic

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 6.1 Primary Objective and Endpoints Section 7.1.1 Dose Limiting Toxicities (DLTs)	Endpoint and DLT definition updated to included American Society for Transplantation and Cellular Therapy (ASTCT) grading for CRS and immune effector cell-associated neurotoxicity syndrome (ICANS)	Safety measure: CRS events will be reported using more current and widely used grading criteria.
Synopsis Section 7.1 Phase 1 (Dose escalation) Section 9.1.3 Directions for APR003 Administration Section 12.1.2 Vital Signs Appendix 1	Monitoring for CRS for a minimum of 6 hours post-dose for the first cycle. If CRS is not observed during the first cycle, monitoring is not necessary on Day 1 of subsequent cycles	Safety measure: to require monitoring for CRS to ensure proper monitoring of patients during the first and subsequent cycles at the discretion of the investigator
Section 9.1.4 APR003 Dose Modifications and Interruptions Table 6 and Table 7 Appendix 1	Given the potential that a patient who undergoes a prolonged APR003 treatment interruption may experience CRS upon retreatment with study drug, patients experiencing an APR003 dose interruption of greater than or equal to 21 consecutive days for any reason, should have their safety monitoring follow that of Cycle 1 Day 1 schedule upon retreatment with APR003. Thus, as is the case in Cycle 1 for new enrollment, patients who missed 21 or more consecutive days of APR003 treatment will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first resumed cycle. If CRS is not observed during this resumed	Safety measure to ensure restarting of CRS monitoring after a drug interruption of 21 consecutive or more days upon restarting of APR003.

Section # and Name	Description of Change	Brief Rationale
	dosing cycle, prolonged monitoring is not necessary on Day 1 of subsequent cycles. If, however, a patient requires an APR003 dose interruption of > 21 consecutive days due to treatment-related toxicities, then the patient should be discontinued from treatment unless otherwise specified based on specific toxicities as defined in Table 6.	
Section 10 Concomitant medications	Clarify reporting duration for concomitant medication Included guidance on the current tocilizumab shortage	Safety Measure: ensure more accurate collection of concomitant medication data. Make sites aware of the current tocilizumab shortage.
Section 10.1 Permitted Concomitant Therapy Section 10.1.4 Infection Prophylaxis Section 10.1.5 Empiric Antibiotics Section 10.1.6 Blood Product Support Section 10.1.7 Medication for Cytokine Release Syndrome (CRS) Section 10.1.8 Fever Antipyretic Therapy Section 10.1.9 Medication for Immune Effector Cell associated Neurologic Syndrome (ICANS) Section 10.1.10 Medication for	Updated to include additional permitted therapy	Safety Measure: provides explicit guidance which medications may be/should be used in the setting of different adverse events such as CRS, or infection.

Section # and Name	Description of Change	Brief Rationale
Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS) Section 10.1.11 Surgery Section 10.1.12 Other Concomitant Medications to Control Side Effects		
Section 12.1.2 Vital Signs Appendix 1 Schedule of Evaluations	Updated vital signs to include respiratory rate and oxygen saturation; increase frequency for monitoring as clinically indicated	Safety Measure: ensure that all patients per protocol will be more closely followed for emergence of CRS
Appendix 10 ASTCT Grading for Cytokine Release Syndrome	Added	Safety Measure
Appendix 11 ACTCT Grading of ICANS	Added	Safety Measure
Appendix 12 Immune-Effector Cell Toxicity Assessment and Management	Added	Safety Measure

2.0 Synopsis

Trial No	APR003-001
Title of Study	A Phase 1 dose escalation study to evaluate safety, tolerability, and pharmacokinetics/pharmacodynamics of APR003 in patients with advanced colorectal cancer (CRC) with malignant liver lesions
Sponsor	Apros Therapeutics, Inc.
Study Phase	Phase 1
Study Sites	Multiple centers in the United States (US).
Indications & Study Population	Advanced, unresectable colorectal cancer (CRC) with metastases to the liver.
Objectives & Corresponding Endpoints	**Primary Objectives** To evaluate the safety and tolerability of single-agent APR003 and to establish the Recommended Phase 2 Dose (RP2D). Corresponding endpoints include: • Incidence and nature of Dose Limiting Toxicities (DLTs) • Incidence, nature, and severity of adverse events graded according to NCI CTCAE v5. American Society for Transplantation and Cellular Therapy (ASTCT) Grading will be utilized for cytokine release syndrome (CRS) (Appendix 10) and immune effector cell-associated neurotoxicity syndrome (ICANS) (Appendix 11). To characterize the pharmacokinetics (PK) of APR003. Corresponding endpoints may include, but are not limited to, the following PK parameters: • Area under the curve (AUC) from time zero to time t (AUC_{0-t}) • AUC from time zero to time infinity ($AUC_{0-\infty}$) • AUC over the dosing interval (AUC_{tau}) • Maximum concentration (C_{max}) • Time-to-maximum concentration (T_{max}) • Elimination half-life ($T_{1/2}$) • Apparent volume of distribution at steady state after administration (V_{ss}/F) • Apparent total plasma clearance (CL/F)

	Secondary Objectives

Study Design

This is a Phase 1 study designed to evaluate the safety, tolerability, and PK profile of APR003 in patients with advanced CRC with metastases to the liver. In addition, PDx and antitumor activity will be explored. It is anticipated that approximately 12-36 patients will be enrolled; however, the actual number of patients enrolled will depend upon multiple factors, including but not limited to, safety/occurrence of DLTs.

The study is designed as a classical 3+3 dose escalation to determine RP2D and will include patients with Stage IV CRC.

The following dose levels are planned for evaluation. Intermediate and/or higher dose levels may be added based upon safety, anti-tumor activity, PK and PDx observations.

Dose Level	Dosage	Incremental Increase
[-1]	25 mg	[1/2x]
1 (starting dose)	50 mg	N/A
2	100 mg	2x
3	175 mg	1.75x
4	250 mg	~1.4x
5	350 mg	1.4x
6	500 mg	~1.4x

A minimum of 3 patients will be enrolled at each dose level. If 1 of 3 patients experiences a DLT during the first 3 weeks (i.e. Cycle 1), an additional 3 patients will be enrolled and treated at that dose level. If 0 of 3 or $\leq$ 1 of 6 patients experience a DLT during Cycle 1, escalation to the next higher dose level will occur. If $\geq$2 of 3 or 6 patients experience a DLT during Cycle 1, dose escalation will be discontinued and either an intermediate dose level will be evaluated or the prior dose level, if at least 6 patients had been evaluated, will be considered the MTD. It is anticipated that approximately 6 dose levels of APR003 will be evaluated, although additional dose levels may be considered based upon the observed safety profile, anti-tumor activity and/or pharmacodynamic observations.

A DLT is defined as any AE that is not clearly due to progression of the patient's malignancy, occurs within the first 21 days of treatment initiation

	(i.e., Cycle 1) and that meets at least one of the non-hematologic or hematologic criteria below: Non-Hematologic DLT: Any ≥ Grade 3 non-hematologic toxicity according to the Common Toxicity Criteria for Adverse Events Version 5 (CTCAE v5) *except for the following*: • Grade 3 nausea, vomiting, or diarrhea lasting ≤ 72 hrs will not be considered a DLT • Grade 3 fatigue lasting ≤ 7 days • Grade 3 chills lasting ≤ 72 hrs • Grade 3 allergic or hypersensitivity reactions lasting ≤ 24 hrs • Grade 3 increases in total bilirubin of any duration in patients with Gilbert's Syndrome. (Note: Grade 4 increases in bilirubin of any duration and in any patient regardless of Gilbert's Syndrome, will constitute a DLT) • Grade 3 increases in liver transaminases lasting < 7 days (Note: Grade 3 increases in liver transaminases with concurrent Grade 2 increases in bilirubin of any duration, consistent with Hy's Law, will constitute a DLT) • Any Grade 4 increase in liver transaminases • Grade 3 or 4 clinical laboratory abnormalities that are reversible to ≤ Grade 1 or baseline status within 72 hrs that do not require continuous monitoring, or that are considered *not* clinically significant by the Principal Investigator Hematologic DLT: • Grade 4 neutropenia [absolute neutrophil count (ANC) < 0.5 x 10^9/L] • Grade 3 neutropenia (ANC < 1.0 x 10^9/L) lasting > 14 days • ≥ Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L with a fever ≥ 38.3ºC) • Grade 4 thrombocytopenia (< 25.0 x 10^9/L) • ≥ Grade 3 thrombocytopenia associated with clinically significant bleeding • Any hematologic toxicity resulting in death (i.e. Grade 5) In addition, any other AE that is felt to be treatment-limiting in the medical opinions of the Principal Investigator and the Sponsor's Medical Monitor may be considered a DLT. Treatment of the first 3 patients in each dose level cohort will be staggered such that consecutive patients will initiate treatment at least 2 days apart. Upon selection of the RP2D, all patients who remain on treatment may have the option to be dose modified to receive the RP2D. Intra-patient dose

	escalation to the RP2D may be permitted for patients who (1) have not experienced a DLT, (2) have not experienced any treatment-related Grade 3 or higher AEs and (3) following approval from the Sponsor Medical Monitor. Similarly, patients whose dose is above the RP2D may be dose reduced to the RP2D following approval from the Sponsor Medical Monitor. All patients must have completed at least 3 treatment cycles and have had at least 1 post-baseline tumor evaluation prior to dose modification. The RP2D of APR003 monotherapy may be selected based on one or more of the following: (1) the maximum tolerated dose (MTD), which is defined as the highest dose level in which the rate of DLTs is <33% in 6 patients, (2) maximum administered dose (MAD), defined as the highest dose level tested in the study if no MTD is identified, (3) anti-tumor, PK and/or PDx results, and/or (4) the occurrence, nature and severity of toxicities occurring after Cycle 1. The RP2D will not exceed the MTD. **Treatment and Long-Term Follow-Up Periods** During the Treatment Period, APR003 will be administered orally (po) once weekly in 21-day cycles. Patients will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first cycle. If CRS is not observed during the first cycle, monitoring is not necessary on Day 1 of subsequent cycles. Patients will be evaluated in the clinic according to the schedule described in Appendix 1. Patients will be permitted to continue on treatment for up to 1 year, or until an early discontinuation event, or the sponsor decides to terminate the study, whichever occurs first. Reasons for early discontinuation include but are not limited to; disease progression (PD), unacceptable toxicity, death, Investigator decision, significant protocol violation, patient noncompliance, or withdrawal of consent. Due to the potential for pseudoprogression and/or delayed response, patients with an initial assessment of PD by RECIST v1.1., should, whenever possible, continue on study treatment until disease progression is radiologically confirmed. Confirmation of PD is defined as radiographic demonstration of progressive disease in two consecutive imaging evaluations performed 4-8 weeks apart. Upon treatment discontinuation and after the End of Treatment (EOT) visit, patients will enter the Long-Term Follow-Up (LTFU) period and be followed for disease progression and survival for up to 1 year. **Evaluation Committees** The Safety Review Committee (SRC) will review and evaluate the safety of APR003 throughout the study. The SRC is comprised of the Sponsor Medical Monitor and Principal Investigator from each participating site. The SRC will

	review and discuss all key safety data and determine whether enrollment into the next higher dose level cohort may proceed.
Number of Patients	~12-36 patients are planned for this trial.
Eligibility Criteria	**Inclusion Criteria** 1. Histopathological diagnosis of advanced, unresectable CRC with malignant liver lesions. 2. Age ≥ 18 years at the time of consent. 3. Patient must have disease that is considered non-surgically resectable. 4. Patient must have disease that is relapsed or persistent/refractory to at least two prior systemic treatment regimens for locally advanced or metastatic disease considered to be standard-of-care (SOC). Patients who were previously not considered candidates for intensive treatment, who have not received SOC agents due to contraindications, and/or who have had <2 lines of therapy may be eligible with clear documentation and approval from the Sponsor Medical Monitor. Specific requirements are outlined below: a. Patients must have previously received an irinotecan or oxaliplatin-based therapy, as well as a targeted antibody therapy for metastatic disease b. Patients whose tumors are MSI-H/dMMR must have previously received checkpoint inhibitor therapy 5. Has at least 1 malignant lesion that is considered to be measurable according to RECIST v1.1 criteria. The lesion site must be measured accurately in at least one dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of: a. 10 mm by CT scan b. 10 mm by caliper measurement c. 20 mm by chest X-ray d. Malignant lymph nodes must be ≥ 15 mm in short axis when assessed by CT scan 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 7. Life expectancy of > 3 months. 8. Adequate organ and marrow function within 14 days of planned treatment initiation on Cycle 1 Day 1 (C1D1), as defined below:

	a. Absolute neutrophil count (ANC) ≥ 1,500 cells/μL. Patients must not have received growth factors (e.g., G-CSF) within 14 days of Screening. b. Platelet count ≥ 100,000/μL. Patients must not have received platelet transfusions within 14 days of Screening. c. Hemoglobin ≥ 8 g/dL. Patients must not have received pRBC transfusions within 28 days of Screening. d. Total and direct serum bilirubin ≤ 1.5x upper limit of normal (ULN). For patients with Gilbert's Syndrome, total serum bilirubin must be ≤ 3x ULN. e. AST and ALT ≤ 3x ULN f. Serum albumin >3 g/dL. g. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5x ULN. This applies only to patients who are not receiving therapeutic anticoagulation. Patients receiving therapeutic anticoagulation (e.g., low molecular weight heparin or warfarin) should be on a stable dose. h. Serum creatinine ≤ 1.5x ULN, or creatinine clearance (CrCl) ≥ 60 mL/min based on the Cockcroft-Gault formula. 9. Resolution of all treatment-related toxicities, except alopecia, anemia, and peripheral neuropathy, from any previous cancer therapy to ≤ Grade 1 at Screening. Patients with ongoing Grade 2 alopecia, anemia and/or peripheral neuropathy are eligible. 10. Female patients must have a negative serum or urine pregnancy test within 72 hours of Cycle 1 Day 1. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. 11. Patients must agree to use adequate birth control methods from the time of informed consent and for up to 6 months following treatment discontinuation. a. Sexually active females of child-bearing potential must agree to use two methods of birth control that includes at least one barrier. b. Sexually active males must agree to use an acceptable barrier method of birth control. c. For patients who are not sexually active: at the discretion of the Principal Investigator, sexual abstinence may be considered to be an acceptable method of contraception. The Principal Investigator should consider the reliability of sexual abstinence in relation to the patient's usual lifestyle. Periodic abstinence (e.g., calendar, post-ovulation symptothermal methods, etc.) is not considered to be an acceptable method of contraception.

	12. Willing and able to provide informed consent and to comply with the study protocol, in the Investigator's judgment. **Exclusion Criteria** 1. Chemotherapy, or other systemic small molecule therapy for the treatment of the primary malignancy, within 5 half-lives of Cycle 1 Day 1. 2. Radiation therapy, immunotherapy, or other biological therapy (e.g., monoclonal antibodies) within 28 days prior to Cycle 1 Day 1. 3. Treatment with an unapproved investigational agent or device within 28 days (or 5 half-lives for small molecule agents) prior to Cycle 1 Day 1. 4. Presence of clinically significant malignant ascites. 5. Has a primary immunodeficiency diagnosis (e.g., X-linked agammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, acquired immune deficiency syndrome, etc.). 6. Is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior Screening. Intranasal and inhaled corticosteroids, or systemic corticosteroids at physiological doses (≤ 10 mg/day of prednisone, or an equivalent corticosteroid) are permitted. 7. Known hypersensitivity to APR003 excipients. 8. Any other current or previous malignancy within the past three years *EXCEPT* a) adequately treated basal cell or squamous cell skin cancer, b) carcinoma *in situ* of the cervix, c) prostate cancer with stable prostate specific antigen (PSA) levels for 3 years, d) or other neoplasm that, in the opinion of the Principal Investigator and with the agreement of the Sponsor's Medical Monitor, will not interfere with study-specific endpoints. 9. Current or history of central nervous system (CNS) metastases. 10. Patients with malignant lesions within the immediate proximity of the biliary tract and who, in the opinion of the Principal Investigator, are at risk of biliary obstruction. 11. Active autoimmune disease requiring systemic steroid treatment (e.g., disease modifying anti-rheumatic agent, corticosteroids, or other immunosuppressive drugs). Physiologic hormone/steroid replacement

	therapy (e.g., thyroxine, glucocorticoids for treatment of adrenal insufficiency) is permitted. 12. Patients who are unable to receive medication *per os* (po), or who have refractory nausea and/or vomiting, uncontrolled diarrhea, malabsorption (e.g., Crohn's disease, ulcerative colitis, etc.), significant small bowl resection or gastric bypass surgery, or other situation that may preclude adequate absorption. 13. Major surgery within 28 days prior to Cycle 1 Day 1. 14. Active infection requiring parenteral antibiotics, antivirals, or antifungals within 14 days of Cycle 1 Day 1. Patients with infections requiring only oral antibiotics may be considered following approval by the Sponsor Medical Monitor. 15. Cardiac abnormalities including: a. Symptomatic ischemia b. Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics, unstable atrial fibrillation) are excluded from enrollment. 1st degree AV block or asymptomatic LAFB/RBBB may be eligible for enrollment c. Corrected QT interval using Fridericia's method (QTcF) > 480 ms, family history of Long QT syndrome, heart failure, hypokalemia, or other risk factor for Torsades de pointes d. Myocardial infarction in the previous six months e. Congestive heart failure (New York Heart Association class III to IV) 16. Patients who are pregnant, lactating or breastfeeding. 17. Patients who are known to have HIV infection/ seropositivity. 18. Patients with active Hepatitis virus infection (include Hepatitis A, B, and/or C). Patients with positive Hepatitis B surface antigen (HBsAg) with detected Hepatitis B virus (HBV) DNA or positive Hepatitis C antibody with detected Hepatitis C virus (HCV) RNA are excluded. 19. Patients with active CMV infection/reactivation. 20. Prior liver or other organ transplantation.

	21. Patients who are receiving treatment with medications that are prohibited on study that cannot be discontinued prior to study entry and that are considered to be any of the following: a. Other antineoplastic agents b. Patients receiving concomitant medications that prolong the QT/QTc interval (Appendix 8 in the protocol) are excluded unless such agents can be discontinued prior to the initiation of study therapy. 22. Allergy to meat products or gelatin. 23. Known psychiatric disorders, substance abuse, or other medical conditions that would interfere study compliance or interpretation of study results, or that would make the patient inappropriate for entry into the study.
Study Treatments	All patients will be treated with APR003, an orally administered agonist of TLR7. APR003 will be administered once weekly, on an empty stomach (patients must not eat for at least 2 hours before and 1 hour after study drug administration). Premedication with acetaminophen and diphenhydramine is allowed per discretion of the investigator.
Statistical Methods	It is anticipated that between ~12-36 patients will be enrolled into this trial. **Safety Analyses**: All patients who receive at least one dose of APR003 will be included in the safety population. All safety analyses will be performed on the safety population. Adverse Events (AE) will be coded according to the MedDRA version 22.1 adverse event dictionary. Results will be tabulated to examine AE frequency, organ systems affected, and relationship to study treatment. The results of clinically significant laboratory test changes will be evaluated similarly. Safety data will be examined on an ongoing basis to ensure safety of the study patients and compliance with the trial rules. Adverse events leading to dose modifications (i.e., dose reduction, dose delayed or dose not administered), as well as AEs leading to treatment discontinuation will be summarized and listed. Patients who discontinue prior to receiving at least 3 doses of APR003 in Cycle 1 for reasons other than a DLT will not be considered evaluable for DLTs or the MTD assessment and will be replaced.

	PK/PDx Analyses: Individual and mean plasma concentrations of APR003 and APR003 metabolites by time point will be descriptively summarized in tables and graphs by dose level. Summary statistics include n, arithmetic mean, median, SD, geometric mean, coefficient of variation (CV) (%) and geometric CV (%), minimum and maximum. The pharmacokinetics (PK) of APR003 will be summarized by estimating the following: • total area under the curve from time zero to time t (AUC_{0-t}) • maximum concentration (C_{max}) • time to maximum concentration (T_{max}) • apparent total plasma clearance (CL/F) • apparent volume of distribution at steady state after administration (Vss/F) • terminal half-life ($T_{1/2}$) (as appropriate for data collected) [redacted]

3.0 Table of Contents

List of Tables

4.0 List of Abbreviations and Definitions of Terms

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ADA	Anti-drug antibodies
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
AUC_{0-t}	area under the curve from time zero to time t
$AUC_{0-\infty}$	area under the curve from time zero to time infinity
AUC_{tau}	area under the curve over the dosing interval
AV	atrioventricular
BCG	Bacillus Calmette-Guerin
CL/F	total plasma clearance
C1D1	Cycle 1 Day 1
C2D1	Cycle 2 Day 1
CapeOX	Capecitabine/Oxaliplatin
CBC	complete blood count
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DC	dendritic cell
DCR6	Disease Control Rate at 6 months
DLT	Dose Limiting Toxicity

dMMR	deficient mismatch repair
DOR	Duration of Response
DRF	dose-range finding
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FIH	first-in-human
FOCBP	females of child-bearing potential
FOLFIRI	FU/Leucovorin/Irinotecan
FOLFOX	FU/Oxaliplatin/Leucovorin
FOLFOXIRI	FU/Oxaliplatin/Leucovorin/Irinotecan
FU	fluorouracil
G-CSF	granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GI	gastrointestinal
HIV	human immunodeficiency virus
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN	interferon
IL	interleukin
INR	international normalized ratio
IP10	Interferon-γ-inducible protein 10
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors in immunotherapy trials
IV	intravenous(ly)
LAFB	left anterior fascicular block
LTFU	Long-Term Follow-Up
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MLN	mesenteric lymph node

MMR	Measles/Mumps/Rubella
MMRV	Measles/Mumps/Rubella/Varicella
MSI-H	microsatellite instability-high
MSI-L	microsatellite instability-low
MSS	microsatellite stable
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	natural killer
ORR	objective response rate
OS	Overall Survival
PAMP	pathogen-associated molecular patterns
PD	Progressive Disease
PDx	pharmacodynamic(s)
PD1 or PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	Progression Free Survival
PK	pharmacokinetic(s)
PO	*per os* (oral administration)
PR	partial response
pRBC	packed red blood cell
PSA	prostate specific antigen
PT	prothrombin time
QTcF	corrected QT interval using Fridericia's method
RBBB	right bundle branch block
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SD	standard deviation
SOC	standard of care
SRC	Safety Review Committee
$T_{1/2}$	elimination half-life
TIL	tumor-infiltrating lymphocyte
TLR	toll-like receptor

T_{max}	time to maximum concentration
TNF-α	tumor necrosis factor-α
ULN	Upper limit of normal
V_{ss}/F	volume of distribution at steady state after administration

5.0 Introduction

5.1 Background Information on the Disease to be Treated

The liver is a common major organ site of cancer metastasis, particularly for tumors of the gastrointestinal tract including colorectal cancer (CRC). The immunosuppressive microenvironment of the liver is thought to play a key role in the lack of anti-tumor immunity in patients with liver lesions and the lack of tumor response to checkpoint inhibition with anti-programmed cell death protein 1 (anti-PD1) agents (Joyce & Fearon 2015, Brodt 2016). Although a number of other tumor types, both gastrointestinal (GI) and non-GI, involve metastases to the liver, this first-in-human (FIH) trial of APR003 will focus on CRC with liver metastases.

5.1.1 Colorectal Cancer (CRC)

CRC is the third most common cancer world-wide and the second leading cause of cancer-related death in the developed world (Ferlay 2015, Siegel 2017). Among CRC patients, more than 50% with advanced and/or unresectable disease will develop liver metastasis during the course of their disease (Tomlinson 2007), the majority of which will not be considered surgically resectable at the time of diagnosis. For patients with advanced and/or unresectable disease or those whose disease recurs following surgical resection, a variety of systemic chemotherapy regimens are typically used. For initial therapy of metastatic disease in patients who qualify for intensive therapy, the National Comprehensive Cancer Network (NCCN) guidelines suggest 1 of 5 regimens: 5-fluorouracil (FU)/Oxaliplatin/Leucovorin (FOLFOX), FU/ Leucovorin/Irinotecan (FOLFIRI), Capecitabine/Oxaliplatin (CapeOX), infusional 5-FU/Leucovorin or capecitabine or FU/Oxaliplatin/Leucovorin/Irinotecan (FOLFOXIRI). Despite the availability of these intensive chemotherapeutic regimens for advanced CRC, progression-free survival and overall survival remain poor; approximately 8.6 months progression-free survival; 17-month overall survival in patients treated with FOLFOX or CapeOX ± cetuximab (Maughan 2011). Furthermore, CRC remains largely non-responsive to PD-1 blockade, except for a small subset of patients whose tumors demonstrate microsatellite instability (i.e., “MSI-high”) and, consequently, have an extremely high mutational burden (Le 2015).

5.2 Role of the Immune System and the Liver

The ability of the liver to suppress systemic antigen-specific T cell responses, so called “liver tolerance”, has been well described in the literature in the context of both liver

transplantation and exposure of antigens through the portal circulation (Crispe 2006). Recently, the presence of liver metastasis was associated with decreased progression-free survival in both melanoma and non-small cell lung carcinoma patients treated with pembrolizumab. Furthermore, liver metastasis was associated with reduced $CD8^+$ tumor-infiltrating lymphocytes (TILs) within distant non-hepatic, metastatic lesions (Tumeh 2017). Therapies directed at reducing the tolerogenic bias of the liver and inducing a local increase in immune-modulatory cytokines may have a role in promoting the anti-tumor immune response needed for the successful treatment of liver metastases and associated distant metastases with cancer immunotherapies like anti-PD-1 antibodies.

5.3 Immune Agonism and Toll-like Receptors (TLRs)

Toll-like receptors (TLRs) are a family of proteins that detect a wide range of conserved pathogen-associated molecular patterns (PAMPs) and are key drivers of innate immune activation. TLR7 is highly expressed in plasmacytoid dendritic cells and B lymphocytes and is located within the endosome where it normally functions as a sensor for single-stranded viral RNA. Activation of TLR7 results in enhanced antigen processing and presentation mechanisms, the upregulation of costimulatory molecules critical for cross-priming of cytotoxic T cells, and the production of a myriad of cytokines, such as type I and type II interferons (IFNs), tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-12. In addition, TLR7 activation promotes the production of chemokines, such as interferon-γ-inducible protein 10 (IP10), which further function to bridge the gap between innate and adaptive immunity by attracting monocytes, macrophages, T cells, natural killer (NK) cells, and dendritic cells (Prinz 2003, Dufour 2002, Schwabe 2006, Lee 2007).

Several small molecule TLR agonists have demonstrated potential therapeutic efficacy against malignant disorders (Smith 2018). The TLR7 agonist, imiquimod, has previously demonstrated the ability to promote a local anti-tumor immune response when administered topically and is approved for the treatment of superficial basal cell carcinoma (Aldara® package insert). The anti-tumor effect of imiquimod is multifactorial and is hypothesized to act by recruitment of tumor-infiltrating plasmacytoid DCs and macrophages activated by cytokines and chemokines that ultimately drive increased major histocompatibility complexes (MHC)-I expression and CD8+ TILs in basal cell carcinoma (Walter 2010).

TLR7 activation in the liver of patients with malignancies that are metastatic to the liver may similarly lead to innate immune activation, release of tumor-associated antigens and, ultimately, enhanced anti-tumor immune responses. Specifically, a strong innate immune activator may convert the immunosuppressive liver/tumor microenvironment into a locally immunogenic state, leading to both a reversal of liver tolerance and generation of tumor-

specific T cell responses both locally and systemically. Thus, the successful development of effective synthetic innate immune activators may expand the fraction of patients that can respond to immunotherapies, such as anti-PD-1 blockade.

Numerous approaches to developing synthetic innate immune agonists that effectively mimic PAMPs have been employed over the past decade. Currently, there are over 20 innate immune agonists that are undergoing development in clinical trials for cancer therapy (Braunstein 2018). The majority of these innate immune agonists elicit dramatic changes to the tumor microenvironment by increasing IFN response genes, increasing leukocyte infiltration, and in particular, enhancing the tumor-specific CD8+ T cell response to drive tumor eradication (Aznar 2017). Unfortunately, clinical applications of low molecular weight TLR7 agonists have largely been limited due to broad and systemic exposure of this class of compounds driving immune cell activation in many tissues that result in high levels of systemic cytokines that contribute to tolerability issues and potential "TLR tolerance" (Dudek 2007, Engel 2011, Bourquin 2011). The Sponsor is developing a small molecule TLR7 agonist, APR003, that concentrates in the GI, liver, and kidneys, with limited systemic exposure. This approach is designed to increase the therapeutic window of a TLR7 agonist by minimizing the side-effects associated with generalized systemic immune activation and inflammation.

5.4 Background Information on the Investigational Product (APR003)

The APR003 drug product is a capsule, which contains the active drug substance A221-CA and GRAS excipients (mannitol and magnesium stearate). The intended route of administration is oral delivery. APR003 is designed using medicinal chemistry principles derived from an analysis of liver-targeting compounds (Tu 2013). Additionally, APR003 is designed to have a short half-life and low volume-of-distribution, which minimizes undesired systemic TLR7 activation. The purpose of designing a TLR7 agonist with these pharmacokinetic characteristics was maximize the ability to counteract the immunosuppressive effects of the GI tract and liver microenvironments (GI tract and liver) on a patients' overall anti-tumor immunity while minimizing the potential "TLR tolerance" that can be associated with systemic TLR7 agonism.

Importantly, despite local drug concentration in the liver, GI, and kidneys robust pharmacodynamic (PDx) response can be measured by the induction of serum IP10 and blood *ISG15*, two sensitive interferon-response markers. These markers will be utilized to evaluate on-target immune activation.

5.4.1 Non-clinical Experience

Safety Pharmacology (IB Section 2.4.3.3)

The results of the safety pharmacology cardiovascular testing indicate little-to-no potential for QT prolongation. In an in vitro human ether-a-go-go related gene (hERG) potassium channel screening assay, using manual-patch clamp technique, the IC50 was shown to be >30 μM A221. This concentration was the highest tested, corresponds to 11,175 ng/mL, and is a 210-fold margin over 59.4 ng/mL, the highest maximum concentration (Cmax) plasma level achieved in the pivotal toxicology studies after conservatively correcting for an unbound plasma level of 15% (monkey Cmax of 396 ng/mL × 0.15 = 59.4 ng/mL). Therefore, at the concentrations tested, A221-CL-3 had no significant inhibition on the potassium currents passing through cloned hERG channels stably expressed in Human Embryonic Kidney 293 (HEK 293) cells. In support of a lack of effect on QT prolongation, no change was observed in QTc interval during the pivotal monkey toxicology study.

For additional detailed information, please refer to the Investigator's Brochure.

5.4.1.1 Pharmacology

APR003 is a potent and selective TLR7 agonist, with activity across mouse, monkey, and human cells. APR003 has demonstrated anti-tumor efficacy in several syngeneic orthotopic models of colorectal and liver cancer, as a single agent and in combination with anti-PD-1/-L1. Mechanistic studies in these models demonstrated that APR003 induces a greater frequency of activated cross-presenting dendritic cells in the liver/GI draining lymph nodes, and increased tumor antigen-specific CD8+ T cells within the tumor microenvironment, thereby confirming the mechanism of action. IFNα and downstream IP-10/ISG are the key pharmacodynamic markers of TLR7 activation that are responsible for the therapeutic effect of APR003. In fact, it has previously been demonstrated that type I IFNα is required for CD8+ T cell-mediated anti-tumor responses (Fuertes 2011), and that blocking of IFNα receptor has been shown to negate the antitumor efficacy of similar innate agonists (Sivick 2018). The cytokines that were not induced by APR003 in monkeys, such as TNFα and IL-10, have been attributed to cause poor tolerability and/or reduced efficacy (Sivick 2018).

TLR7 agonism also induces chemokines such as interferon-γ-inducible protein 10 (IP-10), which functions to bridge the gap between innate and adaptive immunity by attracting monocytes, macrophages, T cells, NK cells, and dendritic cells (Prinz 2003, Dufour 2002, Schwabe 2006, Lee 2007). IP-10, as well as interferon-stimulated gene 15 (ISG15) are sensitive interferon-response markers utilized to confirm pre-systemic target engagement.

The in vivo pharmacodynamic (PDx) response to APR003 was assessed in mice and cynomolgus monkeys. In C57BL/6 mice, a single oral dose of APR003 at 30 mg/kg induced type I IFN transcription in the small intestines, liver, and mesenteric lymph nodes, followed by upregulation of interferon-stimulated genes (ISGs) in these tissues (*Isg15*, *Mx1*, *Ip-10*). In C57BL/6 and ICR mice, oral administration of APR003 induced serum IP-10, TNFα, and IL-6 dose-dependently. Serum IP-10 and liver ISGs (*Ip-10, Isg15, Mx1*) were elevated at 0.3 mg/kg compared to concurrent vehicle control group and reached a plateau at 30 mg/kg and above, while TNFα and IL-6 elevations were not detected until 3 mg/kg and 30 mg/kg, respectively. Similar to mouse pharmacology, high levels of IP-10 and *ISG15* were induced in monkeys after APR003 oral administration. IFNα was induced transiently and was consistently detected at high dose. However, in contrast to mice, only low levels of IL-6 were induced (dose independently), and no TNFα or IL-10 were detected in monkeys.

In the current study, APR003 target engagement and TLR7 agonism will be evaluated by measuring peripheral blood levels of IP-10 and/or *ISG15*, as well as other pathway-related cytokines.

5.4.1.2 Non-clinical Pharmacokinetics

APR003 is designed to concentrate in the GI and liver with low peripheral tissue distribution. Plasma half-lives are short and volume of distribution is low across species. Tissue PK studies in mice after oral dosing showed approximately 20- to 30-fold liver exposure over serum, and 10-fold kidney exposure over serum. Tissue distribution in mice showed the highest APR003 concentrations in the stomach, intestines, liver, and kidney. In these tissues, APR003 exhibited similar half-lives to plasma (between 5 to 7 hours) and is mostly excreted (>99%) by 72 hours, suggesting lack of tissue accumulation. *In vitro* studies demonstrated APR003 to be a substrate of various intestinal transporters (OATP1A2, OATP2B1), liver transporter (OATP1B1), and kidney transporters (OAT3, MATE1, MATE2-K). Excretion studies showed orally administered APR003 was mostly unabsorbed as it passed through the GI tract and excreted through the feces. Taken together, these results support a PK profile whereby APR003 concentrates in the GI/liver and has low peripheral (non-target) tissue distribution, except for the kidney (2- to 3-fold less than liver). Given the intended once-weekly dosing regimen in human, tissue accumulation is unlikely even after multiple doses.

5.4.1.3 Non-clinical Toxicology

Mouse and cynomolgus monkey were selected as the species for toxicity testing. Monkeys are known to display a TLR7 tissue expression pattern and immunostimulatory cytokine

release profile that closely mirrors humans (Junt 2015, Ketloy 2008, Messaoudi 2011, Thompson 2017). In humans and monkeys, TLR7 is mainly expressed in plasmacytoid dendritic cells (pDCs) and memory B-cells but have been also reported to be expressed in monocytes under certain conditions (Thompson 2017, Zarember 2002). In contrast, mice have prominent TLR7 expression in monocytes/macrophages, which is believed to be the reason for greater sensitivity and exaggerated responses to TLR7 agonism in this species compared to monkeys and humans (Clarke 2009, Junt 2015, Huber 2006).

5.4.1.3.1 Rodent Toxicology Studies

In a 4-week GLP study in mice, the toxicity and toxicokinetics of APR003 were evaluated at doses of 30 mg/kg, 100 mg/kg, or 300 mg/kg, administered once weekly (5 doses). One female treated with 100 mg/kg was found dead after the final dose on Day 29. Inflammatory cell infiltration in multiple organs was observed on microscopic evaluation and the death was considered to be related to exaggerated sensitivity to TLR7 agonism in rodents. No other deaths occurred. Clinical observations of loose/watery stool and a reversible decrease in mean body weight at 300 mg/kg were noted during the dosing phase of the study. Decreases in PLT count occurred at all doses. Non-reversible increases in mean absolute and relative liver and spleen weights occurred at all APR003 dose levels and correlated microscopically with lymphocytic infiltrates in the liver and increased cellularity of the white pulp of the spleen. APR003-related histopathologic observations of lymphocytic infiltrates in the kidney, liver, lacrimal gland, submandibular salivary gland, and prostate gland were seen at all doses and were consistent with on-target pharmacology and tissue distribution of APR003. Lymphocytic infiltrates in the kidney, liver, lacrimal gland, submandibular salivary gland, and prostate gland persisted at the end of the recovery period.

The no-adverse-effect level (NOAEL) in mice, which is considered to be a species that is much more sensitive to TLR7 agonism compared to humans, was 30 mg/kg and the severely toxic dose in 10% of the mice (STD10) was > 300 mg/kg.

5.4.1.3.2 Cynomolgus Monkey Toxicology Studies

In a 4-week GLP study in cynomolgus monkeys, the toxicity and toxicokinetics of APR003 were assessed at doses 15 mg/kg, 50 mg/kg, or 150 mg/kg, administered once weekly for a total of 5 doses. Goblet cell hyperplasia in the jejunum and/or ileum was seen in 3 of the 10 monkeys treated with 50 mg/kg. Similar findings were not noted at the 150 mg/kg dose. Additionally, mild, and transient increases in ALT and bilirubin was observed at the 150 mg/kg dose; no correlating histopathologic findings were observed in the liver.

APR003 and its active metabolite, A329, were detected in liver and kidney samples collected at the terminal necropsy (24 hours post last dose), with liver/plasma and kidney/plasma ratios of approximately 20-fold and 15-fold, respectively, for both APR003 and A329, consistent with tissue distribution in mice.

In cynomolgus monkeys, the NOAEL, which was also the highest non-severely toxic dose (HNSTD), of APR003 was 150 mg/kg, the highest dose level administered in the 4-week GLP toxicology study. Effects related to pharmacological response were observed at ≥ 15 mg/kg (i.e., elevated IP-10, *ISG15* mRNA, and IL-6), and related transient slight decreases in WBC and LYM and transient slight increases in ALT and bilirubin, with no histologic correlate, were observed at 150 mg/kg. The No Observed Adverse Effect Level (NOAEL) was determined to be 150 mg/kg, where the plasma AUC0-t and Cmax of A221 on Day 1 were 1110 hr*ng/mL and 396 ng/mL, and the plasma AUC0-t and Cmax of A329 (metabolite) on Day 1 were 596 hr*ng/mL and 193 ng/mL (male and female values combined).

In this 4-week monkey GLP toxicology study to observe the effects of A221-CA on cardiovascular system and respiratory frequency when administered via nasogastric gavage. In this study, cynomolgus monkeys were randomized into 4 groups with 10 animals in each group (5 males and 5 females), which were dose with vehicle control (0.5% CMC-Na/0.5% Tween-80), or test article of 15, 50, 150 mg/kg, respectively ECG parameters (PR interval (PR), RR interval(RR), QRS complex duration (QRS), QT interval (QT), corrected QT interval (QTcf), heart rate (HR)), blood pressure parameters (systolic blood pressure(SBP), diastolic blood pressure(DBP), mean arterial blood pressure(MABP)) and respiratory frequency examinations were performed once during the acclimation period (baseline), four times at dosing period (2 and 24 hrs post dosing on D1 and D22), and once at the end of recovery period.

Comparing with the vehicle control group, no test article-related abnormality was noted in blood pressure parameters (SBP, DBP, MABP), ECG parameters (PR, RR, QRS, QT, QTcF, HR), and respiratory frequency in animals of each test article-treated groups.

In conclusion, no risk was identified in the cardiovascular and respiratory safety pharmacology readouts as part of this 4-week monkey GLP study.

5.4.1.4 Genotoxicity

In a mini-Ames assay, APR003 was not mutagenic in *S. typhimurium*, TA98 and TA100, with or without metabolic activation.

5.4.2 Selection of the Starting Dose

Since APR003 is an immune-activating drug, the starting dose was selected using the minimal anticipated biologic effect level (MABEL) approach according to established regulatory standards (ICH S9; Saber 2016). APR003 target activation was evaluated in both in vitro and in vivo test systems.

IP-10 was determined to be the most sensitive in vitro cytokine readout in primary cells across species. Furthermore, IP-10 (protein) was determined to be the most sensitive and robust in vivo pharmacodynamic (PDx) readout of TLR7 activation across species, supported by literature and data obtained with APR003 (Lopatin 2013). Because TLR7 expression in monkeys is more similar to humans compared to mice, in vivo monkey PDx was used to calculate the human starting dose. Results from pharmacology, pharmacokinetics and toxicology studies were utilized for determination of the APR003 starting dose. The approach incorporated data on the PK/PDx relationship, species differences between animal models and humans and allometric scaling of data from animals to the projected human starting dose.

A dose of 50 mg APR003 was selected based on the aforementioned algorithm and consideration of an additional margin of safety.

5.4.3 Clinical Experience

5.4.3.1 Toxicity of TLR Therapies

Multiple TLR agonists have been shown to have systemic inflammatory toxicities including Grade 3 and 4 cytokine release syndrome (CRS). Additional common drug related adverse events (AEs) are pyrexia, fatigue, chills, decreased lymphocyte count, and nausea.

Cytokine-release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) can be fatal if not recognized early. Patients should be hospitalized as soon as they develop a symptom or sign of toxicity, and caregivers must be taught to recognize symptoms of ICANS.

The first clinical manifestation of CRS is pyrexia. It usually starts with fever that can exceed 40°C, and includes other symptoms such as malaise, headache, myalgias, and tachycardia. Possible manifestations include organ dysfunctions, cytopenias, and coagulopathy. In severe cases, patients can develop life-threatening capillary leakage with hypoxia and hypotension.

The standard of care for CRS is Actemra® (tocilizumab), an anti-IL-6 receptor antagonist. If the patient does not respond to Actemra® (tocilizumab), corticosteroids can be effective in reversing CRS. Some data suggest that the anti-IL-6 monoclonal antibody siltuximab or the IL-1 receptor antagonist anakinra may have clinical efficacy. In CRS, patients can require vasopressors to correct hypotension and oxygen supply or intubation for hypoxia.

ICANS may occur as an adoptive cell-related encephalopathy syndrome. The clinical manifestations of ICANS are very wide ranging, as toxicity does not affect a specific region of the central nervous system. They include encephalopathy (confusion or delirium), expressive aphasia or language disturbance, motor weakness, myoclonus or tremor, headache, seizures, and a depressed level of consciousness. In rare cases patients can rapidly develop diffuse cerebral oedema. Expressive aphasia seems to be a typical symptom. ICANS can occur almost simultaneously with CRS or even after CRS has resolved. ICANS is usually self-limiting, and most symptoms reverse in three to four weeks, with persistent abnormalities being uncommon. For ICANS, the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading is based on 5 elements: the 10-point immune effector cell-associated encephalopathy (ICE) score, depressed level of consciousness, seizure, motor findings, and elevated intracranial pressure/cerebral edema (Appendix 11). Severity can range from grade 1 to grade 4, with the grade determined by the most severe event. The ICE score is a tool that measures alterations in speech, orientation, handwriting, and concentration (Appendix 11). Severe ICANS develops almost only in patients who have experienced CRS, with severity being influenced by disease type, disease burden, patient's age, and treatment history. For grading and management, refer to Appendix 10 and Appendix 11.

As of the data cut off of 01 December 2021, 11 subjects with advanced colorectal cancer have been treated with APR003, 6 at 25 mg, 4 at 50 mg and 1 at 100 mg, dose levels -1 to 2 (Table 1). At dose level 2 (100 mg) a subject experienced an SAE (Cytokine Release Syndrome). Table 1 identifies enrollment dose levels, Table 2 indicates the frequency of adverse events, and Table 3 adverse events by dose level.

Table 1. Enrollment by Dose Level

Subject Identifier	Sex	Age	Dose Level	Stage at Entry
100--1-101	Male	64	DOSE LEVEL -1: 25 MG	IV
100--1-102	Male	49	DOSE LEVEL -1: 25 MG	IVC
100--1-104	Male	47	DOSE LEVEL -1: 25 MG	IV
100-01-101	Male	51	DOSE LEVEL 1: 50 MG	IVB
100-01-104	Male	64	DOSE LEVEL 1: 50 MG	IVB
101--1-105	Female	47	DOSE LEVEL -1: 25 MG	IVC
101-01-103	Male	60	DOSE LEVEL 1: 50 MG	IVB
101-02-101	Female	52	DOSE LEVEL 2: 100 MG	IV
102--1-103	Male	52	DOSE LEVEL -1: 25 MG	IVB
102-01-102	Male	52	DOSE LEVEL 1: 50 MG	IVB
103--1-106	Female	74	DOSE LEVEL -1: 25 MG	IVB

Table 2. Frequency of All Adverse Events Regardless of Causality

AE Preferred Term	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-Threatening	Grade 5 Death	Subjects
Chills	5 (45.5%)	5 (45.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (81.8%)
Pyrexia	8 (72.7%)	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (72.7%)
Nausea	7 (63.6%)	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (72.7%)
Vomiting	6 (54.5%)	3 (27.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (72.7%)
Lymphopenia	1 (9.1%)	1 (9.1%)	4 (36.4%)	0 (0.0%)	0 (0.0%)	5 (45.5%)
Fatigue	4 (36.4%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (36.4%)
Cytokine release syndrome	1 (9.1%)	1 (9.1%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	3 (27.3%)
Tumour pain	3 (27.3%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)
Neutropenia	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Pain	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Abdominal pain upper	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Blood creatinine increased	2 (18.2%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Headache	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Flushing	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Hydronephrosis	2 (18.2%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Urinary tract infection	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)*
Cough	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Flank pain	2 (18.2%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Abdominal pain	2 (18.2%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Diarrhoea	2 (18.2%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Back pain	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Dyspnoea	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Anaemia	0 (0.0%)	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Dizziness	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
COVID-19	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Flatulence	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Chest discomfort	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Haematuria	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)

AE Preferred Term	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-Threatening	Grade 5 Death	Subjects
Blood pressure increased	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Blood alkaline phosphatase increased	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hypotension	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Aspartate aminotransferase increased	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Myalgia	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Nail pigmentation	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Nasal congestion	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Alanine aminotransferase increased	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Neuropathy peripheral	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)*
Night sweats	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Oral herpes	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Iron deficiency anaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)*
Platelet count decreased	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Proteinuria	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hypokalaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)*
Renal colic	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Seasonal allergy	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Taste disorder	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Thirst	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Tinea infection	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Tumour flare	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hypocalcaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)*
Type 2 diabetes mellitus	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Ureteral disorder	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Dysuria	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)

AE Preferred Term	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-Threatening	Grade 5 Death	Subjects
Weight decreased	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Constipation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)*
Blood creatine increased	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Cellulitis	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Cystitis	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hyperhidrosis	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hypertension	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Oedema peripheral	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pain in extremity	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pancreatitis	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pleural effusion	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Procedural pain	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pyelonephritis	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Sinusitis bacterial	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Blood bilirubin increased	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Colon cancer	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hypoglycaemia	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hypoxia	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Lipase increased	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Oral candidiasis	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Disease progression	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (9.1%)

*One instance of each is in the adverse event database without an associated grade: urinary tract infection, neuropathy peripheral, iron deficiency anaemia, hypokalaemia, hypocalcaemia, constipation

Table 3. Adverse Events by Dose Level

AE Preferred Term	DOSE LEVEL -1: 25 MG	DOSE LEVEL 1: 50 MG	DOSE LEVEL 2: 100 MG	Total Subjects
	N=6	N=4	N=1	N=11
Chills	5 (83.3%)	3 (75.0%)	1 (100.0%)	9 (81.8%)
Vomiting	5 (83.3%)	2 (50.0%)	1 (100.0%)	8 (72.7%)
Pyrexia	5 (83.3%)	2 (50.0%)	1 (100.0%)	8 (72.7%)
Nausea	4 (66.7%)	3 (75.0%)	1 (100.0%)	8 (72.7%)
Lymphopenia	3 (50.0%)	2 (50.0%)	0 (0.0%)	5 (45.5%)
Fatigue	3 (50.0%)	1 (25.0%)	0 (0.0%)	4 (36.4%)
Cytokine release syndrome	1 (16.7%)	1 (25.0%)	1 (100.0%)	3 (27.3%)
Tumour pain	1 (16.7%)	2 (50.0%)	0 (0.0%)	3 (27.3%)
Blood creatinine increased	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Anaemia	1 (16.7%)	1 (25.0%)	0 (0.0%)	2 (18.2%)
Neutropenia	1 (16.7%)	1 (25.0%)	0 (0.0%)	2 (18.2%)
Urinary tract infection	1 (16.7%)	0 (0.0%)	1 (100.0%)	2 (18.2%)
Abdominal pain upper	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Abdominal pain	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Cough	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Hydronephrosis	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Headache	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Diarrhoea	0 (0.0%)	1 (25.0%)	1 (100.0%)	2 (18.2%)
Flushing	1 (16.7%)	1 (25.0%)	0 (0.0%)	2 (18.2%)
Dyspnoea	1 (16.7%)	1 (25.0%)	0 (0.0%)	2 (18.2%)
Flank pain	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Back pain	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
Pain	0 (0.0%)	2 (50.0%)	0 (0.0%)	2 (18.2%)
Flatulence	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Dizziness	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Haematuria	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Cystitis	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
COVID-19	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)

AE Preferred Term	DOSE LEVEL -1: 25 MG	DOSE LEVEL 1: 50 MG	DOSE LEVEL 2: 100 MG	Total Subjects
	N=6	N=4	N=1	N=11
Hyperhidrosis	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Lipase increased	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Colon cancer	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Malignant neoplasm progression	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Myalgia	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Nasal congestion	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Chest discomfort	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Cellulitis	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Night sweats	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Oedema peripheral	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pain in extremity	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pancreatitis	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pleural effusion	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Procedural pain	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Pyelonephritis	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Blood pressure increased	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Renal colic	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Sinusitis bacterial	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Taste disorder	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Thirst	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Tinea infection	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Blood bilirubin increased	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Type 2 diabetes mellitus	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Ureteral disorder	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Blood alkaline phosphatase increased	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Aspartate aminotransferase increased	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)

AE Preferred Term	DOSE LEVEL -1: 25 MG	DOSE LEVEL 1: 50 MG	DOSE LEVEL 2: 100 MG	Total Subjects
	N=6	N=4	N=1	N=11
Weight decreased	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Alanine aminotransferase increased	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Hypotension	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)
Nail pigmentation	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)
Oral herpes	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)
Dysuria	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
Proteinuria	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)
Seasonal allergy	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)
Tumour flare	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (9.1%)
Blood creatine increased	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Constipation	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Hypertension	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Hypocalcaemia	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Hypoglycaemia	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Hypokalaemia	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Hypoxia	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Iron deficiency anaemia	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Neuropathy peripheral	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Oral candidiasis	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)
Platelet count decreased	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (9.1%)

Summary of Serious Adverse Events

As of 01 December 2021, three subjects have experienced serious adverse events. One for post-surgical pain, one for cytokine release syndrome, and one for malignant neoplasm progression. Additional, three adverse events of interest occurred, one Grade 1 and one Grade 2 cytokine release syndrome and one Grade 2 pancreatitis. Details of these events may be found in the Investigator Brochure.

5.4.3.2 Risk Assessment

Potential risks associated with the study intervention and study procedures and measures to control the risks are summarized in the table below (Table 4). Detailed information about the potential risks and reasonably expected AEs in general, are found in the Investigator's Brochure. Mitigation strategies are discussed in the concomitant medication section and the appendices.

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study. This study will be performed in compliance with the protocol, International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) and applicable regulatory requirements. Aspects of the study concerned with the investigational product(s) will meet the requirements of US FDA – Good Manufacturing Practice (US GMP).

Table 4. Risk Assessment for APR003

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: APR003		
Cytokine Release Syndrome (CRS)	Patients can present with fever, rigor, malaise, headache, nausea/vomiting, or more severe, life-threatening symptoms of hypoxia, pulmonary edema, tachycardia, hypotension, aphasia, confusion, or seizures.	Premedication for CRS prophylaxis in all subjects will be administered per institutional guidelines and after discussion and review of data between the Sponsor, Apros Medical Monitor or designee and Investigator(s) (Section 10.1.7).
Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)	HLH and MAS may occur in the setting of CRS. Clinical and laboratory features of MAS include fever, increased ferritin levels, pancytopenia, hemophagocytosis in bone marrow or lymph nodes, fibrinolytic coagulopathy, and liver dysfunction.	Subjects may receive treatment including Actemra® (tocilizumab) and corticosteroids given intravenously. Canakinumab may also be used (Section 10.1.10).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Infections and febrile neutropenia	The occurrence of infections and febrile neutropenia is common following infusion with the use of lymphodepletion and adoptive cell therapies.	Subjects will be monitored for signs and symptoms of infection and treated appropriately. Subjects, at the discretion of the Investigator, will be given anti-infective agents and G-CSF as needed. Infection prophylaxis: Subjects, at the discretion of the Investigator, will be given anti-infective agents as needed Section 10.1.4. Fungal infection: Antifungal agents can be initiated and given either orally or as an IV dose (Section 10.1.4).
Neurologic adverse events (AEs) and immune effector cell associated neurologic syndrome (ICANS)	Neurologic AEs may occur with high grade CRS.	Subjects will receive aggressive treatment including corticosteroids. Actemra® (tocilizumab) may be administered if neurotoxicity is accompanied by CRS (Sections 10.1.7 and 10.1.9).
Prolonged cytopenia	Thrombocytopenia, neutropenia, and anemia, and should be carefully monitored.	Blood counts should be monitored as prolonged neutropenia is associated with increased risk of infection.
Tumor lysis syndrome (TLS)	TLS occurs when tumor cells release their contents into the blood stream, either spontaneously or due to treatment, leading to metabolic disturbances including hyperuricemia, hyperkalemia, hypophosphatemia, and hypocalcemia.	Management of cardiac and neuromuscular abnormalities and preservation of kidney function are most important. Allopurinol can be used to reduce the hyperuricemia and rasburicase can be used to preserve or improve renal function Section 10.1.10.
Viral reactivation	Viral infections are very commonly associated with lymphodepletion and adoptive cell therapy infusion.	Herpes or Epstein Barr virus: Subjects can receive valacyclovir orally or acyclovir intravenously if the patient cannot take oral antiviral medications after lymphodepletion Section 10.1.4.
Nausea and diarrhea	A general risk with cell therapies.	Prophylactic medication can be used at the Investigator's discretion with Sponsor approval (Section 10.1)

5.5 Program Development

Biologically, APR003 has the potential to impact any cancer type with metastases to the liver. The intended initial evaluation of and planned first indication is for the treatment of advanced CRC with metastases to the liver.

Following determination of the monotherapy RP2D, the anti-tumor activity of APR003 as a single agent will be evaluated. In addition, the safety and anti-tumor activity of APR003 in combination with PD1/PD-L1 checkpoint inhibition may also be considered.

6.0 Study Objectives

6.1 Primary Objectives and Endpoints

The primary objective(s) of the study include the following:

Phase 1 Dose Escalation

- To evaluate the safety and tolerability of single-agent APR003 and to establish the Recommended Phase 2 Dose (RP2D). The corresponding endpoints include:
  - Incidence and nature of Dose Limiting Toxicities (DLTs)
  - Incidence, nature, and severity of adverse events graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5. ASTCT Grading will be utilized for CRS (Appendix 10) and ICANS (Appendix 11).
- To characterize the PK of APR003. Corresponding endpoints may include, but are not limited to, the following PK parameters:
  - Area under the curve (AUC) from time zero to time t (AUC_{0-t})
  - AUC from time zero to time infinity ($AUC_{0-\infty}$)
  - AUC over the dosing interval (AUC_{tau})
  - Maximum concentration (C_{max})
  - Time-to-maximum concentration (T_{max})
  - Elimination half-life ($T_{1/2}$)
  - Apparent volume of distribution at steady state after administration (V_{ss}/F)
  - Apparent total plasma clearance (CL/F)

[redacted]

7.0 Study Design & Plan

This is a Phase 1 study designed to evaluate the safety, tolerability, and PK of APR003 monotherapy in patients with advanced, unresectable CRC with metastases to the liver. In addition, PDx, and antitumor activity will be explored. It is anticipated that approximately 12-36 patients will be enrolled; however, the actual number of patients enrolled will depend upon multiple factors, including but not limited to, safety/occurrence of DLTs.

7.1 Phase 1 (Dose escalation)

The Dose Escalation is designed as a classical 3+3 to determine the RP2D.

Table 5 shows the dose levels planned for evaluation. Intermediate and/or higher dose levels may be added based upon safety, anti-tumor activity, PK and PDx observations.

Table 5. Planned Dose Levels

Dose Level	Dosage	Incremental Increase
[-1]	25 mg	[1/2x]
1 (starting dose)	50 mg	N/A
2	100 mg	2x
3	175 mg	1.75x
4	250 mg	~1.4x
5	350 mg	1.4x
6	500 mg	~1.4x

A minimum of 3 patients will be enrolled at each dose level. If 1 of 3 patients experiences a DLT during the first 3 weeks (i.e., Cycle 1), an additional 3 patients will be enrolled and treated at that dose level. If 0 of 3 or ≤ 1 of 6 patients experience a DLT during Cycle 1, escalation to the next higher dose level will occur. If ≥2 of 3 or 6 patients experience a DLT during Cycle 1, dose escalation will be discontinued and either intermediate dose level will be evaluated or the prior dose level, if at least 6 patients had been evaluated, will be considered the maximum tolerated dose (MTD). It is anticipated that approximately 6 dose levels of APR003 will be evaluated, although additional dose levels may be considered based upon the observed safety profile, anti-tumor activity and/or PDx observations.

Treatment of the first 3 patients in each dose level cohort will be staggered such that consecutive patients will initiate treatment at least 2 days apart.

Patients will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first cycle. If CRS is not observed during the first cycle, monitoring is not necessary on Day 1 of subsequent cycles

7.1.1 Dose-Limiting Toxicities (DLTs)

The following definition of DLTs will be applied. A DLT is defined as any AE that is not clearly due to progression of the patient's malignancy, which occurs within the first 21 days of

treatment initiation (i.e., Cycle 1) and that meets at least one of the non-hematologic or hematologic criteria below:

Non-Hematologic DLT:

- Any ≥ Grade 3 non-hematologic toxicity according to the CTCAE v5 or ASTCT ≥ Grade 3 Grade for CRS and ICANS *except for the following*:
  - Grade 3 nausea, vomiting, or diarrhea lasting ≤ 72 hrs will not be considered a DLT
  - Grade 3 fatigue lasting ≤ 7 days
  - Grade 3 chills lasting ≤ 72 hrs
  - Grade 3 allergic or hypersensitivity reactions lasting ≤ 24 hrs
  - Grade 3 increases in total bilirubin of any duration in patients with Gilbert's Syndrome. (Note: Grade 4 increases in bilirubin of any duration and in any patient regardless of Gilbert's Syndrome, will constitute a DLT)
  - Grade 3 increases in liver transaminases lasting < 7 days (Note: Grade 3 increases in liver transaminases with concurrent Grade 2 increases in bilirubin of any duration, consistent with Hy's Law, will constitute a DLT)
  - Any Grade 4 increase in liver transaminases
  - Grade 3 or 4 clinical laboratory abnormalities that are reversible to ≤ Grade 1 or baseline status within 72 hrs, that do not require continuous monitoring, or that are considered not clinically significant by the Principal Investigator

Hematologic DLT:

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 0.5 x 10^9/L)
- Grade 3 neutropenia (ANC < 1.0 x 10^9/L) lasting > 14 days
- ≥ Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L with a fever ≥ 38.3ºC)
- Grade 4 thrombocytopenia (< 25.0 x 10^9/L)
- ≥ Grade 3 thrombocytopenia associated with clinically significant bleeding
- Any hematologic toxicity resulting in death (i.e., Grade 5)

In addition, any other AE that is felt to be treatment-limiting in the medical opinion of the Principal Investigator and the Sponsor's Medical Monitor may be considered a DLT.

7.2 Patient Replacement

In general, patients will not be replaced on study. However, if a patient is considered as non-evaluable for the DLT evaluation, enrollment of a new patient to the current cohort will be considered if there are less than the required number of evaluable patients. In order to be considered DLT-evaluable, patients must receive at least 3 doses of APR003 in Cycle 1, unless they experience a DLT (see Section 15.2.2.2) Enrollment of new patients may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable patients is achieved within the DLT cohort.

All reasons for patient replacement in DLT and efficacy analyses will be described.

7.3 Evaluation Committees

Safety will be reviewed on an ongoing basis. The Safety Review Committee (SRC), comprised of the Sponsor Medical Monitor and Principal Investigator (or designee) from each participating site, will review and evaluate the safety of APR003 throughout the study. The SRC will review and discuss all key safety data and determine whether enrollment into the next higher dose level cohort may proceed.

7.4 Study Design Rationale

The proposed first-in-human (FIH) trial is a Phase 1 study consisting of a dose escalation of single-agent APR003 to identify the RP2D. The purpose of this study is to evaluate the safety and tolerability profile of APR003 monotherapy and to identify the single-agent recommended Phase 2 dose (RP2D), as well as to characterize the pharmacokinetic profile of APR003. This is the first time APR003 will be administered to humans. Thus, the dose escalation part of this study is required to characterize the safety and tolerability of APR003.

The traditional "3 + 3" design was selected because it is the prevailing method for conducting Phase 1 cancer clinical trials (Storer 1989) and supports the identification of a dose of APR003 for which the rate of DLTs is less than 33%. Based on the mechanism-of-action and distribution of APR003, it is reasonable to make the classical assumption that toxicity will increase with increasing dose.

7.5 Early Study Termination

The study can be terminated at any time for any reason by the Sponsor. Reasons for study termination include, but are not limited to:

- occurrence of > 10% deaths in Phase 1a that are not due to progression of the patient's primarily malignancy
- occurrence of >1 DLT at Dose Level -1

In addition, the Safety Review Committee may decide to terminate the study for reasons such as an overall Phase 1 APR003 toxicity profile.

Should study termination be necessary, all patients on study treatment should be seen as soon as possible for the End of Treatment (EOT) visit and the assessments for EOT should be performed as described in the Schedule of Evaluations (Appendix 1). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing institutional review boards (IRBs) and/or independent ethics committees (IECs) of the early termination of the trial.

8.0 Patient Population and Study Eligibility Criteria

8.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for inclusion in the study:

1. Histopathological diagnosis of advanced, unresectable CRC with malignant liver lesions.
2. Age ≥ 18 years at the time of consent.
3. Patient must have disease that is considered non-surgically resectable.
4. Patient must have disease that is relapsed or persistent/refractory to at least two prior systemic treatment regimens for locally advanced or metastatic disease considered to be standard-of-care (SOC). Patients who were previously not considered candidates for intensive treatment, who have not received SOC agents due to contraindications, and/or who have had <2 lines of therapy may be eligible with clear documentation and approval from the Sponsor Medical Monitor. Specific requirements are outlined below:
    a. Patients must have previously received an irinotecan or oxaliplatin-based therapy, as well as a targeted antibody therapy for metastatic disease
    b. Patients whose tumors are MSI-H/dMMR must have previously received checkpoint inhibitor therapy
5. Has at least 1 malignant lesion that is considered to be measurable according to RECIST v1.1 criteria. The lesion site must be measured accurately in at least one dimension (longest diameter in the plane of measurement to be recorded) with a minimum size of
    a. 10 mm by CT scan
    b. 10 mm by caliper measurement
    c. 20 mm by chest X-ray
    d. Malignant lymph nodes must be ≥ 15 mm in short axis when assessed by CT scan
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Life expectancy of > 3 months.
8. Adequate organ and marrow function within 14 days of planned treatment initiation on Day 1, Cycle1 (C1D1), as defined below:
    a. Absolute neutrophil count (ANC) ≥ 1,500 cells/μL. Patients must not have received growth factors (e.g., G-CSF) within 14 days of Screening.

b. Platelet count ≥ 100,000/μL. Patients must not have received platelet transfusions within 14 days of Screening.

c. Hemoglobin ≥ 8 g/dL. Patients must not have received pRBC transfusions within 28 days of Screening.

d. Total serum bilirubin ≤ 1.5x upper limit of normal (ULN). For patients with Gilbert's Syndrome, total serum bilirubin must be ≤ 3x ULN.

e. AST and ALT ≤ 3x ULN

f. Serum albumin >3 g/dL

g. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) ≤ 1.5x ULN. This applies only to patients who are not receiving therapeutic anticoagulation. Patients receiving therapeutic anticoagulation (e.g., low molecular weight heparin or warfarin) should be on a stable dose.

h. Serum creatinine ≤ 1.5x ULN, or creatinine clearance (CrCl) ≥ 60 mL/min based on the Cockcroft-Gault formula.

9. Resolution of all treatment-related toxicities, except alopecia, anemia, and peripheral neuropathy, from any previous cancer therapy to ≤ Grade 1 at Screening. Patients with ongoing Grade 2 alopecia, anemia and/or peripheral neuropathy are eligible.

10. Female patients must have a negative serum or urine pregnancy test within 72 hours of Cycle 1 Day 1. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements.

11. Patients must agree to use adequate birth control methods from the time of informed consent and for up to 6 months following treatment discontinuation.

    a. Sexually active females of child-bearing potential must agree to use two methods of birth control that includes as least one barrier.

    b. Sexually active males must agree to use an acceptable barrier method of birth control.

    c. For patients who are not sexually active: at the discretion of the Principal Investigator, sexual abstinence may be considered to be an acceptable method of contraception. The Principal Investigator should consider the reliability of sexual abstinence in relation to the patient's usual lifestyle. Periodic abstinence (e.g., calendar, post-ovulation symptothermal methods, etc.) is not considered to be an acceptable method of contraception.

12. Willing and able to provide informed consent and to comply with the study protocol, in the Investigator's judgement.

8.2 Exclusion Criteria

Patients who meet one of the following criteria will be excluded from the study:

1. Chemotherapy, or other systemic small molecule therapy for the treatment of the primary malignancy, within 5 half-lives of Cycle 1 Day 1.
2. Radiation therapy, immunotherapy, or other biological therapy (e.g., monoclonal antibodies) within 28 days prior to Cycle 1 Day 1.
3. Treatment with an unapproved investigational agent or device within 28 days (or 5 half-lives for small molecule agents) prior to Cycle 1 Day 1.
4. Presence of clinically significant malignant ascites
5. Has a primary immunodeficiency diagnosis (e.g., X-linked agammaglobulinemia, common variable immunodeficiency, severe combined immunodeficiency, acquired immune deficiency syndrome, etc.).
6. Is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior Screening. Intranasal and inhaled corticosteroids, or systemic corticosteroids at physiological doses (≤ 10 mg/day of prednisone, or an equivalent corticosteroid) are permitted.
7. Known hypersensitivity to APR003 excipients.
8. Any other current or previous malignancy within the past three years *EXCEPT*
   a) adequately treated basal cell or squamous cell skin cancer, b) carcinoma *in situ* of the cervix, c) prostate cancer with stable prostate specific antigen (PSA) levels for 3 years, d) or other neoplasm that, in the opinion of the Principal Investigator and with the agreement of the Sponsor's Medical Monitor, will not interfere with study-specific endpoints.
9. Current or history of central nervous system (CNS) metastases.
10. Patients with malignant lesions within the immediate proximity of the biliary tract and who, in the opinion of the Principal Investigator, are at risk of biliary obstruction.
11. Active autoimmune disease requiring systemic steroid treatment (e.g., disease modifying anti-rheumatic agent, corticosteroids, or other immunosuppressive drugs). Physiologic

hormone/steroid replacement therapy (e.g., thyroxine, glucocorticoids for treatment of adrenal insufficiency) is permitted with approval of the Sponsor Medical Monitor.

12. Patients who are unable to receive medication *per os* (po), or who have refractory nausea and/or vomiting, uncontrolled diarrhea, malabsorption (e.g., Crohn's disease, ulcerative colitis, etc.), significant small bowl resection or gastric bypass surgery, or other situation that may preclude adequate absorption.
13. Major surgery within 28 days prior to Cycle 1 Day 1.
14. Active infection requiring parenteral antibiotics, antivirals, or antifungals within 14 days of Cycle 1 Day 1 Patients with infections requiring only oral antibiotics may be considered following approval by the Sponsor Medical Monitor.
15. Cardiac abnormalities including:
    a. Symptomatic ischemia
    b. Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics, unstable atrial fibrillation) are excluded from enrollment. 1st degree AV block or asymptomatic LAFB/RBBB may be eligible for enrollment.
    c. Corrected QT/QTc interval using Fridericia's method (QTcF) > 480 ms, family history of Long QT syndrome, heart failure, hypokalemia, or other risk factor for Torsades de pointes.
    d. Myocardial infarction in the previous six months
    e. Congestive heart failure (New York Heart Association class III to IV)
16. Patients who are pregnant, lactating or breastfeeding.
17. Patients who are known to have HIV infection/ seropositivity.
18. Patients with active Hepatitis virus infection (include Hepatitis A, B and/or C). Patients with positive Hepatitis B surface antigen (HBsAg) with detected Hepatitis B virus (HBV) DNA or positive Hepatitis C antibody with detected Hepatitis C virus (HCV) RNA are excluded.
19. Patients with active CMV infection/reactivation.
20. Prior liver or other organ transplantation

21. Patients who are receiving treatment with medications that are prohibited on study that cannot be discontinued prior to study entry and that are considered to be any of the following:
    a. Other antineoplastic agents
22. Patients receiving concomitant medications that prolong the QT/QTc interval (Appendix 8 in the protocol) are excluded unless such agents can be discontinued prior to the initiation of study therapy. Allergy to meat products or gelatin.
23. Known psychiatric disorders, substance abuse, or other medical conditions that would interfere study compliance or interpretation of study results, or that would make the patient inappropriate for entry into the study.

8.3 Patient Numbering and Treatment Assignment

8.3.1 Method of Assigning Patients to Treatment Groups

The enrollment and treatment assignment will be centrally managed by the Sponsor (or designee). When a treatment cohort is open for enrollment, sites will complete and submit a Patient Registration Form along with patient eligibility supporting documents for each potential patient to the Sponsor (or designee). The Sponsor (or designee) will assign a patient number and treatment cohort for each patient that is accepted into the study. Sites cannot enroll or start dosing the patient without receiving the assigned patient number and treatment cohort from the Sponsor (or designee).

8.3.2 Treatment Assignment

All patients will receive APR003 monotherapy. The starting dose of APR003 will be determined by the dose escalation cohort to which the patient is enrolled. Patients who remain on study treatment at the time of RP2D selection may have the option of dose modification to the RP2D following discussion and approval of the Sponsor Medical Monitor.

9.0 Study Treatments

9.1 Treatments Administered

All patients will receive APR003, an orally bioavailable agonist of TLR7. In the absence of unacceptable treatment-related toxicity or disease progression, patients may receive the assigned study treatment for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor.

9.1.1 APR003 Description

APR003 is a small molecule TLR7 agonist that is orally administered and is in development for the treatment of CRC with malignant liver lesions.

APR003 will be supplied as 25 mg and 100 mg opaque off-white hard gelatin capsules (Sizes 3 and 00, respectively) by the Sponsor. For additional details, please refer to the Pharmacy Manual. The pharmacist or study staff will supply the appropriate dose for each dose cohort.

9.1.2 Storage and Labeling

At a minimum, each bottle label shipped to the sites will provide the following information: lot number, study identification, required storage conditions, directions for use, and region-specific caution statements (including "Caution: New Drug – Limited by United States law to investigational use" language).

APR003 accountability records will be maintained by the pharmacy or designated drug preparation area at the study site. Upon receipt of APR003 supplies, the pharmacist or designated drug handler will inventory APR003 and complete the designated section of the shipping form. The shipping/inventory form must be sent to Sponsor (or designee), as instructed.

APR003 should be stored at controlled room temperature 15°C to 25°C (59°F to 77°F). All study supplies must be kept in a restricted access area.

A complete dispensing log must be maintained for all APR003 dispensed and all capsules of APR003 must be accounted for.

9.1.3 Directions for APR003 Administration

Planned Phase 1 dose levels are described in Section 7.1. Patients will be asked to keep a diary to record APR003 administration.

The following applies to APR003 dosing:

- Prior to each dose of APR003, premedication may be used (as specified in Section 9.1.3.1).
- APR003 will be administered orally, once weekly, in 21-day cycles. APR003 will be taken on the Days 1, 8 and 15 of each treatment cycle. Patients will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first cycle. If CRS is not observed during the first cycle, monitoring is not necessary on Day 1 of subsequent cycles
- APR003 should be taken on an empty stomach (patients must not eat for at least 2 hours before and 1 hour after APR003 administration). Patients should be instructed to record both the date and time of the dosing. It is recommended that patients take APR003 first thing in the morning on scheduled dosing days (except for PK sampling days). Note: on PK sampling days, patients should be instructed not to take their APR003 dose until instructed to do so in the clinic.
- On days when blood for PK samples will be collected and study drug administered, *APR003 must be administered in the clinic*.
- On each clinic day, the site will administer APR003 after all required procedures are complete. The patient should be counseled not to take their APR003 dose at home on the day of the clinic visit. APR003 will then be dispensed to the patient.
- Each dose should be taken with a glass of water (at least 8 oz) and consumed over as short a time as possible unless otherwise instructed. Patients should be instructed to swallow the capsules whole and not to chew, crush or open them. If the patient is assigned to a dose level where multiple capsules are to be taken, the capsules should be taken consecutively, within as short an interval as possible.
- If a patient misses to take their dose of study drug on the scheduled day, they should take APR003 within 72 hours after the missed dose but remain on the original dosing schedule. If more than 72 hours have elapsed, the patient should omit the dose and inform the site as soon as possible.
- The date and time of actual APR003 dosing should be reported in the drug diary and eCRFs.

If emerging clinical data (e.g., safety, tolerability, and/or PK relationships to PDx, and/or activity) suggest that a different regimen (e.g., frequency of administration) may be appropriate for APR003, the dosage of study drug will be determined and implemented by the Sponsor and may include a protocol amendment.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be reported in the eCRF.

9.1.3.1 Premedications

The following premedications may be used prior to each dose of APR003. This should be done in accordance with clinical site policy and best judgement of the Principal Investigator.

- Oral acetaminophen, 1000 mg, to be taken 20 minutes prior to APR003
- Oral diphenhydramine, 25 mg, to be taken 20 minutes prior to APR003

The dose of acetaminophen and diphenhydramine listed above are provided as suggestions only. Any and all premedication should be consistent with institutional policy and the best judgement of the treating physician. We requested that steroids not be used prophylactically prior to APR003 dosing.

After APR003 dosing, additional medications may be used according to the discretion of the Principal Investigator. These include but are not limited to use of tocilizumab, prednisone, additional acetaminophen and diphenhydramine, and nonsteroidal anti-inflammatory drugs.

Additional guidance can be obtained from the Apros Medical Monitor.

9.1.4 APR003 Dose Modifications and Interruptions

For patients who do not tolerate the protocol-specified dosing schedule, including during Cycle 1 of Phase 1, dose adjustments are permitted in order to allow the patient to continue study drug. *Dose adjustments must be made following discussion with and approval from the Sponsor Medical Monitor.* All dose modifications should be based on the worst preceding toxicity (NCI CTCAE version 5.0) and follow the guidelines provided in Table 6.

Given the potential that a patient who undergoes a prolonged APR003 treatment interruption may experience CRS upon retreatment with study drug, patients experiencing an APR003 dose interruption of greater than or equal to 21 consecutive days for any reason, should have their safety monitoring follow that of Cycle 1 Day 1 schedule upon retreatment with APR003. Thus, as is the case in Cycle 1 for new enrollment, patients who missed 21 or more consecutive days of APR003 treatment will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first resumed cycle. If CRS is not observed during this resumed dosing cycle, prolonged monitoring is not necessary on Day 1 of subsequent cycles.

If, however, a patient requires an APR003 dose interruption of > 21 consecutive days due to treatment-related toxicities, then the patient should be discontinued from treatment unless otherwise specified based on specific toxicities as defined in Table 6.

In exceptional situations, study drug may continue even if the patient experienced one of the treatment stopping rules (Table 6) or has required a dose interruption of > 21 days. The decision to allow continuation of treatment will be made on a case-by-case basis following documented discussion between Sponsor Medical Monitor and the Investigator. If a patient remains on study despite a dose interruption of > 21 days, i.e., patient has evidence of clinical benefit and in the opinion of the investigator it is in the best interest of the patient to remain on study, then the rationale for remaining on study and the decision and documentation of the discussion with the sponsor must be available in the source documentation and described as an investigator comment in the eCRF.

Table 6. APR003 Dose Modification and Supportive Care Guidelines for Treatment-Related Toxicities[d]

Worst toxicity CTCAE[a] Grade (v5.0)	Recommended dose modifications for APR003	Other Management Recommendations
Hematologic		
Neutropenia (ANC/neutrophils decreased)		
Grade 3 (ANC < 1.0 - 0.5 X 10^9/L) and/or febrile neutropenia	Hold APR003 until ANC is ≥ 1.0 X 10^9/L or baseline. If treatment delay is ≤ 7 days, restart at same dose. If treatment delay is > 7 but ≤ 21 days, restart one dose level lower If treatment delay is > 21 days, discontinue treatment	Supportive care as clinically indicated; growth factors are permitted on study. During Cycle 1, growth factor administration should not be administered prophylactically; growth factors may be administered for documented Grade 4 neutropenia following discussion with the Sponsor Medical Monitor
Grade 4 (ANC < 0.5 X 10^9/L)	Hold APR003 until ANC is ≥ 1.0 X 10^9/L or baseline. If treatment delay is ≤ 7 days, restart one dose level lower. If treatment delay is > 7 days, discontinue treatment	
Thrombocytopenia (platelet count decreased)		
Grade 3 (Platelets < 50-25 X 10^9/L) without bleeding	Hold APR003 until platelet count is ≥ 75 X 10^9/L. If treatment delay is ≤ 7 days, restart at same dose If treatment delay is > 7 but ≤ 21 days, restart one dose level lower If treatment delay is > 21days, omit dose and discontinue treatment	Supportive care as clinically indicated; blood and platelet transfusions, and growth factors are permitted on study
Grade 4 (Platelets < 25 X 10^9/L) or Grade 3 with bleeding	Hold APR003 until platelet count is ≥ 75 X 10^9/L. If treatment delay is ≤ 7 days, restart one dose level lower. If treatment delay is > 7 days, discontinue treatment	
Renal		
Serum creatinine		
Grade 3 (> 3.0 - 6.0 x ULN)	Hold APR003 until resolution to ≤ Grade 1 or baseline, then restart one dose level lower	Supportive care, including oral or IV hydration, as clinically indicated

Worst toxicity CTCAE[a] Grade (v5.0)	Recommended dose modifications for APR003	Other Management Recommendations
	If findings recur on one dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at two dose levels lower; the lowest dose of APR003 allowed is 25 mg once weekly If findings recur again, discontinue treatment	
Grade 4 (> 6.0 x ULN)	Discontinue treatment	
Hepatic[b] (Note: Guidance for hepatotoxicity work up is provided in Section 9.2.1.)		
Grade 3 direct or total[c] bilirubin increase	Hold APR003 until resolution to ≤ Grade 1 and restart one dose level lower If findings recur on one dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at two dose levels lower; the lowest dose of APR003 allowed is 25 mg once weekly If findings recur again, discontinue treatment	Supportive care, including corticosteroids and/or N-acetylcysteine, as clinically indicated
Grade 3 ALT or AST	Hold APR003 until resolution to ≤ Grade 1 and restart one dose level lower If findings recur on one dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at two dose levels lower; the lowest dose of APR003 allowed is 25 mg once weekly If findings recur again, discontinue treatment	
ALT or AST > 3x ULN (or baseline) with concurrent > 2x ULN (or baseline) direct or total bilirubin	Hold APR003 until resolution to ≤ Grade 1 and restart one dose level lower If findings recur again, discontinue treatment	
Grade 4 AST or ALT	Discontinue treatment	
Cardiac		
QTc prolongation (Fridericia	Grade 1 Assess electrolytes and concomitant medications	Monitor with serial ECGs until QTcF is ≤

Worst toxicity CTCAE[a] Grade (v5.0)	**Recommended dose modifications for APR003**	**Other Management Recommendations**
Formula)	Correct any electrolyte abnormalities, or hypoxia Continue at the same dose level Grade 2 Assess electrolytes and concomitant medications Correct any electrolyte abnormalities, or hypoxia Continue at the same dose level Grade 3 Withhold dose Assess electrolytes and concomitant medications Correct any electrolyte abnormalities, or hypoxia. Upon recovery to Grade ≤1 resume treatment at one dose level lower	500 msec
Grade 4 QTc prolongation (Fridericia Formula)	Discontinue treatment	
Infections and Infestations		
Grade 3 or 4 infection	Hold APR003 until resolution to ≤ Grade 1 and clinically stable, and restart one dose level lower	Supportive care and antibiotic/antifungal/antiviral intervention as appropriate

Worst toxicity CTCAE[a] Grade (v5.0)	Recommended dose modifications for APR003	Other Management Recommendations
Other Non-Immune-Related, Non-Hematologic Toxicity		
Grade 3	Hold APR003 until resolution to ≤ Grade 1 or baseline and restart one dose level lower If findings recur on one dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at two dose levels lower; the lowest dose of APR003 allowed is 25 mg once weekly If findings recur again, discontinue treatment	Supportive care as clinically indicated
Grade 4	Discontinue treatment	
Immune-Mediated, Non-Hematologic Toxicity		
Grade 2 diarrhea or colitis	Hold APR003 until resolution to ≤ Grade 1 and restart one dose level lower If findings recur on one dose level lower, hold until resolves to ≤ Grade 1 or baseline and restart at two dose levels lower; the lowest dose of APR003 allowed is 25 mg once weekly If findings recur again, discontinue treatment	Supportive care, including IV fluids as clinically indicated. Consider corticosteroids if colitis lasts > 5 days after drug interruption
Grade 3 diarrhea or colitis	Hold APR003 until resolution to ≤ Grade 1 and restart one dose level lower If findings recur again, discontinue treatment	Supportive care, including IV fluids and corticosteroids, as clinically indicated. Consider GI endoscopy
Grade 4 diarrhea or colitis	Discontinue treatment	Supportive care, including IV fluids and corticosteroids, as clinically indicated. Consider GI endoscopy
Grade 2 Pneumonitis or Nephritis	Hold APR003 until resolution to ≤ Grade 1 and completion of corticosteroid taper; restart one dose level lower If findings recur again, discontinue treatment	Supportive care, including corticosteroids, as clinically indicated
≥ Grade 3 Pneumonitis or	Discontinue treatment	

Worst toxicity CTCAE[a] Grade (v5.0)	Recommended dose modifications for APR003	Other Management Recommendations
Nephritis		
Grade 3 Hyper- or Hypothyroidism	Hold APR003 until resolution to ≤ Grade 1 and clinically stable, and restart one dose level lower If findings recur again, discontinue treatment	Supportive care as clinically indicated
Grade 4 Hyper- or Hypothyroidism	Discontinue treatment	
Other Grade 3 immune-related, non-hematologic toxicity	Hold APR003 until resolution to ≤ Grade 1 and completion of corticosteroid taper (if administered) and restart one dose level lower If findings recur again, discontinue treatment	Supportive care, including corticosteroids, as clinically indicated
Other Grade 4 immune-related, non-hematologic toxicity	Discontinue treatment	

[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)

[b] The hepatic dose modification guidelines should be followed for deranged liver transaminases and bilirubin as defined in the above table if not definitively due to progressive disease in the view of the treating physician.

[c] Determine whether hyperbilirubinemia is direct vs. indirect; if indirect, rule out hemolysis. If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then restart one dose level lower and continue treatment at the discretion of the investigator and in consultation with the Sponsor Medical Monitor.

[d] Given the potential that a patient who undergoes a prolonged APR003 treatment interruption may experience CRS upon retreatment with study drug, patients experiencing an APR003 dose interruption of greater than or equal to 21 consecutive days for any reason, should have their safety monitoring follow that of Cycle 1 Day 1 schedule upon retreatment of APR003. Thus, as is the case in Cycle 1 for new enrollment, patients who missed 21 or more consecutive days of APR003 treatment will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first resumed cycle. If CRS is not observed during this resumed dosing cycle, prolonged monitoring is not necessary on Day 1 of subsequent cycles. If, however, a patient requires an APR003 dose interruption of > 21 consecutive days due to treatment-related toxicities, then the patient should be discontinued from treatment unless otherwise specified based on specific toxicities as defined in Table 6.

9.1.5 APR003 Treatment Compliance

The importance of treatment compliance should be emphasized to the patient. Patients will be given take-home kits and detailed instructions on how to take medications at home. Patients will be instructed to return all used and unused study drug containers at each study visit. Patient compliance with the dosing regimen will be assessed by reconciliation of the used and unused study drug at each clinic visit. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided for the study. Compliance will be monitored and documented by site personnel on the appropriate form. The site personnel will question the patient regarding adherence to the dosing regimen by reviewing dosing dates and times on the used bottles, recording the number of capsules and strengths returned, the date returned, and determining treatment compliance before dispensing new medication to the study patient.

9.1.6 Investigational Product Accountability

The investigator or designee must maintain an accurate record of the study drug received, patients to whom study drug is dispensed, study drug lost or accidentally or deliberately destroyed. The investigator or designee must retain all unused or expired study supplies until the monitor has confirmed the accountability data. Drug accountability will be noted by the monitor during site visits and at the completion of the study. Patients will be asked to return all unused study drug and packaging on a regular basis and at the end of the study or at the time of study drug discontinuation.

9.1.7 APR003 Disposal and Destruction

The Sponsor will provide written notification to each study site regarding the destruction of the study drug supply, which can be destroyed by a third party.

Drug supply may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor in a prior agreement.

9.2 Warnings and Precautions

Based on the mechanism of action of APR003 (i.e., immune activation via TLR7 agonism) and drug distribution, there is a potential for immune-related adverse reactions, in particular, immune-related hepatitis, colitis and nephritis. Investigators should closely follow liver transaminases and bilirubin, serum BUN and creatinine, and results of

urinalyses, as well as evaluate patients with diarrhea, blood in the stool, abdominal pain, and weight loss.

9.2.1 Elevations in Transaminases and/or Bilirubin

All patients should be followed closely for treatment-emergent jaundice; nausea and/or vomiting; right-sided abdominal pain; bilirubinuria; coagulopathies, thrombocytopenia, or easy bruising; anorexia; and increased AST, ALT and/or bilirubin. Patients with treatment-emergent elevated liver transaminases and/or bilirubin ≥ 2x ULN or baseline should receive a complete work-up for hepatotoxicity, including hepatology consult. Concomitant medications, including alternative and herbal treatments, should be evaluated for potential contribution to hepatotoxicity and discontinued whenever possible. Imaging (ultrasound, CT, or MRI) should be performed to rule out biliary obstruction and tumor progression in the liver. Anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), Epstein Barr virus (EBV) IgM, and cytomegalovirus (CMV) PCR should be performed as clinically indicated. A liver biopsy should be considered in patients with persistent ≥ 2x AST/ALT elevation above ULN or baseline, or in patients with ≥ Grade 3 elevations (Sanjeevaiah 2018).

9.2.2 Gastrointestinal Adverse Reactions

All patients should be followed closely for the occurrence of or worsening of diarrhea and/or blood in the stool. Intravenous fluids should be considered and corticosteroids administered for colitis as clinically indicated. A lower GI endoscopy should be considered for patients with ≥ Grade 3 colitis.

9.2.3 Nephritis and Renal Dysfunction

All patients should be followed closely for signs and symptoms of nephritis and/or renal dysfunction, such as increase serum creatinine, reduced urine output or oliguria, hematuria and/or edema. Increased frequency of monitoring (every 3 days) should be considered for patients with Grade 2 increased creatinine (>1.5x to 3x ULN or baseline). Nephrology consultation and corticosteroids should be considered for patients with ≥ Grade 3 increased serum creatinine.

9.3 Follow-up for Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed-up per Table 7 below or more frequently as clinically indicated until resolution or stabilization of the event.

All patients must be followed up for adverse events and serious adverse events for at least 30 days following the last dose of study drug or until new anticancer therapy has been initiated, whichever occurs first.

Suggested recommendations for follow-up of patients experiencing selected toxicities are described in Table 7.

Table 7. Follow-up Evaluations for Selected Toxicities

Toxicity	Follow-up evaluation
Hematologic	If ≥ CTCAE grade 3 – 4 neutropenia or febrile neutropenia or thrombocytopenia has been demonstrated, these parameters should be repeated at least once a week (or more frequently per institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.
Renal	If serum creatinine ≥ CTCAE grade 3 has been demonstrated, this parameter should be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline.
Hepatic	If direct bilirubin ≥ 3 x ULN, and ALT is ≥ CTCAE grade 3, these parameters should be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline.
Cardiac	If a QTcF > 500 msec has been demonstrated and no contraindicated medicines have been identified: • the ECG should be repeated, ensuring the patient is rested • draw a blood sample for APR003 PK analysis • Evaluate serum potassium and magnesium, and consider other potential confounding clinical factors (e.g., oxygenation, cardiac ischemia) • monitored the patient with serial ECGs until the QTcF is ≤ 500 msec.
Prolonged QTc interval	Grade 1 • Assess electrolytes and concomitant medications • Correct any electrolyte abnormalities, or hypoxia • Continue at the same dose level Grade 2 • Assess electrolytes and concomitant medications

Toxicity	Follow-up evaluation
	• Correct any electrolyte abnormalities, or hypoxia • Continue at the same dose level Grade 3 • Withhold dose • Assess electrolytes and concomitant medications • Correct any electrolyte abnormalities, or hypoxia. • Upon recovery to Grade ≤1 resume treatment at one dose level lower Grade 4 • Discontinue
Other Toxicities	Patients who experience treatment-limiting toxicities must be evaluated at least once a week following demonstration of the toxicity until resolution to grade 1 or to the patient's baseline. Given the potential that a patient who undergoes a prolonged APR003 treatment interruption may experience CRS upon retreatment with study drug, patients experiencing an APR003 dose interruption of greater than or equal to 21 consecutive days for any reason, should have their safety monitoring follow that of Cycle 1 Day 1 schedule upon retreatment with APR003. Thus, as is the case in Cycle 1 for new enrollment, patients who missed 21 or more consecutive days of APR003 treatment will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first resumed cycle. If CRS is not observed during this resumed dosing cycle, prolonged monitoring is not necessary on Day 1 of subsequent cycles. If, however, a patient requires an APR003 dose interruption of > 21 consecutive days due to treatment-related toxicities, then the patient should be discontinued from treatment unless otherwise specified based on specific toxicities as defined in Table 6.

10.0 Concomitant Medications

The patient must be told to notify the study site about all medications he/she takes, including ongoing medications during the Screening period and any new medications taken after the start of the study drug. All prescription, over-the-counter, and herbal medications, in addition to supplements, should be reported until 30 days after last administration of the study drug.

Participating sites that enroll into APR003-001 must have on-site, immediate access to tocilizumab, and ensure tocilizumab is available for each patient for administration within 2 hours after APR003 is administered, if needed for treatment of CRS. If there is a local shortage of tocilizumab, 1 dose of tocilizumab must be available on-site for each patient for immediate administration (within 2 hours). There should also be access to an additional dose of tocilizumab within 8 hours after each previous dose of tocilizumab administered to each patient, if needed.

Therefore, sites who do not have adequate supplies of tocilizumab should not be allowed to enroll patients into APR003-001.

10.1 Permitted Concomitant Therapy

In general, the use of any concomitant non-cancer medication/therapy, including over-the-counter (OTC) medications deemed necessary for the care of the patient or to treat AEs is permitted during the study except for those specified as prohibited in Section 10.3. Medications required to treat AEs, manage cancer symptoms, concurrent stable diseases, and supportive care agents, such as packed red blood cell transfusions (PRBCs) (with the exception of the DLT evaluation period, see below), pain medications, anti-emetics, and anti-diarrheal agents are allowed. The use of any other potential new concomitant medications may be discussed between the investigator and the Sponsor Medical Monitor on a case-by-case basis.

Patients taking permitted concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The days of full pharmacokinetic blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of full PK sampling, if medically feasible.

10.1.1 Anti-diarrheal Treatment

Anti-diarrheal treatment is recommended at the first sign of diarrhea. As a recommendation, initial management of diarrhea should include dietary modifications, extra fluid, and loperamide.

10.1.2 Hematopoietic Growth Factors and Transfusions

Transfusions or growth factor support should not be used prophylactically during the DLT window unless clinically indicated by institutional and/or ASCO guidelines (Smith 2006).

If during the DLT evaluation period, growth factors are used within 7 days from the onset of neutropenia grade ≥ 3, the event will be considered a DLT. Patients treated with growth factors targeting the myeloid lineage (e.g., G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior to Screening are not eligible for study enrollment.

Similarly, if during the DLT evaluation period, platelet transfusions are required for supportive management of the patient, the event will be considered a DLT. Patients requiring platelet transfusions within 14 days of Screening are not eligible for study enrollment.

Patients who receive RBC transfusions within 28 days of Screening are not eligible for study enrollment. However, after study enrollment, RBC transfusions and growth factors targeting the erythroid lineage (e.g., erythropoietin and darbepoetin) are allowed at any time.

10.1.3 Anti-Coagulation

Anti-coagulation is permitted if the patients are already at stable doses of warfarin or stable doses of low molecular weight heparin for > 2 weeks at the time of first dose of study treatment. INR should be monitored as clinically indicated per investigator's discretion. However, ongoing anti- coagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

10.1.4 Infection Prophylaxis

Subjects should receive preventive and anti-infection medications for fungal infections, pneumocystis pneumonia, herpes virus, and varicella-zoster virus according to institutional guidelines. In the absence of institutional guidelines, refer to the Infection

Prophylaxis Considerations for IEC Therapies (IEC MDACC 2020) for recommendations on the following medications:

Filgrastim (Granulocyte Colony-Stimulating Factor, G-CSF, Filgrastim, Neupogen)**:** Filgrastim may recommended to be administered subcutaneously at a dose of 300ug/day per institutional practice to reduce the duration of neutropenia and incidence of infection. Dose and route of administration may be altered as clinically indicated.

Pentamidine and sulfamethoxazole/trimethoprim (SMZ/TMP): As clinically indicated pentamidine inhaled or IV within one week prior to C1D1 and then transition to sulfamethoxazole/trimethoprim (SMZ/TMP) by 3-4 weeks if counts have recovered is recommended per institutional standard of care to prevent Pneumocystis Jirovecii Pneumonia. SMZ/TMP should continue for at least one year and until CD4 > 200 cells/μL for two consecutive measurements Dapsone (in G6PD deficient patients), or atovaquone may be substituted for SMZ/TMP.

Valacyclovir: Subjects with positive HSV or VZV serology should be given valacyclovir orally per institutional standard of care. Acyclovir may be substituted for Valacyclovir to prevent the occurrence of herpes virus infections in patients who cannot take oral medications.

Entecavir: Subjects who are positive for HBsAg or HBcAb should receive entecavir per institutional standard. Tenofovir alafenamide or Tenofovir disopoxil fumarate may be substituted. Infectious Disease and/or Hepatology should be consulted if not already following. Subjects should be monitored for HBV DNA PCR once a month while on prophylaxis and for a year after stopping.

Anti-fungal

- **Fluconazole:** It is recommended that low-risk patients receive fluconazole for fungal prophylaxis in accordance with institutional guidelines until ANC > 0.5 K/μL for 3 consecutive days without growth factor support. The drug may be given via IV in patients unable to take it orally.
- **Posaconazole:** It is recommended that high-risk patients with leukemia, recent allogenic transplant, prior history of mold infection, neutropenia lasting ≥ 14 days, Grade 3 or 4 CRS/ICANS, those who receive ≥ 3 days of corticosteroids, or those who develop hemophagocytic lymphohistiocytosis (HLH). If corticosteroids are given, continue Posaconazole for at least 1 month after completion of corticosteroids. Posaconazole should continue until clinically indicated. Do not stop posaconazole prophylaxis if ANC < 1K/μL. Voriconazole or isavuconazole

may be used if the patient had previously been taking them. In the event Posaconazole, voriconazaole, isavuconazole, or echinocandin are contraindicated or pose affordability/access issues, then use fluconazole for prophylaxis and consider aspergillus antigen testing at least once a week during corticosteroids and for at least a month after completion of corticosteroids. Patients not meeting high risk definitions will be considered to be at low risk for fungal infections and should receive prophylaxis as detailed above.

NOTE: Other anti-infective agents may be substituted at the discretion of the treating physician.

10.1.5 Empiric Antibiotics

Subjects should be started on broad-spectrum antibiotics in accordance with current institutional guidelines or at a minimum, a fever of 38.3°C once or two temperatures ≥ 38.0°C at least one hour apart, and an ANC <500/mm^3. Treatment with antibiotics should continue until ANC>500/mm^3 for 3 consecutive days without growth factor support. Infectious disease consultation should be obtained for all subjects with unexplained fever or any infectious complications and if the patient is allergic to quinolones and cephalosporins. Antibiotic coverage for central venous catheters may be provided at the discretion of the investigator.

10.1.6 Blood Product Support

Using daily CBCs as a guide, the subject will receive platelets and packed red blood cells as needed. All blood products will be irradiated and transfused per institutional guidelines and/or standard of care.

10.1.7 Medication for Cytokine Release Syndrome (CRS)

CRS is commonly observed following immune-based biotherapeutics. Subjects can present with fever, rigor, malaise, headache, nausea/vomiting, or more severe, life-threatening symptoms of hypoxia, pulmonary edema, tachycardia, hypotension, aphasia, confusion, or seizures. Early recognition of CRS is important (e.g., monitoring of symptoms, cytokines, CRP, and ferritin); however, diagnosis is difficult due to the non-specific symptoms that are observed. Recommendations for treatment and the grading system is based on Lee et al., 2019 and is shown in Appendices 10 and 11.

Premedication for CRS prophylaxis in all patients per institutional guidelines will be administered after discussion and review of data between Sponsor, Apros Medical Monitor or designee and Investigator(s).

10.1.8 Fever (≥ 38.3°C; ≥ 101°F) Antipyretic Therapy

If grade 1 fever dose not respond to antipyretics/analgesics as needed after 24 hours initiate Actemra® (tocilizumab) therapy 8 mg/kg to be repeated every 4 to 6 hours as needed if no improvement in fever after 3 days. Dexamethasone 10 mg therapy may be administered concurrently.

Total acetaminophen (APAP) utilization is not to exceed 2 g/day.

10.1.9 Medication for Immune Effector Cell-Associated Neurologic Syndrome (ICANS)

ICANS occurs frequently following immune-based biotherapeutics and like CRS, is associated with rapid cytokine increases and high tumor burden as well as other factors. Severe ICANS is associated with increased CSF protein levels, encephalopathy, and other signs of neurotoxicity. Aggressive treatment is suggested and includes administering corticosteroids. Actemra® (tocilizumab) may be administered if neurotoxicity is accompanied by CRS (Appendices 10 and 11).

10.1.10 Medication for Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

Clinical and laboratory features of MAS include fever, increased ferritin levels, pancytopenia, hemophagocytosis in bone marrow or lymph nodes, fibrinolytic coagulopathy, and liver dysfunction. Specific treatment includes administration of Actemra® (tocilizumab) and corticosteroids given intravenously. Canakinumab may also be used. Refer to (Center, 2020) for medication for Tumor Lysis Syndrome (TLS).

TLS occurs when tumor cells release their content in the blood stream, either spontaneously or due to treatment, leading to metabolic disturbances including hyperuricemia, hyperkalemia, hypophosphatemia, and hypocalcemia. The incidence and severity of TLS depends on tumor volume, potential for the tumor to lyse and patient characteristics. Management of cardiac and neuromuscular abnormalities and preservation of kidney function are most important.

Allopurinol can be used to reduce hyperuricemia and rasburicase can be used to preserve or improve renal function.

Because hyperkalemia can cause sudden death due to cardiac arrhythmias, patients should limit potassium and phosphorus intake during the TLS risk period (0 to 3 months).

Frequent measurements of serum electrolytes, continuous cardiac monitoring and the administration of oral sodium polystyrene are recommended. Symptomatic hypocalcemia should be treated with calcium supplementation; non-symptomatic hypocalcemia does not require treatment.

10.1.11 Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and the dose of APR003 required to minimize the risk of impaired wound healing and bleeding has not been determined.

10.1.12 Other Concomitant Medications to Control Side Effects

Concomitant medications to control side effects of therapy may be given per institutional standard of care.

10.2 Permitted Concomitant Therapy to be Used with Caution

Organic anion transporting polypeptides 1A2 and 1B1 (OATP1A2 and OATP1B1, respectively) are believed to play a central role in the absorption and liver-directed distribution of APR003. In addition, APR003 is a substrate of CYP3A4. Therefore, the concomitant use of drugs that are inhibitors of OATP1A2 and OATP1B1, or that affect CYP3A4 (inducers or inhibitors) may impact the pharmacokinetic profile of APR003. Whenever possible, such agents should be avoided during study participation and discontinued fourteen (14) days prior to first drug administration. If such agents cannot be avoided, site must collect the information per the eCRF guidelines for concomitant medications, including the drug name, dosage, duration, and duration of administration. In addition, unscheduled PK evaluations should be obtained in the event of AEs considered related to the use of these agents concurrently with APR003.

Drugs that impact gastric pH should not be administered during study participation whenever possible. In particular, proton pump inhibitors or H_2-blockers should be avoided. Patients must discontinue these agents at least 7 days prior to Cycle 1 Day 1. If gastric acid management is necessary, antacids such as such as milk of magnesia, Tums®, Pepto-Bismol®, etc., is preferred and should not be administered within 24 hours of APR003 administration. Please contact the Sponsor Medical Monitor for additional guidance.

A list of these agents that are inhibitors of OATP1A2 and OATP1B1, inducers/inhibitors of CYP3A4, and PPIs/H_2-antagonists is provided in Appendix 8. The Sponsor will monitor for potential increased adverse events in patients concurrently administered sensitive CYP450 substrates or substrates with a narrow therapeutic range, as APR003 is a cytokine modulator.

10.3 Prohibited Concomitant Therapy

Anti-cancer therapies and investigational agents other than those specified in this protocol are prohibited during the study. Similarly, systemic corticosteroids or other form of immunosuppressive therapy (other than inhaled or intranasal, or physiological steroid replacement) are also prohibited during the study unless requirement for the management of a toxicity. In addition, the medications agents that are known or possible risk of QT prolongation prohibited. Please refer to Appendix 9.

11.0 Visit Schedule and Assessments

11.1 Study Flow and Visit Schedule

The detailed schedule of evaluations is provided in Appendix 1.

11.1.1 Screening

A written informed consent form (ICF) approved by the Sponsor. and by the appropriate IRB or IEC will be obtained by the study site before any study specific procedures are initiated. After a patient signs the study ICF, the investigator or study site personnel should determine patient eligibility.

The clinical screening period starts once a patient has provided written informed consent to participate in the study. Patients will be evaluated against study inclusion and exclusion criteria and safety assessments.

Data will be collected on patient characteristics including demographic information, relevant medical history and current medical conditions, diagnosis and extent of cancer, prior anticancer therapies, prior medication/significant non-drug therapies, and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

Most screening assessments must be completed within 28 days prior to the first dose of study medication. Screening safety laboratory tests (e.g., hematology, serum chemistry panel, coagulation tests, urinalysis) must be performed within 14 days of C1D1. For females of child-bearing potential, a serum or urine pregnancy test must be performed within 72 hrs of the first dose of study drug. Radiologic tumor evaluation should be conducted within 14 days of C1D1; however, tumor assessments up to 28 days prior to the first dose will be acceptable. The Screening tumor assessment will provide the baseline tumor measurements, which will be used to determine future responses and/or progression.

Any procedure collected as part of patients' standard of care can be referenced to meet screening criteria even if performed before the ICF for this study has been signed, as long as the evaluation was performed within the required window period prior to the planned first dose, data are entered into the appropriate eCRF page, and source documents are available at the site for verification during monitoring visits. Acceptable procedures include hematology, serum chemistry, thyroid function (TSH, T3 and T4, 12-lead ECG, tumor imaging, urinalysis, hepatitis B and C serologies, and HIV serology.

Please refer to Appendix 1 for a detailed description of all Screening procedures.

11.1.1.1 Screen Failures

A patient who signed an ICF but did not satisfy inclusion/exclusion criteria will be considered a screen failure. Demographic information, informed consent, and Inclusion/Exclusion pages, as well as the reason for screen failure must be reported for all screen failure patients. No other data will be entered into the clinical database for patients who are screen failures. For patients who fail screening, AEs related to study procedures will be reported in the database up to the screen failure date.

Rescreening is permitted in this study. If a patient fails any of the inclusion or exclusion criteria, at the agreement of the Sponsor Medical Monitor and the investigator, the patient may be rescreened after a suitable period of time (the exact length is dependent upon the reason for the screen failure). Any patient who is rescreened will be issued a new patient number that will be linked to the original patient number. A patient may only fail screening once.

11.1.2 Treatment Period

During the treatment period, the patient must follow the Investigator's instructions with regards to contraception, concomitant medications, and dosing regimen. A treatment cycle is defined as 21 days (3 calendar weeks) for the purposes of scheduling procedures and evaluations. Patients may continue study treatment for up to 1 year or until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient request.

For details of assessments during the treatment period, refer to Appendix 1.

11.1.3 Treatment Discontinuation

All patients will be permitted to continue on treatment for up to 1 year, or until an early discontinuation event, whichever occurs first. Reasons for early discontinuation include, but are not limited to:

1. Progressive disease (PD).*
2. Unacceptable toxicity.
3. Request by the patient to withdraw.

4. Administration of medications that are prohibited while on study, including but not limited to, non-protocol chemotherapy, immunotherapy, or anti-tumor hormonal therapy, other experimental drugs, systemic corticosteroids or other form of immunosuppressive treatment, or other agents listed in Appendix 9.
5. Patients whose treatment is delayed due to treatment-related toxicities for more than 21 days.
6. Death
7. Pregnancy
8. Investigator decision
9. Significant protocol violation
10. Patient noncompliance
11. Study termination by the Sponsor.

*Due to the potential for pseudoprogression and/or delayed response, patients with an initial assessment of PD by RECIST v1.1., should, whenever possible, continue on study treatment until disease progression is radiologically confirmed. Confirmation of PD is defined as radiographic demonstration of progressive disease in two consecutive imaging evaluations performed 4-8 weeks apart.

At the time a patient permanently discontinues study drug, the End of Treatment (EOT) visit should be scheduled as soon as possible (within 30 days), at which time all of the assessments listed for the EOT visit will be performed (Appendix 1). An End of Treatment Disposition eCRF page should be completed, giving the date and reason for stopping the study drug. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. Treatment discontinuation is not considered as the end of the study. Upon treatment discontinuation, patients will enter the Long-Term Follow Up period.

11.1.4 Long-term Follow-up

Long-term follow-up information, including survival status and the first subsequent anticancer therapy, will be obtained for all surviving subjects who discontinue study therapy. Information will be collected at approximately 3- to 6-month intervals at the Sponsor's discretion through 2 years. This information will be gathered via telephone or e-mail with the subjects/caregivers or referring physician offices. Data will be collected in the source documents (e.g., subject medical record) and transcribed into the eCRF.

11.1.5 Withdrawal of Consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained for up to 25 years or longer if required under local law and analyzed at a later date. Other analyses may include other potentially relevant biomarkers and/or safety. This may also include the development of ways to detect, monitor or treat cancer.

If a patient withdraws consent, the investigator or designee must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Study drug must be discontinued, and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

12.0 Assessment Types

12.1 Safety & Tolerability Assessments

Safety endpoints include the following:

- Incidence and nature of DLTs.
- Incidence, nature, and severity of adverse events, including clinically significant laboratory values, graded according to NCI CTCAE v5.

12.1.1 Physical Examination

Physical examinations will take place at the visits specified in Appendix 1. Complete physical exams are required at Screening, C1D1 and EOT. More frequent or complete physical examinations may be performed at the discretion of the investigator and if clinically indicated.

An abbreviated and symptom-directed physical exam will occur at all other visits as indicated in Appendix 1 unless the investigator considers a complete physical examination necessary.

Significant findings that were present prior to the signing of ICF must be included in the Medical History eCRF page.

12.1.2 Vital Signs

Vital signs (body temperature, heart rate, blood pressure and respiratory rate) and oxygen saturation must be performed before dosing and as indicated in Appendix 1, and according to the standards at each institution. Patients will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first cycle. If CRS is not observed during the first cycle, monitoring is not necessary on Day 1 of subsequent cycles.

Vital signs will be assessed on the scheduled day, even if study drug is being withheld. More frequent examinations may be performed at the discretion of the investigator and as clinically indicated. Abnormal findings that are considered to be clinically significant must be reported as an AE on the AE eCRF.

As clinically indicated, vital signs will be measured as an out-patient and recorded in the patient diary and reported to the investigative site.

12.1.3 Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as indicated in Appendix 1. Height will be measured only at Screening/baseline.

12.1.4 Performance Status

The ECOG performance status (Table 8) will be assessed as indicated in Appendix 1, irrespective of the time of dosing.

Table 8. Eastern Cooperative Oncology Groups Performance Status (ECOG)

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

12.1.5 Laboratory Evaluations

Each site's local, CLIA-certified laboratories will be used for the analysis of all safety laboratory evaluations. Refer to Appendix 4 for a list of all the safety laboratory parameters that should be measured. Samples will be collected at the specified time points as indicated in Appendix 1. More frequent assessments may be performed if clinically indicated, or at the investigator's discretion; these should be recorded on the Unscheduled Visit eCRFs.

Abnormal laboratory values that are considered by the investigator to be clinically significant (e.g., require an interruption or delay to study drug, lead to clinical symptoms, or require therapeutic intervention) must be reported as an AE in the AE eCRF.

At study start, the Sponsor must be provided with a copy of each site's local laboratory certification and tabulation of the normal ranges for each parameter required. The local laboratory normal ranges should be kept up to date on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, the Sponsor must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Hematology, chemistry, coagulation, urinalysis, and pregnancy local clinical laboratory parameters collection plan and requirements are detailed in Appendix 1 and Appendix 4.

12.1.6 Electrocardiogram (ECG)

Standard 12 lead ECGs will be performed as per the assessment schedule provided in Appendix 1. More frequent examinations may be performed at the discretion of the investigator and as clinically indicated.

All ECGs will be performed in triplicate (3 sequential ECGs spaced over a 5-minute period, approximately).

Significant findings must be recorded either as Medical History (if present before the first dose of study treatment) or as an AE on the AE eCRF page (if newly occurring or worsening since treatment initiation).

If an abnormal ECG is obtained at any time and is considered clinically significant, the patient's electrolytes must be reviewed and repeat ECG measurements done after correction of any electrolyte abnormalities. Whenever an ECG with a QTcF change from baseline > 60 msec or a new absolute QTcF ≥ 501 msec result is observed in patients on study drug, an unscheduled PK sample to assess concentration APR003 should be obtained; the time of sample collection and time of dosing should be noted.

Generally, baseline and all corresponding time point ECGs should not be collected within 3 hours after food or beverage consumption and should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and heart rate.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (i.e., the timing of the PK collections overrides the timing of the ECG collections).

At each time point (see the Schedule of Evaluations, Appendix 1), 3 consecutive ECGs will be performed at approximately 2 minutes apart to determine the mean QTcF interval; the average of the triplicate ECG measurements collected at each pretreatment time point on Day 1 will serve as each subject's time-controlled baseline QTc value. If the mean QTcF is prolonged (≥45 msec from the baseline or is ≥500 msec), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTcF of ≥45 msec from the baseline; or is ≥500 msec, immediate correction for reversible causes

(including electrolyte abnormalities, hypoxia, and concomitant medications for drugs with the potential to prolong the QTcF interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTcF interval falls below ≥45 msec from the baseline; or is ≤500 msec. If QTcF interval reverts to less than 45 msec from the baseline; or is ≤500 msec, and in the judgment of the investigator(s) and sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTcF intervals rise above ≥45 msec from the baseline; or is ≥500 msec the investigational product will be held until the QTcF interval decreases to ≤45 msec from the baseline; or is ≤500 msec.

Note: If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or earlier at the discretion of the investigator); or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or earlier at the discretion of the investigator).

Once the QTcF interval decreases to ≤45 msec from the baseline or ≤500 msec, patients may restart the investigational product at the next lowest dose level. If the QTcF interval has still not decreased to ≤45 msec from the baseline or ≤500 msec after 2 weeks, or if at any time a patient has a QTcF interval >515 msec or becomes symptomatic, the patient will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

Prior to concluding that an episode of QTcF interval prolongation is due to investigational product, thorough consideration should be given to potential precipitating factors (e.g., change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at the time of the event.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed below in Table 9.

Table 9. ECG Values of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: i.e., rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
    - Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
    - Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).
    - Type II second-degree (Mobitz II) AV block.
    - Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the ECG laboratory to the investigator, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

Clinically significant findings must be discussed and documented with the Sponsor prior to enrolling the patient in the study.

Tumor response will be determined locally according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 5) and the modified RECIST criteria for immunotherapeutics (iRECIST) (Appendix 6). The local investigator's assessment will be used for the efficacy endpoint analyses and for treatment decision making.

12.2.1 Imaging Requirements

Imaging assessments (Table 10) will be performed at screening/baseline, preferably within 14 days of start of treatment (Day -14 to Day -1 prior to C1D1). All CT, MRI or PET/CT scans will image the chest/abdomen/pelvis. Assessment modality should stay consistent over the course of the study unless precluded by clinical status (e.g., renal insufficiency precludes contrast administration).

Table 10. Imaging Assessments and Collection

Procedure	Screening/Baseline	During Treatment/Follow-up
CT, PET/CT* or MRI with contrast enhancement (Chest, Abdomen, Pelvis) *if PET/CT is the preferred method for imaging, the CT portion must be of the same resolution as a diagnostic CT	Required	Every 3 cycles (± 5days), e.g., C4D1, C7D1, C10D1, etc.
Brain CT or MRI with contrast	As clinically indicated; required if there is clinical evidence of brain metastasis	Not Applicable. Presence of CNS metastases is an exclusion criterion

Any imaging assessments already completed within 28 days of the planned C1D1 as part of the patient's standard-of-care, including before signing the main study ICF, can be considered as the baseline images for this study.

Subsequent radiologic tumor assessments will be performed every 3 cycles (e.g., C4D1, C7D1, C10D1, etc.) ± 5 days Patients assessed to have either complete response (CR), partial response (PR), or progressive disease (PD) will undergo a confirmatory CT scan 4- 8 weeks later. Whenever possible, patients with progressive disease should remain on treatment until a subsequent radiologic tumor evaluation confirms PD.

Sites of known or suspected bone disease may be assessed by ^{18}F NaF PET scan, ^{99}Tc bone scan, or CT/MRI according to local clinical practice. Bone metastases may only be considered as non-target lesions.

In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments should be performed according to the originally planned schedule unless a scan has been performed within 30 days.

Note: The radiological assessment should be performed prior to any tumor biopsy procedure because inflammation and edema caused by the procedure may affect the imaging evaluation.

12.3 Pharmacokinetic, Pharmacodynamic and Immunogenicity Assessments

12.3.1 Pharmacokinetic (PK) Assessments

A primary objective of this study is to characterize the PK of APR003 at different dose levels. Although APR003 is designed to have limited systemic distribution, with exposure concentrated in the liver and GI tract, standard PK evaluations are key to understanding the relationship between dose and actual systemic levels.

Serial blood samples will be collected from all patients at all dose levels to characterize the PK of APR003 according to the schedule provided in Appendix 2.

On the day of the PK sampling, APR003 must be administered in the clinic on an empty stomach (patients should not eat for at least 1 hour before APR003 administration, and for 2 hours after). The exact dates and times of dosing and sampling must be recorded on a PK blood and collection log in a 24-hour format.

Residual samples from this study may also be used for exploratory analysis to further characterize the PK and any metabolite(s), or PDx, as necessary.

If any of the scheduled sampling times are missed or a sample is not drawn according to this schedule, the actual collection date and time will be recorded, and the remaining samples will be collected on schedule whenever possible.

If vomiting occurs within 4 hours following study drug administration on the day of PK blood sampling, no additional study medication should be taken in an effort to replace the material that has been vomited. Any vomiting during a treatment cycle must be recorded in the Adverse Events eCRF and the Sponsor Medical Monitor notified. Because APR003 is only administered once weekly, the Sponsor may request that another day of PK sample be scheduled as unscheduled visits.

If any of the following events occurs, an unscheduled PK sample should be collected:

- If a patient treated with the study drug experiences an AE that results in an unscheduled visit or fits the criteria of a SAE or DLT, as determined by the investigator. The date and time of last dose should be recorded.
- Whenever an ECG with a QTcF change from baseline > 60 msec or a new absolute QTcF ≥ 501 msec result is known. The exact time of sample collection should be noted in the unscheduled eCRF.

For details on sample handling, please refer to the study the Laboratory Manual.

12.3.1.1 Analytical Method

Plasma APR003 concentrations will be measured using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assay. The lower limit of quantification (LLOQ) of APR003 is targeted to be approximately 0.1 ng/mL.

13.0 Safety Monitoring and Reporting

13.1 Adverse Events

13.1.1 Definitions and Reporting

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a medicinal product and which does not necessarily have a causal relationship with the study drug. AEs include any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study drug(s) under study.

- The documentation of non- serious AEs and SAEs begins following the patient's first dose.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the dosing on C1D1 is considered to be a pre-existing condition that must be listed on the Medical History eCRF and should not be considered an AE unless the condition worsens in intensity or frequency after study drug start on Day 1 (e.g., Grade 2 nausea prior to Cycle 1 Day1 becomes Grade 3 nausea after first dose on Cycle 1 Day1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before C1D1 and, in the opinion of the investigator, is felt to be secondary to a study-related procedure should be reported on the Medical History eCRF and noted as "study procedure-related".

All Adverse Events (AEs) from the time of first study drug dose through 30 days after the last dose of the study drug or until a new anti-cancer therapy is initiated, whichever is shorter, must be documented in the medical record and reported on the AE electronic Case Report Form (eCRF). AEs considered to be possibly related to study drug should be followed to resolution or stabilization.

The grading of AEs will be done using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. In addition, for each AE, the investigator must indicate the attribution of the AE to study drug (i.e., related or unrelated), and the attribution of the AE to the malignancy.

13.1.2 Laboratory Test and Vital Sign Abnormalities

13.1.2.1 Definitions and Reporting

Laboratory and vital sign abnormalities should only be reported as AEs if they are considered to be clinically significant by the investigator (i.e., associated with clinical symptoms and/or require treatment). Not every laboratory abnormality or abnormal vital sign qualifies as an adverse event. A laboratory test result or vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study drug (e.g., treatment interruption or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Results in more frequent follow-up assessments or further diagnostic investigation.
- Clinically significant in the investigator's judgment.

13.1.3 Documenting Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the course of the study. An AE should be documented as a single medical diagnosis whenever possible. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the patient at each study visit.

All AEs occurring after the patient's first dose through the treatment termination visit must be reported, regardless of whether or not the AEs are considered drug-related until 30 days after the last dose or until new anticancer therapy is initiated, whichever is shorter. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the patient, will be recorded.

At each visit during the study, the patient will be assessed for the occurrence of new and ongoing AEs. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Severity

- Seriousness
- Action taken regarding study drug
- Corrective treatment, if given
- Outcome
- Investigator's assessment of causality

13.2 Serious Adverse Events (SAEs)

13.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Death
- Life-threatening (i.e., the patient was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe).
- Inpatient hospitalization or prolongation of existing hospitalization (i.e., the AE required at least a 24-hour in-patient hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a patient exposed to the molecule or investigational product before conception or during pregnancy).
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.2.2 SAE Reporting

SAE collection starts from the time of first study drug dose through 30 days after the last dose of the study drug or until a new anti-cancer therapy is initiated, whichever is shorter.

All SAEs, whether related or unrelated to study drug, must be immediately reported to the sponsor or its designees within 24 hours of the investigator's awareness of the event via EDC. In the event that the EDC is not available, paper forms may be used. In the event of questions regarding SAE reporting, the site may contact:

Safety Contact Information:

Medpace Clinical Safety

Medpace SAE hotline – USA:
Telephone: +1-800-730-5779, dial "3" or +1-513-579-9911, dial "3"
Facsimile: +1-866-336-5320 or +1-1-513-570-5196
E-mail: medpace-safetynotification@medpace.com

1. Email your SAE form to [Drug safety contact] email address, copying the Sponsor Medical Monitor.
2. Provide the name of the PI, your name, the telephone number where you can be reached and the protocol name and title.
3. Immediately forward the SAE form and any supporting documentation to [drug safety contact], copying the Sponsor Medical Monitor. This must be done within 24 hours of becoming aware of the event.

The investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow a patient with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the patient has left the study, and that additional investigations may be requested by the sponsor.

13.3 Assessment of Severity: AE and SAE Grading

The severity assigned to an AE (Table 11) should be graded according to NCI CTCAE criteria v. 5.0.

Table 11. Definitions of Adverse Events Severity

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. The AE does not interfere with routine activities. The patient may experience slight discomfort.
Grade 2 (Moderate)	Moderate; minimal, local, or noninvasive intervention indicated. The AE interferes with routine activities. The patient may experience significant discomfort.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated. The patient is unable perform routine activities. The patient may experience intolerable discomfort or pain.
Grade 4 (Life- Threatening)	Life-threatening consequences: urgent intervention indicated.
Grade 5 (Fatal)	Death due to AE

Based on the NCI Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

13.4 Assessment of Causality

The causality of each AE should be assessed and classified by the investigator as "related" or "not related". An event is considered related if there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

Categories of Attributions for "related" events:

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

Categories of Attributions for "unrelated" events:

- Unlikely related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

13.5 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study drug must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form within 24 hours of learning of its occurrence.

Pregnancy outcomes should be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes and details of the birth should be obtained from the mother.

14.0 Data Collection and Management

14.1 Data Confidentiality

Information about study patients will be kept confidential and secured in accordance with applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI

In the event that a patient revokes authorization to collect or use PHI, all information collected prior to the revocation of patient authorization will continue to be used by the Sponsor. For patients who have revoked authorization to collect or use PHI, the investigator and study site should attempt to obtain permission to collect follow-up safety information (e.g., has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, in order to prevent unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

14.2 Clinical Monitoring

Representatives of the Sponsor (or designee) will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and study site staff as well as any appropriate communications by mail, fax, email, or telephone. The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data.

In accordance with GCP, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

14.3 Data Collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until training. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff.

The principal investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Blood and tumor samples for PK and PDx evaluations will be collected by sites and sent to a central laboratory for processing. Radiological data will be acquired by the sites and interpreted locally.

14.4 Database Management and Quality Control

For studies using eCRFs, Sponsor personnel (or designee) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

15.0 Statistical Considerations

15.1 Sample Size Justification

It is anticipated that between 12-36 patients will be enrolled into this trial. Patients who discontinue prior to receiving at least 3 doses of APR003 in Cycle 1 for reasons other than a DLT will not be considered evaluable for DLTs and will be replaced.

15.2 Analysis Populations

15.2.1 All Enrolled Population

The All Enrolled population includes all patients who are enrolled into the study after signing an informed consent form.

15.2.2 Safety and DLT Evaluable Populations

15.2.2.1 Safety Population

The Safety population includes all patients who received at least one full or partial dose of study treatment. Patients will be analyzed according to the treatment they actually received as a first dose. Except for the summary of DLTs, the safety population will be used for all safety analyses. All tables will be presented for each dose escalation cohort. Listings will include all patients' data regardless of analysis population.

15.2.2.2 DLT Evaluable Population

The DLT-evaluable population includes all patients who either receive at least 3 doses of APR003 in Cycle 1, or who experience a DLT. Patients who discontinue prior to receiving the requisite amount of study treatment for reasons other than a DLT (for example, withdrawal of consent, rapidly progressive disease, protocol violation, etc.) will not be considered evaluable for DLTs and will be replaced.

[redacted]

15.2.4 Pharmacokinetic Analysis Population

The PK analysis population consists of all dosed patients who provide adequate PK samples for the characterization of PK parameters. A profile is considered evaluable if all of the following conditions are satisfied:

- Patient receives one of the planned treatments
- Patient did not vomit within 4 hours after the dosing of APR003

Note: patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. Specific time points might be removed from the analysis set if technical issues with the sample are reported (e.g., sampling issues, missing information). These patients and data points will be identified at the time of analysis.

15.3 Pharmacokinetic and Pharmacodynamic Analyses

15.3.1 Pharmacokinetic (PK) Analyses

Descriptive statistics (mean, SD, CV% or median [range]) will be presented on all parameters for each dose level group. All patients treated at the same dose level will be analyzed together.

Individual and mean plasma concentrations of APR003 and APR003 metabolites by time point will be descriptively summarized in tables and graphs by dose level. Summary statistics include n, arithmetic mean, median, standard deviation (SD), geometric mean, coefficient of variation (CV) (%) and geometric CV (%), minimum and maximum.

Pharmacokinetic endpoints include, but are not limited to, the following parameters:

- Area under the curve (AUC)
- AUC from time zero to time t (AUC_{0-t})
- AUC from time zero to time infinity ($AUC_{0-\infty}$)
- AUC over the dosing interval (AUC_{tau})
- Maximum concentration (C_{max})
- Time-to-maximum concentration (T_{max})
- Elimination half-life ($T_{1/2}$)
- Apparent volume of distribution at steady state after administration (V_{ss}/F)

- Apparent total plasma clearance (CL/F)

The PK of APR003 will be summarized and date presented as appropriate for data collected. Additional PK analyses will be conducted as appropriate.

[redacted]

15.4 Patient Disposition

Patient disposition will be summarized, including of patients who enrolled in the study, of patients in various analysis populations, of patients who completed the treatment, discontinued treatment early, and the reasons for treatment discontinuation, as well as summary for those patients who completed the study, terminated study early, and the reasons for early study termination.

Patient disposition information and patients excluded from various analysis populations will be listed.

15.5 Demographics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline body weight) will be summarized and listed. Categorical baseline characteristics (e.g., sex, ethnicity, and race) will be summarized by frequency and percentage.

A listing for all demographic characteristics will be provided.

15.6 Baseline Characteristics

Baseline characteristics summary will include the following:

- Disease history, such as time since cancer diagnosis, site of disease involvement, and time since metastases;

- Prior therapies, such as prior systemic therapy, number of prior chemotherapy, and Prior surgery; and
- Baseline disease characteristics, such as ECOG PS and tumor burden.

15.7 Prior and Concomitant Medications

Each medication will be coded to a preferred term and an Anatomic Therapeutic Classification (ATC) code using WHODrug dictionary. Prior concomitant medication is defined as any medication ended prior to the first day of the study drug. The number and percentage of patients taking each prior or concomitant medication will be displayed by medication class, preferred term, and dose cohort.

15.8 Efficacy Analyses

Imaging (CT, MRI, PET/CT) assessments will be used for all efficacy assessments of anti-tumor activity on study. Tumor assessment will be evaluated by investigators per both RECIST v1.1 and iRECIST.

Objective response rate (ORR), disease control rate lasting ≥ 6 months (DCR6) duration of response (DOR), and progression-free survival (PFS) will be defined using the rules of both RECIST v1.1 (see Appendix 5) and iRECIST (see Appendix 6). The results for DOR and PFS using the different evaluation methods will both be reported. The primary ORR endpoint will be based upon RECIST v1.1.

- ORR is defined as the proportion [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

15.9 Safety Analyses

All safety analyses, except for the evaluation of DLTs, will be performed on the safety population, defined in Section 15.2.2.1. The evaluation of DLTs for dose escalation decision making purposes will be performed on the DLT-evaluable population, defined in Section 15.2.2.2.

15.9.1 Extent of Exposure

The planned dose, actual dose, number of doses, cumulative exposure, and duration of exposure to APR003 will be listed and summarized by means of descriptive statistics for each Phase 1 dose escalation cohort in the clinical study report.

The reason for discontinuation from study treatment will be summarized and listed, along with dates of first and last doses of study drug for each patient.

15.9.2 Adverse Events (AEs)

Adverse Events (AEs) will be coded according to the MedDRA. Results will be tabulated to examine AE frequency, severity, organ systems affected, and relationship to study treatment. Adverse events will be summarized as follows:

- All AEs by Grade
- All Grade 3/4/5 AEs
- All AEs related to APR003
- AEs leading to study drug discontinuations, interruption, reductions by Grade
- All SAEs by Grade
- All SAEs related to APR003 by Grade

DLTs will be listed and their incidence summarized by primary system organ class, worst grade based on the CTCAE version 5.0, and type of adverse event for each dose escalation cohort. DLT-evaluable population will be used for these summaries.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and treatment group for each study part.

15.9.3 Vital Signs

Vital signs and the corresponding change from baseline values will be summarized by dose escalation group and scheduled time point. *All treatment-emergent abnormal and clinically significant findings must be reported as AEs.*

15.9.6 Safety Monitoring

Safety data will be reviewed by the Safety Review Committee (SRC) at the end of each dose escalation cohort (i.e., after 3 or 6 patients have been enrolled and all patients have completed the DLT-evaluation period [Cycle 1]). The SRC is comprised of the Sponsor Medical Monitor and the Principal Investigator (or designee) from each participating site. Safety data will be examined on an ongoing basis by the SRC to ensure safety of the study patients and compliance with the trial rules. Ethical, Legal, and Administrative Issues.

15.10 Good Clinical Practice

The procedures described in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by GCP, as described in ICH guideline E6 and in FDA 21 CFR parts 11, 50, 54, 56, and 312. Compliance with GCP provides public assurance that the rights, safety, and well-being of trial subjects are protected and are consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

15.11 Subject Information and Informed Consent

Before being admitted to the clinical study, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to the subject. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will comply with GCP, ICH, and all US federal regulatory requirements. The document must be in a language understandable to the subject.

After reading the informed consent form (ICF), the subject must give consent in writing prior to screening. To confirm the subject's consent, the person obtaining informed consent will sign and date the document at the time of consent. A signed consent document must be given to the subject, and an original will be retained by the Investigator. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

15.12 Institutional Review Board/Independent Ethics Committee

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB with a cover letter or a form listing the documents submitted, their

dates of issue, and the site for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirement.

Formal approval by the IRB should preferably mention the study title, protocol number, study site, date of site approval, date of ICF approval, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The Investigator will promptly report to the IRB any new information that would adversely affect the safety of the subjects or the conduct of the study. The Investigator will obtain approval from the IRB for any change(s) in any aspect of the study, such as modification(s) of the protocol, ICF, written information to be provided to subjects, and/or other procedures. The Investigator will submit periodic reports to the IRB on the progress of the study, as required. Upon completion of the study, the Investigator will provide the IRB with a final report of the outcome of the study.

The Investigator or designee must keep a record of all communication with the IRB. This record also applies to any communication between the Investigator and the regulatory authorities.

16.0 References

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17.0 Appendices

Appendix 1. Schedule of Evaluations

Evaluation	Screening	Cycle 1				Cycle 2 and Cycle 3		Cycle 4+	End of Treatment[22]
		Day 1	Day 2	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 11 (± 2 days)	Day 1 (± 5 days)	
Informed consent	X								
Inclusion/Exclusion	X								
Medical history & Demographics	X								
Cancer history and prior therapies, BRAF, MSI, CEA	X								
ECOG Performance Status	X	X		X	X	X	X	X	X
Physical Exam[1,2]	X	X	[symptom-directed physical exam]						X
Vital Signs[1]	X	X	X	X	X	X	X	X	X
Hematology[1, 3, 4]	X	X	X	X	X	X		X	X
Serum Chemistry[1, 5, 6, 7]	X	X	X	X	X	X	X	X	X
TSH, T3 and T4[8]	X							X	X
Coagulation[1, 9]	X	[as clinically indicated]				X		[as clinically indicated]	X
Pregnancy test[1, 10]	X	X							X

Evaluation	Screening	Cycle 1				Cycle 2 and Cycle 3		Cycle 4+	End of Treatment[22]
		Day 1	Day 2	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 11 (± 2 days)	Day 1 (± 5 days)	
Urinalysis[1]	X	X	X	X	X	X		X	X
12-lead ECG[1,11]	X	X	[as clinically indicated]			X	[as clinically indicated]		X
CEA carcinoembryonic antigen	X						Every 3 cycles		X
Imaging & Tumor Assessment[12, 13]	X							Every 3 cycles (e.g., C4D1, C7D1, C10D1, etc.)	X
HBsAg, HBcAb[14], anti-HCV[15], anti HIV-1 and 2	X								
APR003 Administration[16]		X		X	X	X		X	
Peripheral blood for PK[17]		X	X		X				
Peripheral blood for PDx & exploratory biomarkers[18]		X	X		X	X		Every 3 cycles (e.g., C4D1 C7D1, C10D1, etc.)	X
Archival Tumor Biopsy[19]	X								
Review Treatment Diary[20]						X	X	X	X
Drug Accountability						X		X	X

Evaluation	Screening	Cycle 1				Cycle 2 and Cycle 3		Cycle 4+	End of Treatment[22]
		Day 1	Day 2	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 1 (± 2 days)	Day 11 (± 2 days)	Day 1 (± 5 days)	
CRS/ICANS Evaluation[24]		X		X	X	X		X	
Adverse Events[21]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

1. Safety evaluations (e.g., physical exam, vital signs (body temperature, heart rate, blood pressure and respiratory rate) and oxygen saturation, hematology, serum chemistry, coagulation, pregnancy test, urinalysis, ECG, etc.) must be performed prior to study drug administration on treatment days. Height is collected only at Screening Visit. Weight will be collected at Day 1 of each cycle. Patients will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first cycle. If CRS is not observed during the first cycle, monitoring is not necessary on Day 1 of subsequent cycles
2. Complete physical exam is required at only at Screening and End of Treatment. Symptom-directed physical exams will be performed at all other visits
3. Screening hematology must be obtained within 14 days prior to C1D1. Hematological evaluation includes a CBC with differential and platelet count.
4. Starting on Cycle 2 Day 1, hematological evaluation is only required on Day 1 of each cycle. Interim evaluations should occur as clinically indicated. Hematological evaluation is required at EOT.
5. Complete metabolic panel are required at all timepoints. Screening serum chemistry evaluation must be obtained within 14 days prior to C1D1. Please refer to Appendix 4 for additional details.
6. Starting on Cycle 4 Day 1, serum chemistry evaluation are only required on Day 1 of each cycle. Interim evaluations should occur as clinically indicated. Please refer to Appendix 4 for additional details.
7. Fasting glucose is only required at Screening or pre-dose on Cycle 1 Day 1, and every 3 cycles thereafter (e.g., Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1) and at End of Treatment.

8. Thyroid function tests should be obtained approximately every 6 weeks following treatment initiation
9. Coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR), thrombin time (as clinical indicated) and fibrinogen (as clinically indicated) must be performed prior to all biopsy procedures
10. A pregnancy test (serum or urine) is required for all females of child-bearing potential (FOCBP) within 72 hrs of the first dose of study treatment. If the Screening evaluation is performed within 72 hrs of C1D1, the test does not need to be repeated.
11. Triplicate ECGs must be completed after the patients has been in a supine position for at least 5 minutes. On Cycle 1 Day 1 and Cycle 2 Day 1 an ECG will be performed prior to APR003 dosing and 30 minutes (± 5 minutes) after dosing
12. PET/CT is required at Screening, at the time of suspected disease progression, at EOT for all patients. A PET/CT scan & tumor evaluation is also required at C1D1 if a clinically significant increase in tumor burden from the Screening evaluation is suspected. Beginning at Cycle 1 Day 1, imaging and tumor evaluation will occur approximately every 3 cycles (i.e., Cycle 4 Day 1, Cycle 7 Day 1, etc.), or more frequently as clinically indicated. Imaging at EOT does not need to be repeated if the reason for treatment discontinuation is due to imaging-documented tumor progression.
13. Tumor evaluations of initial response, deeper response, or initial disease progression must be confirmed by a subsequent imaging evaluation performed within 4-8 weeks in accordance with iRECIST criteria.
14. Positive Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb) should prompt evaluation of HBV DNA. Patients with an active infection are not eligible for study participation.
15. Positive Hepatitis C antibodies should be followed by HCV RNA levels. Patients with an active infection are not eligible for study participation.
16. APR003 is administered orally once weekly, on Days 1, 8, and 15 of each treatment cycle. All doses during Cycle 1 (C1D1, C1D8 and C1D15) and at Day of 1 of every cycle APR003 will be administered in the clinic, after pre-treatment evaluations have been performed. All other doses will be self-administered by the patient at home. Patients should be instructed to take APR003 an empty stomach. Premedication with acetaminophen and diphenhydramine is allowed per discretion of the investigator. Patients will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first cycle. If CRS is not observed during the first cycle, monitoring is not necessary on Day 1 of subsequent cycles. Given the potential that a patient who undergoes a prolonged APR003 treatment interruption may experience CRS upon retreatment with study drug, patients experiencing an APR003 dose interruption of greater than or equal to 21 consecutive days for any reason, should have their safety monitoring follow that of Cycle 1 Day 1 schedule upon retreatment with APR003. Thus, as is the case in Cycle 1 for new enrollment, patients who

missed 21 or more consecutive days of APR003 treatment will be monitored for CRS with vital signs performed every 2 hours for a minimum of 6 hours post-dose for the first resumed cycle. If CRS is not observed during this resumed dosing cycle, prolonged monitoring is not necessary on Day 1 of subsequent cycles. If, however, a patient requires an APR003 dose interruption of > 21 consecutive days due to treatment-related toxicities, then the patient should be discontinued from treatment unless otherwise specified based on specific toxicities as defined in Table 6.

17. Peripheral blood samples for PK evaluation will be obtained. On C1D1, samples will be obtained at pre-dose, and at 0.5, 1, 2, 4, 6, 8 and 24 hrs after dosing. On C1D15, samples will be obtained at pre-dose, and at 0.5, 1, 2, 4, 6 and 8 hr after dosing. On C2D1, samples will be obtained at pre-dose, and at 0.5, 1, 2, 4, and 6 hrs after dosing. Please refer to, Appendix 2 for more details
18. Peripheral blood samples for PDx and biomarker evaluations should be obtained at all specified timepoints. On C1D1 and C1D15, a series of samples will be obtained. On C2D1, samples will be obtained at pre-dose, and at 0.5, 1, 2, 4, and 6 hrs after dosing. Please refer to Appendix 3 for more details. PDx and biomarker evaluations may include, but are not limited to, anti-drug antibodies, cytokine levels (e.g., IL-2, IL-4, IL-6, IL-8, IL-10, IFN-α, TNF-α, T and B-cell enumeration.
19. An archival sample should be submitted whenever adequate samples are available. Please refer to the Laboratory Manual for archival sample specifications.
20. All patients will be required to maintain a diary of study drug self-administration. The diary must be reviewed at each study visit and administration deviations reported starting at Cycle 2. All dosing performed in Cycle 1 are taken at the clinic.
21. The adverse event reporting period begins at signed Informed Consent and continues until 30 days after the last dose of study treatment, or until initiation of subsequent anti-cancer therapy, whichever occurs first.
22. The EOT visit must occur within 30 days of the last dose of study drug.
23. Long-term follow-up: Information about survival status and the first subsequent anticancer therapy will be collected at approximately 3- to 6-month intervals at the Sponsor's discretion through 2 years. This information will be gathered via telephone or email with the subjects/caregivers or referring physician offices.
24. Every 2 hours signs and symptoms will be reviewed of CRS for up to 6 hours post dose for the first three drug administrations after which 6 hours post dose then as clinically indicated (e.g., fever, fatigue, nausea, vomiting, chills, hypotension, rash, wheezing). In addition, blood pressure, pulse

oximetry, heart rate, respiratory rate and body temperature will be recorded until 2 consecutive cycles have transpired where no symptoms of CRS are reported

Appendix 2. Pharmacokinetics (PK) Detailed Schedule of Events

Cycle / Day	Scheduled time relative to dosing
C1D1	Pre-dose AM
	30 min post 1st dose ± 5 min
	1 hour post 1st dose ± 5 min
	2 hours post 1st dose ± 5 min
	4 hours post 1st dose ± 10 min
	6 hours post 1st dose ± 10 min
	8 hours post 1st dose ± 10 min
	24 hours post 1st dose ± 1 hr (i.e., C1D2)
C1D15	Pre-dose AM
	30 min post 1st dose ± 5 min
	1 hour post 1st dose ± 5 min
	2 hours post 1st dose ± 5 min
	4 hours post 1st dose ± 10 min
	6 hours post 1st dose ± 10 min
	8 hours post 1st dose ± 10 min
C2D1	Pre-dose AM
	30 min post 1st dose ± 5 min
	1 hour post 1st dose ± 5 min
	2 hours post 1st dose ± 5 min
	4 hours post 1st dose ± 10 min
	6 hours post 1st dose ± 10 min
Unscheduled	In the event of a treatment-related AE, whenever feasible

Appendix 3. Pharmacodynamics (PDx) Detailed Schedule of Events

Cycle / Day	Scheduled time relative to dosing
C1D1 *Peripheral Blood Sample*	Pre-dose
	1 hour post 1st dose ± 5 min
	2 hours post 1st dose ± 5 min
	4 hours post 1st dose ± 10 min
	6 hours post 1st dose ± 10 min
	8 hours post 1st dose ± 10 min
	24 hours post 1st dose ± 1 hr (i.e., C1D2)
C1D15 *Peripheral Blood Sample*	Pre-dose
	1 hour post 1st dose ± 5 min
	2 hours post 1st dose ± 5 min
	4 hours post 1st dose ± 10 min
	6 hours post 1st dose ± 10 min
	8 hours post 1st dose ± 10 min
C2D1 *Peripheral Blood Sample*	Pre-dose AM
	30 min post 1st dose ± 5 min
	1 hour post 1st dose ± 5 min
	2 hours post 1st dose ± 5 min
	4 hours post 1st dose ± 10 min
	6 hours post 1st dose ± 10 min
Every 3 Cycles thereafter (e.g., C4D1, C7D1, C10D1, etc.) *Peripheral Blood Sample*	Pre-dose AM

Appendix 4. Laboratory Evaluations

Hematology (Peripheral Blood Sample)	• hemoglobin
	• hematocrit
	• red blood cell (RBC) count
	• RBC Indices:
	  o Mean corpuscular volume (MCV)
	  o Mean corpuscular hemoglobin (MCH)
	  o Mean cell hemoglobin concentration (MCHC)
	  o %Reticulocytes*
	• white blood cell (WBC) count with differential
	• platelet count

Serum Chemistry (Peripheral Blood Sample)	• comprehensive metabolic panel, including
	  o sodium, potassium, bicarbonate (total CO_2) and chloride, calcium (total), magnesium (total), phosphorus (inorganic), uric acid
	  o blood urea nitrogen (BUN) and creatinine (Cr)
	  o albumin and total protein
	  o alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, lactate dehydrogenase (LDH)
	  o amylase, lipase
	  o Triglycerides
	  o glucose. Fasting glucose is required at either Screening or C1D1, every 3 cycles thereafter (e.g., C4D1, C7D1, C10D1, etc.) and at End of Treatment
	  o Creatine kinase as clinically indicated

Coagulation	• prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ration (INR) • Thrombin time (as clinically indicated) • Fibrinogen (as clinically indicated)
Thyroid Function Tests	• thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4)

Serology	• Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • HIV I and II • Hepatitis C Virus (qualitative and quantitative) • HBsAg (hepatitis B surface antigen) • HBcAb (hepatitis B core antibody) • HBsAb (hepatitis B surface antibody) Optional Infectious Disease Screening as clinically indicated • Herpes virus 6 and 7 • EBV • T spot to assess for exposure or history of tuberculosis anti-HTLV antibody HTLV I II Ab • RPR syphilis • CMV IgG and IgM • Covid 19 antigen and antibody
Markers of Inflammation	• C-reactive protein (CRP)* • Ferritin* • Cytokine panel* • D-dimer*
Other	• serum or urine pregnancy test (β-HCG) for females of child-bearing potential is required; must be negative within 72 hrs of C1D1. If Screening evaluation is within 72 hrs of C1D1, the test does not need to be repeated
Other Specialty Tests (autoimmune hepatitis work-up)	The following tests should be performed in patients with treatment-emergent increases in transaminases and/or bilirubin • anti-nuclear antibody (ANA) • anti-smooth muscle antibody (ASMA) • Epstein Barr Virus IgM • Cytomegalovirus (PCR)
Other disease specific labs as clinical indicated	• Serum iron • Quantitative test EBV by PCR

* To be done at screening and then on treatment only if clinically indicated.

Appendix 5. RECIST v1.1 Response Assessment

Source: Eisenhauer et al, 2009

Sponsor's Note: Confirmatory scans are required approximately 4 weeks after any scan that indicates either an objective response or disease progression

MEASURABILITY OF TUMOR AT BASELINE

A. DEFINITIONS

At baseline, tumor lesions will be categorized measurable or non-measurable as follows.

1. Measurable tumor lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

2. Non-measurable tumor lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

a. Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, **with identifiable soft tissue components**, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

b. Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

c. Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

B. SPECIFICATIONS BY METHODS OF MEASUREMENTS

1. Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

2. Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the subject at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, **if not, the patient should be considered not evaluable from that point forward**.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive* FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

*A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

C. TUMOR RESPONSE EVALUATION

1. Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline will be enrolled into this study.

Measurable disease is defined by the presence of at least one measurable lesion.

2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression.’ In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

D. RESPONSE CRITERIA

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

1. Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): *At least a 30% decrease* in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): *At least a 20% increase* in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute *increase of at least 5 mm*. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will

be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

- When the patient also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

3. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example,

necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

4. Time point response

It is assumed that at each protocol specified time point (i.e., radiographic evaluation of tumor burden), a response assessment occurs. Table 12 and Table 13 provides a summary of the timepoint response status calculation at each time point for patients who have measurable disease at baseline.

Table 12. Time Point Response: Patients with Target (± Non-target) Disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable
Abstracted from Eisenhauer et al, 2009

Table 13. Time Point Response: Patients with Non-target Disease Only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease and NE = not evaluable

A 'Non-CR/non-PD is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

5. Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the electronic case report form (eCRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

Conditions that define 'early progression, early death, and non-evaluability are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

6. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease, will also take into consideration the appearance of new lesions and will depend upon confirmatory scans. *For this study, determinations of either CR, PR or PD require a confirmatory scan at least 4 weeks later.* This is described further in Table 14 below.

Table 14. Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	≥4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR, or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Appendix 6. iRECIST Response Assessment

Source: Seymour L et al, 2017

The RECIST Working Group published iRECIST to provide a standard approach to the evaluation of solid tumors with measurements and assessment of the disease burden in trials that incorporate one or more immunotherapies. Immunotherapeutic agents such as APR003 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as APR003.

iRECIST follows similar recommendations provided by RECIST 1.1 in terms of methods of lesion measurement and size criteria, and the methodology of determining response is also comparable. However, there are some key differences between iRECIST and RECIST v1.1 that are highlighted in Table 15. These differences take into account tumor shrinkage or disappearance following an initial RECIST v1.1. progression. Disease progression by iRECIST requires confirmation at a subsequent assessment, 4-8 weeks after the initial RECIST v1.1. PD determination. Additionally, iRECIST categorizes new lesions as Target or Non-Target. Importantly, the time point response and best overall response by iRECIST may be different from RECIST v1.1 and should be recorded separately.

The following table was modified from EORTC iRECIST Training slides: http://recist.eortc.org/irecist/

Table 15. Comparison of RECIST v1.1 and iRECIST

	iRECIST
Definitions of measurable, non-measurable diseases	Same as RECIST v1.1
Definitions of Target and Non-Target lesions	
Measurement and management of nodal disease	
Calculation of the sum-of-measurements (SOM)	
Definitions of CR, PR, and SD, and their duration	

Confirmation of CR and PR and when applicable	
Definition of progression in Target and Non-Target lesions	First RECIST v1.1 PD is considered unconfirmed for iRECIST, termed i-Unconfirmed Progression (iUPD)
Management of new lesions	Assessed using RECIST 1.1 principles: • Classified as measurable or non-measurable • Up to 5 (2 per site) measured (but not included in the SOM of target lesions identified at baseline) and recorded as new lesions target (NL-T) with an i-sum of measurements (iSOM) • Other new lesions (measurable/non-measurable) are recorded as new lesions non-target (NL-NT) • New lesions do not have to resolve for subsequent iSD or iPR providing that the next assessment did not confirm progression
Time point response after RECIST 1.1 progression	There can be iSD, iPR or iCR after RECIST 1.1 PD • First RECIST 1.1 PD is "unconfirmed" for iRECIST – termed iUPD • iUPD must be confirmed at the next assessment (4-8 weeks) • If confirmed, termed iCPD Time point response is dynamic and based on • Change from baseline (for iCR, iPR, iSD) or change from nadir (for PD) • The last i-response
Confirmation of progression required	First RECIST 1.1 PD is "unconfirmed" for iRECIST; disease progression must be confirmed at the next assessment (4-8 weeks later Treatment past RECIST 1.1 PD is permitted if patient clinically stable • No worsening of performance status • No clinically relevant ↑in disease related symptoms

	• No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)
Collection of reason why progression cannot be confirmed	Record the reason iUPD not confirmed • Not stable • Treatment stopped but patient not reassessed/imaging not performed • iCPD never occurs • Patient has died

Secondary efficacy endpoints based on iRECIST criteria will include the following adaptations (Seymour et al, 2017):

- If radiologic imaging shows initial PD, tumor assessment should be repeated 4-8 weeks later in order to confirm PD. At the discretion of the investigator, patients may continue on study treatment awaiting radiologic confirmation of progression.
- If repeat imaging does not show objective PD (i.e., less than 20% increase in the sum of longest diameters [SLD] compared to nadir), stable or improved previous new lesion (if identified as cause for initial PD), or stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed.
- If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study therapy.
- In determining whether or not the tumor burden has increased or decreased, the site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

- SLD of target lesions remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation

In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained.

This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may continue to receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

Appendix 7. QTcF Calculation

QT correction formula Fridericia:

$$QTcF = QT \div \sqrt[3]{RR}$$

Luo S, Michler K, Johnston P, et al. (2004) A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. Journal of Electrocardiology. 37:81-90.

Appendix 8. Concomitant Medications to be Used with Caution

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study. Combination administration of the study drug with agents that are strong inhibitors of OATP1A2 and OATP1B1 could result in drug-drug interactions (DDI) or food-drug interactions (FDI) that could potentially lead to altered levels of APR003.

The list of medications and foods in the table below is meant to provide guidance only and it is not a comprehensive list. If a patient is required to take an agent that is not in the list, but there may be a risk of DDI or FDI, please contact the Sponsor clinical study team for further advice.

If an agent appears in Table 16, caution should be exercised when the agent is administered during the study.

Please contact the Sponsor Medical Monitor with any questions.

Table 16. Drugs and Foods to be used with Caution while on Study

Category	Drug Names
Strong inhibitors of CYP3A4/5	• boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, cobicistat, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir
Strong inducers of CYP3A4/5	• avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, rifabutin, phenobarbital, mitotane, enzalutamide
Known substrates of CYP3A4 with a narrow therapeutic index	• quinidine, astemizole, terfanadine, cyclosporine, sirolimus, tacrolimus, diergotamine, cisapride, ergotamine, pimozide, alfentanil, fentanyl, thioridazine, diergotamine, dihydroergotamine, ergotamine
Drugs classified as inhibitors of OATP1B1	• atazanavir, clarithromycin, cobicistat, cyclosporine, daclatasvir eltrombopag, erythromycin, gemfibrozil, glecaprevir, lopinavir/Ritonavir, letermovir, paritaprevir, pibrentasvir, sacubitril, saquinavir, simeprevir, telithromycin, teriflunomide, tipranavir, rifampin, velpatasvir, voxilaprevir,
Agents classified as inhibitors of OATP1A2	• fruit juices (apple, grapefruit, orange, pomelo), hesperidins, naringin, rifampicin, rifamycin, verapamil

Category	Drug Names
Drugs which modify gastric pH (antacid, H2 receptors antagonists, and PPIs)	• Antacids (e.g., TUMS®, Maalox®), H2 receptors antagonists: cimetidine, famotidine, nizatidine, ranitidine, proton pump inhibitors (PPI): esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "https://drug-interactions.medicine.iu.edu" Accessed 29 Jan 2019.

Tsai HH, Lin HW, Pickard AS, et al. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systemic literature review. Int J Clin Pract (2012); 62(11):1056-1078.

Yu J, Zhou Z, Tay-Sontheimer J et al. Intestinal Drug Interactions Mediated b OATPs: A Systematic Review of Preclinical and Clinical Findings. J Pharm Sci (2017); 2312-2325.

Appendix 9. QT prolonging Medications to be used with Caution

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, medications below are to be used with caution and drugs classified with a known risk of QT prolongation should be substituted when clinically feasible .

The list of medications in the table below is meant to provide guidance only and it is not a comprehensive list. If a patient is required to take a medication that is not in the list, but there may be a risk of DDI, please contact the Sponsor clinical study team for further advice.

If a drug appears in Table 17, the drug should be considered as prohibited.

Please contact the Sponsor Medical Monitor with any questions.

Table 17. QT Prolonging Medications to be used with Caution while on Study

Category	Drug Names
Drugs classified as known risk of QT prolongation	amiodarone, anagrelide, arsenic trioxide, astemizole (off US mkt), azithromycin, bepridil (off US mkt), chloroquine, chlorpromazine, cisapride (off US mkt), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US mkt), dronedarone, droperidol, erythromycin, escitalopram, flecainide, grepafloxacin (off market worldwide), halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US mkt), mesoridazine (off US mkt), methadone, moxifloxacin, ondansetron, pentamidine, pimozide, probucol (off US mkt), procainamide (oral off US mkt), quinidine, sevoflurane, sotalol, sparfloxacin (off US mkt), sulpiride (not on US mkt), terfenadine (off US mkt), thioridazine, vandetanib
Drugs classified as possible risk of QT prolongation	alfuzosin, apomorphine, aripiprazole, atazanavir, bedaquiline, bortezomib, bosutinib, clozapine, crizotinib, dabrafenib, dasatinib, dexmedetomidine, dihydroartemisinin+piperaquine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin (off US mkt), gemifloxacin, granisetron, iloperidone, isradipine, lapatinib, lithium, mifepristone, mirabegron, mirtazapine, moexipril/hctz, nicardipine, nilotinib, norfloxacin, ofloxacin, olanzapine, oxytocin, paliperidone, pasireotide, pazopanib, perflutren lipid microspheres, pipamperone (not on US mkt), promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin (on non US mkt), saquinavir, sertindole (on non US mkt), sorafenib, sunitinib,

Category	Drug Names
	tacrolimus, tamoxifen, telavancin, telithromycin, tetrabenazine (orphan drug in US), tizanidine, tolterodine, toremifene, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone

FDA Guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Accessed 29 Jan 2019. http://fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm29236 2.pdf.

FDA Guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Accessed 29 Jan 2019. http://fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm29236 2.pdf.

Tsai HH, Lin HW, Pickard AS, et al. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systemic literature review. Int J Clin Pract (2012); 62(11):1056-1078.

Woosley, RL, Heise, CW and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date 29 Jan 2019, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

Appendix 10. ASTCT Grading for Cytokine Release Syndrome[1]

(Note: CRS grade should be determined at least twice daily and any time there is a change in patient's status)

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[2]	Yes	Yes	Yes	Yes
		With		
Hypotension[3]	None	Requiring IV fluids but not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/Or		
Hypoxia[3]	None	Requiring low-flow O_2 via nasal cannula[4] or blow-by	Requiring O_2 via high-flow nasal cannula[4], facemask, nonrebreather mask, or Venturi mask	Requiring O_2 via positive pressure (e.g., CPAP, BiPAP, and mechanical ventilation)

Adapted from (Lee et al., 2019)

CPAP=continuous positive airway pressure

BiPAP=bilevel positive airway pressure

[1]Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[2] Fever is defined as temperature ≥ 38 °C not attributable to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[3] CRS grade is determined by more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5 °C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[4] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

Appendix 11. ASTCT GRADING OF ICANS[1]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[2]	7-9	3-6	0[3]-2	0[3] (patient is unarousable and unable to perform ICE)
Depressed levels of consciousness[4]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[5]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure (ICP)[6]/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[7]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Adapted from (Lee et al., 2019) [1] ICANS grading is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS. N/A indicates not applicable. [2] Refer to ICE Assessment below for ICE Score. [3] A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia or Grade 4 ICANS if the patient is unarousable [4] Depressed level of consciousness should not be attributable to any other cause (e.g., sedating medication) [5] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. [6] Opthamology may be consulted to assess for papilledema if concern for elevated ICP, but otherwise not needed for all patients [7] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.				
ICE Assessment				
Orientation: orientation to year, month, city, hospital: 4 points (1 point each)				
Naming: ability to name 3 objects (e.g., clock, pen, button): 3 points (1 point each)				
Following commands: ability to follow simple commands (e.g., “Show me 2 fingers” or “Close your eyes and stick out your tongue”): 1 point				
Writing: ability to write a standard sentence (e.g., “Our national bird is the bald eagle”): 1 point				
Attention: ability to count backwards from 100 by 10: 1 point				

Score 10: No Impairment

Score 7-9: Grade 1 ICANS

Score 3-6: Grade 2 ICANS

Score 0-2: Grade 3[1] ICANS

Score 0 due to patient unarousable or unable to perform ICE assessment: Grade 4 ICANS

[1]A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia or may be classified as having Grade 4 ICANS if the patient is unarousable

Appendix 12. Immune-Effector Cell Toxicity Assessment and Management

Immune-effector cell toxicity assessment and management should be performed per the CARTOX criteria (https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf).