Protocol AMB-051-02

PROTOCOL TITLE	A Phase 2, Adaptive, Open-Label, Multiple-Dose, Dose-Escalation Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Intravenous AMB-05X in Subjects with Tenosynovial Giant Cell Tumor
PROTOCOL NUMBER	AMB-051-02
US IND NUMBER	100835
REGISTRIES	EUDRACT #: 2020-004870-22 ClinicalTrials.gov Identifier: NCT04938180
INVESTIGATIONAL PRODUCT	AMB-05X monoclonal antibody
DEVELOPMENT PHASE	Phase 2
INDICATION	Tenosynovial giant cell tumor
SPONSOR	AmMax Bio, Inc. [redacted]
PROTOCOL VERSION	2.1
VERSION DATED	18 August 2021

SPONSOR APPROVAL

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Signatures verify that the information in this document is accurate and complete.

INVESTIGATOR'S SIGNATURE

Title: A Phase 2, Adaptive, Open-Label, Multiple-Dose, Dose-Escalation Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Intravenous AMB-05X in Subjects with Tenosynovial Giant Cell Tumor

Protocol Number: AMB-051-02

I confirm that I have read this protocol. I will comply with the protocol, with statutory requirements as described in the United States Code of Federal Regulations (CFR) Title 21 Parts 11, 50, 54, 56, and 312 or local requirements in the countries where the study is performed, with the principles of Good Clinical Practice (GCP) in relevant guidance documents from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and with the ethical principles of the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all study center personnel who participate in the conduct of this clinical study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Principal Investigator Name (printed)	Signature
Date	Study Center Number
Institution Name	City, State or Province, Country

CONTACTS IN THE EVENT OF AN EMERGENCY

SPONSOR	AmMax Bio, Inc.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

A change in administrative information does not require a protocol amendment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (drug classification system)
AUC	area under the curve
BPI	Brief Pain Inventory
CFR	Code of Federal Regulations
CIC	circulating immune complex
COVID-19	coronavirus disease 2019
CR	complete response (in the context of tumor response)
CSF1	colony-stimulating factor 1
CSF1R	colony-stimulating factor 1 receptor
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability & Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-34	interleukin-34
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat (Population)
MRI	magnetic resonance imaging

Abbreviation	Definition
NRS	numeric rating scale
OR	objective response (in the context of tumor response)
ORR	objective response rate (in the context of tumor response)
PD	pharmacodynamic(s)
PD	progressive disease (in the context of tumor response)
PI	Principal Investigator: the investigator who leads study conduct at an individual study center. Every study center has a Principal Investigator.
PK	pharmacokinetic(s)
PP	Per Protocol (Population)
PR	partial response (in the context of tumor response)
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
QTcF	QT interval corrected with Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
ROM	range of motion
SAE	serious adverse event
SAS	Statistical Analysis System
SD	standard deviation
SD	stable disease (in the context of tumor response)
SOC	System Organ Class
SUSAR	suspected, unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TGCT	tenosynovial giant cell tumor
TVS	tumor volume score
ULN	upper limit of normal
VAS	visual analogue scale

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Study Number	AMB-051-02
Study Title	A Phase 2, Adaptive, Open-Label, Multiple-Dose, Dose-Escalation Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Intravenous AMB-05X in Subjects with Tenosynovial Giant Cell Tumor
Investigational Product	AMB-05X drug substance is a human monoclonal antibody against the colony-stimulating factor 1 receptor (CSF1R). The drug product is a [redacted] containing drug substance at a concentration of [redacted]/mL. Drug product is packaged in [redacted] mL glass vials, each containing a deliverable volume of [redacted] mL.
Development Phase	Phase 2
Duration of Study	The expected duration of participation for each subject is approximately 28 weeks. This includes up to 4 weeks for screening, 12 weeks for dosing, and 12 weeks for post-treatment safety and efficacy evaluation.
Objectives	The objectives of this study are to evaluate the safety, efficacy, and pharmacokinetics (PK) of intravenous (IV) AMB-05X in the treatment of tenosynovial giant cell tumor (TGCT)
Primary Endpoint	Frequency and severity of reported treatment-emergent adverse events (TEAEs)
Secondary Endpoints	<u>Efficacy</u> The following efficacy endpoints will be assessed at Week 12: • Proportion of subjects who achieve an overall tumor response (objective response [OR], which includes both complete response [CR] and partial response [PR]) per the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) (Eisenhauer, 2009) • Proportion of subjects with overall response based on tumor volume score (TVS), a TGCT-specific method that calculates tumor volume as a percentage of the estimated maximally distended synovial cavity • Mean change from Baseline in range of motion (ROM) score • Mean change from Baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function score

	• Mean change from Baseline in Worst Stiffness Numeric Rating Scale (NRS) score • Percentage of subjects who respond with a decrease of at least 30% in mean Brief Pain Inventory (BPI) score from Baseline • Mean change from Baseline in BPI score • Mean change from Baseline in Worst Pain NRS score • Mean change from Baseline in EQ-5D-5L health assessment Pharmacokinetics and Pharmacodynamics • Serum (and optional synovial) AMB-05X levels • Serum (and optional synovial) AMB-05X–binding anti-drug antibody (ADA) levels • Serum (and optional synovial) colony-stimulating factor 1 (CSF1) levels

Study Design	This is a Phase 2, open-label, multiple-dose, dose-escalation study with an adaptive design that will enroll up to approximately 48 subjects with TGCT for 12 weeks of open-label treatment with IV AMB-05X. There will be a screening period of up to 4 weeks, a treatment period of 12 weeks, and a post-treatment follow-up period of 12 weeks. Each subject will receive a dose of AMB-05X every 2 or 4 weeks, for a total of 6 or 3 doses over the 12-week treatment period. All subjects, regardless of their dose regimen, will have a study visit every 2 weeks during the treatment period.
	
	A study schema is provided in Section 1.2, and the Schedule of Events is provided in Section 1.3.
	
	Study Visit Schedule
	
	Study visits will occur at the following times:
	• At Screening (Visit 1)
	• During the Treatment Period:
	  ○ At Baseline/Day 1 (Visit 2), within 4 weeks after Screening (subjects receive their first dose of AMB-05X)
	  ○ At Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), Week 8 (Visit 6), and Week 10 (Visit 7)
	  ○ At Week 12 (Visit 8) (end of the Treatment Period and timepoint for assessment of primary and secondary endpoints; no AMB-05X is administered)
	• During the Follow-up Period:
	  ○ At Week 14 (Visit 9) and Week 24 (Visit 10)

Adaptive Dose Cohorts and Data Monitoring Committee

The study will enroll up to approximately 48 subjects total into up to 6 serial dose cohorts, designated Cohorts A through F. Each cohort will be composed of at least 3 and at most 12 subjects.

Dosing will begin with Cohort A at the following starting dose level and regimen:

- An initial priming dose of 4 mg/kg on Day 1
- Followed by 5 maintenance doses of 2 mg/kg administered every 2 weeks (at Weeks 2, 4, 6, 8, and 10)

The dose levels and regimens for subsequent cohorts will be determined by the Sponsor based on an ongoing analysis of available data from the previous cohort(s). The following range of dose levels and regimens may be implemented in subsequent cohorts without a protocol amendment:

Range of Dose Levels		
	Initial Dose on Day 1	**Maintenance Doses**
Minimum	2 mg/kg	1 mg/kg
Maximum	12 mg/kg	8 mg/kg

Although the minimum and maximum specified for the initial dose are both higher than those specified for maintenance doses, the initial dose does not have to be higher than subsequent maintenance doses. While remaining within the range specified, the initial dose may be the same as the subsequent maintenance doses, or the initial dose may be a higher, priming dose.

Allowable Regimens			
	Frequency	**# Doses**	**Schedule**
Minimum	Every 4 weeks	3 doses	Initial dose on Day 1
			2 maintenance doses, at Weeks 4, 8
Maximum	Every 2 weeks	6 doses	Initial dose on Day 1
			5 maintenance doses, at Weeks 2, 4, 6, 8, 10

Thus, the lowest dose that a cohort could receive would be an initial dose of 2 mg/kg on Day 1, followed by 2 maintenance doses of 1 mg/kg every 4 weeks (at Weeks 4 and 8). The highest dose that a cohort could receive would be an initial dose of 12 mg/kg on Day 1, followed by 5 maintenance doses of 8 mg/kg every 2 weeks (at Weeks 2, 4, 6, 8, and 10).

A Sponsor data monitoring committee (DMC) composed of qualified medical/clinical representatives from the Sponsor will review the available

	safety, tolerability, PK, pharmacodynamics (PD), and efficacy data on an ongoing basis and provide recommendations regarding appropriate next steps in study conduct. Study enrollment will begin with an initial 3 subjects in Cohort A. The DMC will begin to review study data after the first 3 subjects complete Week 6 and will continue to review data throughout the study (each time 3 additional subjects [from any cohort] complete Week 12). Whenever a new dose is instituted during the study, the DMC will again review the available data once 3 subjects have completed Week 6 at the new dose. The DMC will pay special attention to any clinically significant adverse events (AEs). Clinically significant AEs include dose-limiting toxicities (DLTs), AEs leading to discontinuation, and adverse events of special interest (AESIs), all considered at least possibly related to study drug. A DLT is defined as any Grade 3 or higher AE or serious adverse event (SAE) considered at least possibly related to study drug. AESIs are defined in Section 7.3.8.2. Based on the recommendations of the DMC, the Sponsor may implement any of the following decisions without a protocol amendment, in the manner of a 3+3 dose-escalation study design: • If none of the first 3 subjects of a cohort experiences a clinically significant AE after 12 weeks on study drug, the Sponsor may elect to begin enrollment of the next cohort. • If exactly 1 subject among the first 3 subjects of a cohort experiences a clinically significant AE, an additional 3 subjects will be enrolled into that cohort. If only 1 of the 6 subjects experiences a clinically significant AE, the Sponsor may then elect to proceed with enrollment of the next cohort. • If exactly 2 subjects among the first 3 subjects of a cohort experience a clinically significant AE, the Sponsor will suspend enrollment in that cohort, and the DMC will make recommendations on next steps, such as suspending further enrollment in that cohort, enrolling another 3 subjects into the cohort, or initiating another cohort at a lower dose. • If exactly 2 subjects in a 6-subject cohort experience a clinically significant AE, the Sponsor may elect to enroll an additional 3 subjects into that cohort at the same dose. If no additional clinically significant AEs occur, the Sponsor may then elect to proceed with enrollment of the next cohort. • If ≥3 subjects in a 3- or 6-subject cohort experience a clinically significant AE, the Sponsor will suspend dosing and enrollment in that cohort and/or any further dose escalation in the study. Additional subjects may be enrolled at a lower dose.

	• If data from the first 3 subjects in a cohort to complete treatment indicate suboptimal drug exposure or efficacy, and there are no significant safety issues such as clinically significant AEs, the Sponsor may elect to discontinue further enrollment in that cohort and proceed directly to the next cohort. • If safety permits according to the rules above (ie, if ≤1/3 of the previous subjects in the cohort experiences a clinically significant AE), the Sponsor may elect to enroll up to 12 subjects per cohort for more conclusive data. • Following the rules above, the Sponsor may elect to enroll the subsequent cohort in a staggered / overlapping manner (initiating enrollment in the next cohort while the current cohort is still completing the study or still enrolling) or sequentially (waiting until more complete data are available from the current cohort before initiating the next cohort). • The Sponsor may discontinue further enrollment and/or suspend/terminate the study (see Section 10.1.7). Subject Dose Reduction Enrolled subjects will begin treatment at the planned dose levels for their assigned cohorts. The Investigator may exercise his/her clinical judgment and consider a reduction in an individual subject's maintenance dose (eg, from 2 mg/kg to 1 mg/kg, 4 mg/kg to 2 mg/kg, or 8 mg/kg to 4 mg/kg) for subjects who experience a DLT. Before implementing a dose reduction for a subject, the Investigator should contact the Medical Monitor to discuss the case. Subjects who are unable to tolerate the lowest dose level specified above will have study drug discontinued.
Dosage and Administration	Dosing will begin with Cohort A with an initial priming dose of 4 mg/kg on Day 1 followed by 5 maintenance doses of 2 mg/kg administered every 2 weeks (at Weeks 2, 4, 6, 8, and 10), for a total of 6 doses over the 12-week treatment period. The allowable range of dose levels and regimens for subsequent cohorts is provided under Study Design. Subjects in subsequent cohorts will receive study drug either every 2 weeks or every 4 weeks. The Sponsor will determine the dose levels and regimens for subsequent cohorts within the allowable range based on an ongoing analysis of available data from the previous cohort(s), as described under Study Design. Study drug will be administered via IV infusion at the study center by qualified study staff. Subjects will remain at the study center for at least 60 minutes after dosing to allow monitoring for any adverse reactions, including any infusion-site reactions.

Assessments	Safety and Tolerability Safety and tolerability will be assessed on an ongoing basis by monitoring AEs (including any SAEs, AEs leading to discontinuation, infusion-site reactions, any other DLTs, and AESIs), physical examinations / vital signs, changes in clinical laboratory values, and ECG results. A DMC composed of qualified medical/clinical representatives from the Sponsor will review available clinical data regularly and provide ongoing recommendations to the Sponsor concerning continuation, modification, or termination of the study. Efficacy 1. Tumor response based on RECIST v1.1 (Eisenhauer, 2009) will be centrally assessed from magnetic resonance imaging (MRI) scans. An OR comprises both CR (defined as disappearance of all tumors) and PR (defined as a ≥30% decrease in the sum of diameters of target tumors from the baseline sum of diameters). 2. Tumor response based on TVS will also be centrally assessed from MRI scans. TVS is a semi-quantitative scoring method developed specifically for assessing TGCT (Tap, 2015) that calculates tumor volume as a percentage of the estimated volume of the maximally distended synovial cavity or tendon sheath and provides a score in 10% increments. A score of 0 indicates no evidence of tumor; a score of 10 indicates a tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath. The overall number of responses and the number of subjects with and without disease progression will be assessed (see Section 7.4.1.3). 3. ROM of the affected joint will be assessed by qualified assessors at the study center and recorded in degrees. At Baseline, the plane of movement with the smallest (worst) relative ROM will be identified; only this plane will be used for evaluating change in ROM subsequently. 4. The PROMIS Physical Function Scale is a 10-question patient-reported outcome (PRO) instrument that assess physical functioning. Questions address either the degree to which the subject's health limits certain physical activities or the degree to which the subject is able to perform certain physical activities. Subjects select a response to each item that is scored on a 5-point scale. 5. The Worst Stiffness NRS is a single-item PRO instrument designed to assess "worst" stiffness at the site of the tumor in the last 24 hours. The instrument uses an 11-point NRS that ranges from 0 ("no stiffness") to 10 ("stiffness as bad as you can imagine"). 6. The BPI Short Form is a PRO instrument used to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily

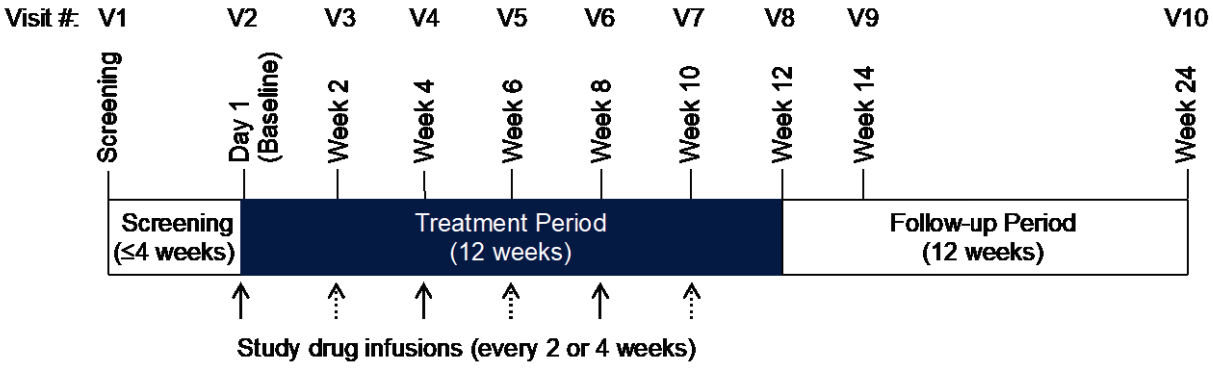
	functioning. Subjects list current pain treatments and rate on a scale from 0 to 10 their worst, least, average, and current pain intensity; how much relief current pain treatments provide; and the degree to which pain interferes with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The Worst Pain NRS is an item in the BPI that assesses a subject's "worst" pain in the last 24 hours. The 11-point NRS for this item ranges from 0 ("no pain") to 10 ("pain as bad as you can imagine"). 7. The EQ-5D-5L is a widely used PRO quality-of-life instrument that asks subjects to select one of 5 levels of severity in each of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and to provide an overall assessment of general health using a visual analogue scale (VAS). <u>Pharmacokinetics and Pharmacodynamics</u> Serum AMB-05X and CSF1 concentrations will be measured at the following visits: • Day 1, Week 4, and Week 8: before dosing and within 15 minutes after the end of infusion • Weeks 2 and 6: o If the subject will receive study drug at the visit, collect the serum sample before dosing. o If the subject will not receive study drug at the visit, collect the serum sample at any time during the visit. • Week 10: o If the subject will receive study drug at this visit, collect serum samples before dosing and within 15 minutes after the end of infusion. o If the subject will not receive study drug at this visit, collect a serum sample at any time during the visit. • Weeks 12, 14, and 24: at any time during the visit Synovial AMB-05X and CSF1 concentrations may be measured pre-dose at Day 1 and pre-dose at the visit associated with the last dose of study drug for each subject (Week 8 or Week 10) as an optional assessment. ADA levels against AMB-05X will be measured from pre-dose serum samples and any synovial samples collected at Day 1, at Week 4, at the visit associated with the last dose of study drug for each subject (Week 8 or Week 10), and at Week 14. Actual dosing and sampling times will be accurately recorded on the electronic case report form (eCRF).

Study Population	This study will enroll up to approximately 48 adult subjects with local or diffuse TGCT in the United States and Europe.
Inclusion Criteria	**A subject may be included in this study if ALL of the following criteria are met:** 1. Male or female ≥18 years of age. 2. Able to communicate well with study staff and understand and comply with the requirements of the study. Reads and voluntarily signs the informed consent form (ICF) and the Health Insurance Portability and Accountability Act (HIPAA) authorization (if applicable) before the conduct of any study-specific procedures. 3. TGCT that has been histologically confirmed by a pathologist. If the diagnosis has not been previously histologically confirmed, biopsy with histological confirmation is required before enrollment. 4. Measurable disease as defined by RECIST v1.1 (except with a minimum size of 2 cm), assessed from MRI scans by a central radiologist. 5. If subject uses prescription analgesic, subject must be on a stable prescription analgesic regimen during the 2 weeks before Baseline. 6. Agrees to follow contraception guidelines (see Section 5.3). 7. Adequate hematologic, hepatic, and renal function at Screening, defined by: • Absolute neutrophil count ≥ 1.5×10^9/L • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 × upper limit of normal (ULN) • Hemoglobin > 10 g/dL • Total bilirubin ≤ 1.5 × ULN (elevated bilirubin secondary to a known, relatively benign condition [eg, Gilbert's syndrome] is not exclusionary) • Platelet count ≥ 100×10^9/L • Serum creatinine ≤ 1.5 × ULN 8. Willing and able to complete the PROMIS Physical Function Scale, Worst Stiffness NRS, BPI, and EQ-5D-5L throughout the study.
Exclusion Criteria	**A subject will be excluded if ANY of the following criteria is met:** 1. Use of any investigational drug within 4 weeks or 5 half-lives (whichever is longer) before Baseline. 2. Use of pexidartinib, any other oral tyrosine kinase inhibitor (eg, imatinib or nilotinib), or any biologic treatment targeting CSF1 or CSF1R within 3 months before Baseline.

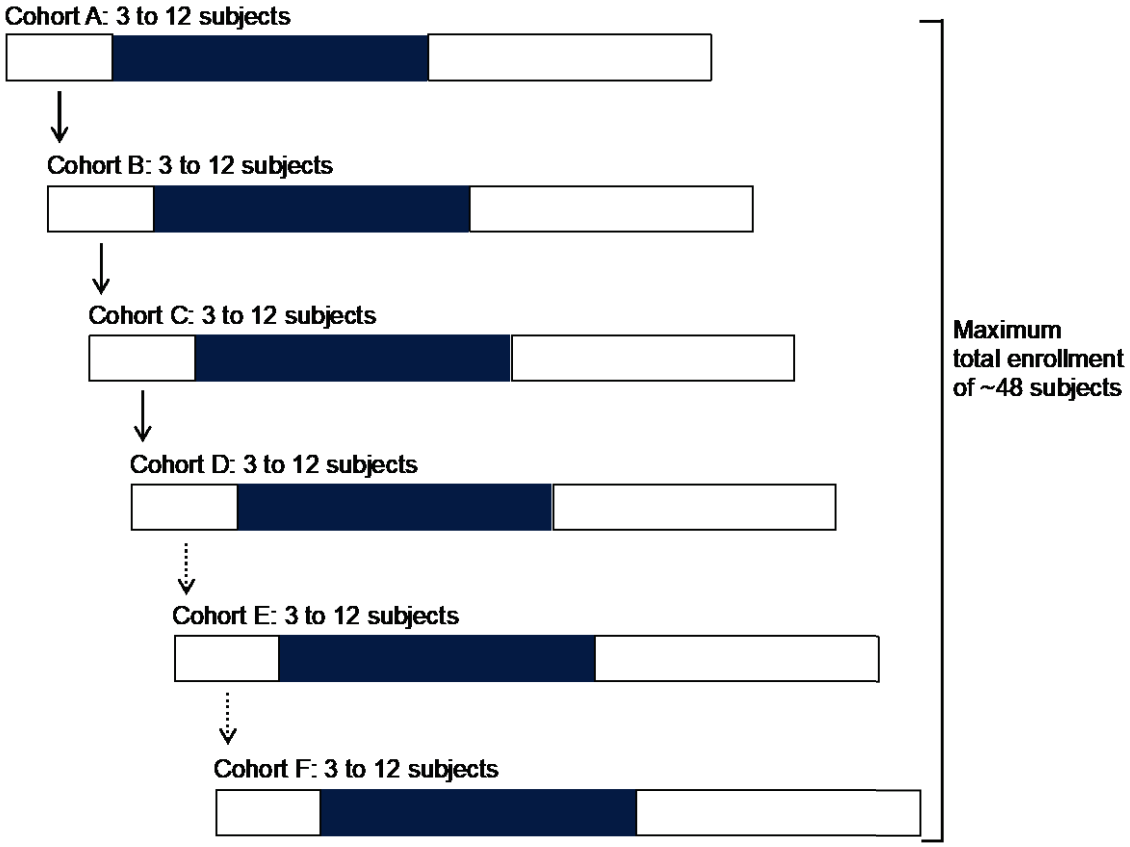
	3. Current or prior radiotherapy within 3 months before Baseline. 4. Current or prior active cancer within 3 years before Baseline that requires/required therapy (eg, surgery, chemotherapy, or radiation therapy), except adequately treated basal or squamous cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix or breast, or prostate carcinoma not requiring treatment apart from active surveillance. 5. Known metastatic TGCT or malignant transformation of diffuse-type TGCT. 6. Any history of complex or reconstructive surgery on the affected joint (eg, involving plates, screws, or metal implants). 7. Hepatitis C virus (HCV) or hepatitis B virus (HBV) or known active or chronic infection with human immunodeficiency virus (HIV). 8. Known active tuberculosis (TB). 9. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the Investigator's opinion, would likely interfere with the subject's study participation or the interpretation of the subject's results. 10. A woman who is pregnant or breastfeeding. For women of childbearing potential, a positive pregnancy test at either Screening or Baseline will be exclusionary. 11. A screening Fridericia-corrected QT interval (QTcF) ≥450 ms (men) or ≥470 ms (women) 12. MRI contraindications (eg, pacemaker, loose metallic implants) 13. History of hypersensitivity to any ingredient in the study drug. 14. History of drug or alcohol abuse within 3 months before Baseline. 15. Has any other severe acute or chronic medical or psychiatric condition or clinically significant laboratory abnormality that may increase the risk associated with study participation/treatment, interfere with interpretation of study results, or, in the Investigator's opinion, make the subject inappropriate for this study. 16. A person who is held in detention as the result of a judicial or official decision or who is in a subordinate relationship to the Sponsor or Investigator. 17. A subject who, in the opinion of the Investigator, should not participate in this study for any reason, including instances where the subject's stability or ability to comply with study requirements is in question.
Statistical Methods	**Sample Size Determination** Based on prior Phase 1 experience and an anticipated treatment effect with AMB-05X in this population, the sample size of 3 to 12 subjects per cohort is

	anticipated to provide sufficient data for PK/PD analysis and an estimate of safety, tolerability, and efficacy. **Analysis Methods** All study data will be summarized by dose cohort and overall using descriptive statistics. **Safety Analyses** Safety analyses will include all subjects who receive at least 1 dose of study drug. All AEs reported will be listed, documenting severity, start and stop date and time, possible relationship to study drug, action taken, and outcome. TEAEs are defined as AEs that occur after the first dose of study drug. Verbatim terms will be mapped to Preferred Terms (PTs) and related System Organ Classes (SOCs) using the Medical Dictionary for Regulatory Activities (MedDRA). PTs and SOCs will be tabulated by dose cohort and overall. All reported AEs will be summarized by the number of subjects reporting each AE, SOC, PT, severity, and relationship to study drug. Multiple occurrences of an AE will be counted only once per subject per SOC and PT in summary tables. Safety labs (including hematology, chemistry, and urinalysis), vital signs, tolerability data, and ECGs will be tabulated using descriptive statistics. Abnormal/out-of-range findings and changes from pre-dose to post-dose will be listed by subject. Shift tables will be provided for all laboratory variables. **Efficacy Analyses** Efficacy endpoints will be summarized using descriptive statistics and 95% confidence intervals. Exploratory hypotheses testing may be conducted using a significance level of 0.05 without adjustment for multiplicity. **Pharmacokinetic Analyses** AMB-05X concentrations will be summarized by dose, regimen, and nominal collection time. If warranted, a population PK analysis may be conducted using data from the current study and relevant data from other clinical studies. In addition, an exposure-response analysis may be attempted using the population approach.

1.2 Schema



Staggered or sequential enrollment:



Legend

→ Will definitely occur
⇢ May occur given adaptive cohort design

1.3 Schedule of Events

	Screening	Treatment Period							Follow-up	
Study Visit[1]	**V1 Screening**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8/ ET**[2]	**V9**[2]	**V10**[2]
Study Week	**≤4 weeks before Baseline**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**24**
Study Day		**1**	**15 ±2**	**29 ±2**	**43 ±3**	**57 ±3**	**71 ±3**	**85 ±3**	**99 ±3**	**169 ±7**
ICF/HIPAA	X									
Assign Subject ID	X									
Demographic data	X									
Medical history	X									
Inclusion/exclusion criteria	X	X								
Tumor biopsy[3]	X									
HBV, HCV, HIV, TB	X									
Weight, height[4]	X	X	X	X	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X			X			X	X	X
12-lead ECG	X	X			X			X		
Pregnancy test[6]	X	X		X		X		X	X	X
Clinical laboratory[7]	X	X	X	X	X	X	X	X	X	X
Serum PK and CSF1[8]		X	X	X	X	X	X	X	X	X

[1] Refer to Appendix 5 for potential changes to study conduct in the context of COVID-19, including the possibility of remote visits.
[2] Early termination procedures consist of Visit 8 (Week 12), Visit 9 (Week 14), and Visit 10 (Week 24) (whichever visits the subject has yet to complete at the time of ET).
[3] For subjects whose TGCT diagnosis has not been previously histologically confirmed, a tumor biopsy will be performed during the screening period after a central radiologist has reviewed the subject's screening MRI scan.
[4] Height will be collected at Screening only.
[5] Vital signs consist of blood pressure, heart rate, temperature, and respiratory rate measured with the subject in a sitting position after having rested for 5 minutes.
[6] For women of childbearing potential, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at subsequent visits indicated.
[7] Blood samples will be collected for chemistry and hematology. A urine sample will be collected for urinalysis. Details on sample collection and processing will be described in the laboratory manual.
[8] Serum samples will be collected for measurement of PK and CSF1 at least once and sometimes twice at each indicated visit. Refer to Section 7.5 for timing of serum sample collection.

	Screening	Treatment Period							Follow-up	
Study Visit[1]	**V1 Screening**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8/ ET**[2]	**V9**[2]	**V10**[2]
Study Week	**≤4 weeks before Baseline**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**24**
Study Day		**1**	**15 ±2**	**29 ±2**	**43 ±3**	**57 ±3**	**71 ±3**	**85 ±3**	**99 ±3**	**169 ±7**
Serum anti–AMB-05X antibody[9]		X		X		with last dose of study drug			X	
Opt'l synovial PK and CSF1[10]		X				with last dose of study drug				
Opt'l synovial anti–AMB-05X antibody[11]		X				with last dose of study drug				
MRI and tumor assessments[12]	X				X			X		X
Joint ROM	X	X			X			X	X	X
PROMIS Physical Function Scale	X	X			X			X		X
Worst Stiffness NRS	X	X			X			X	X	X
BPI Short Form	X	X			X			X		X
EQ-5D-5L	X	X			X			X		X
Study drug infusion every 2 or 4 weeks		X	±	X	±	X	±			
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

Abbreviations: **BPI,** Brief Pain Inventory; **CSF1**, colony-stimulating factor 1; **ECG**, electrocardiogram; **ET**, early termination; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **HIPAA**, Health Insurance Portability and Accountability Act; **HIV**, human immunodeficiency virus; **ICF**, informed consent form; **MRI**, magnetic resonance imaging; **NRS**, Numeric Rating Scale; **PK**, pharmacokinetics; **PROMIS**, Patient-Reported Outcomes Measurement Information System; **ROM**, range of motion; **TB**, tuberculosis.

[9] Serum samples will be collected for anti–AMB-05X antibody at the visits indicated, including the visit associated with the last dose of study drug for each subject (either Week 8 or Week 10).
[10] Optional: Synovial fluid may be collected for measurement of PK and CSF1 pre-dose at the visits indicated.
[11] Optional: Synovial anti–AMB-05X antibody may be measured using any pre-dose synovial samples collected for PK and CSF1 at the visits indicated.
[12] MRI scans will be evaluated centrally by an independent radiologist blinded to a subject's dose.

2 INTRODUCTION

2.1 Tenosynovial Giant Cell Tumor

TGCT, also known as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS), is a rare, locally aggressive and destructive mesenchymal neoplasm that arises in the synovium of joints, bursae, or tendon sheaths (de Saint Aubain Somerhausen, 2013; Staals, 2016).

TGCTs are caused by the excessive production of CSF1 resulting from genomic mutations (balanced translocations) at the CSF1 gene locus of chromosome 1p13 (West, 2006; Cupp, 2007). CSF1 acts at the CSF1R, leading to the proliferation of synovial-like mononuclear cells and recruitment of multinucleate giant cells, foam cells, siderophages, and inflammatory cells, which compose the bulk of the neoplasm (West, 2006; Cupp, 2007; de Saint Aubain Somerhausen, 2013). Although TGCTs are nonmetastatic in nature, they can develop into locally destructive lesions that cause significant local tissue injury, loss of joint function, and impaired quality of life (West, 2006).

The annual incidence of TGCT is estimated to be approximately 43 cases per 1 million individuals (Ehrenstein, 2017; Mastboom, 2017), with approximately 40,000 new cases per year in the US and Europe combined. TGCT most commonly affects individuals between 20 to 50 years of age (Ostuni, 2015). Two TGCT subtypes have generally been recognized: localized (l-TGCT) and diffuse (d-TGCT). Approximately 10% of TGCT are classified as diffuse (Mastboom, 2017). Regardless of subtype, TGCT nearly always involves a single joint, with the knee being the most commonly affected (up to 66% to 80%), followed by the ankle, elbow, shoulder, wrist/hand, and hip (Murphey, 2008).

TGCT presents clinically as a joint swelling or a firm, slowly enlarging mass (Ostuni, 2015). As the disease advances, patients experience attacks of pain, swelling, loss of range of motion, hemorrhagic joint effusions, cartilage destruction, and bone erosion, leading to eventual loss of joint function, impaired quality of life, and severe morbidity (Giustini, 2018; Tap, 2019). Joint replacement or even amputation might be necessary in cases of persistent disease (Staals, 2016). While TGCT is not lethal, it is a serious, chronic, debilitating illness with long-term consequences for joint function and quality of life (Mastboom, 2017).

The standard of care in TGCT is surgical resection via synovectomy (Granowitz, 1976). However, recurrence after surgery is common and occurs in up to 55% of patients with the diffuse subtype (Palmerini, 2015; Brahmi, 2016; Staals, 2016; Mastboom, 2017). Repeated surgeries may be necessary but often lead to further morbidity, complications, and reduced function of affected joints (Staals, 2016). Radiotherapy is occasionally used, typically for larger joints with diffuse lesions, but its use is limited because of late sequelae (Benner, 2020).

In late 2019, pexidartinib, an oral small-molecule tyrosine kinase inhibitor with activity against CSF1R, was approved by the US Food and Drug Administration (FDA) for the treatment of adults with symptomatic TGCT with severe morbidity/functional limitations, not amenable to surgery (Turalio package insert, 2020). Results from the Phase 3 ENLIVEN study showed that pexidartinib was superior to placebo in achieving overall responses per RECIST criteria (39% vs

0%; p<0.0001). However, systemic side effects including serious / life-threatening cases of mixed or cholestatic hepatotoxicity were observed and remain a concern among patients treated with pexidartinib (Tap, 2019; Gelderblom, 2020).

The viability of CSF1R inhibition as a treatment modality for TGCT was further established in an early-stage clinical trial of emactuzumab, a monoclonal antibody that targets CSF1R (Cassier, 2015). Following systemic (IV) administration, 86% of subjects achieved an objective response associated with early onset of symptomatic and functional improvement.

In summary, TGCT is a rare but serious, debilitating chronic illness with limited treatment options. Given the limitations of current treatment options and prior clinical validation of CSF1R as an effective treatment target, AmMax Bio, Inc. is developing AMB-05X, a human monoclonal antibody that inhibits CSF1R, as an IV therapeutic for the treatment of TGCT.

2.2 AMB-05X

AMB-05X is an antagonistic, fully human antibody (immunoglobulin G, type 2 [IgG2]) specific to the extracellular domain of human CSF1R (also known as c-FMS). AMB-05X potently blocks both CSF1- and interleukin-34 (IL-34)–mediated proliferation of growth factor–dependent human myelomonocytic cells in vitro. It effectively interacts with CSF1R in monkeys but not in other species such as rodents.

2.3 Summary of Nonclinical Data

Refer to the Investigator's Brochure (IB) for additional information on nonclinical studies of AMB-05X.

2.3.1 Pharmacology

AMB-05X binds with high affinity to CSF1R expressed on the surface of human myelomonocytic cells (AML-5 cells) and to cynomolgus monkey CSF1R expressed on the surface of human embryonic kidney cells transformed by adenovirus (2936E cells).

AMB-05X inhibits CSF1-induced phosphorylation of human CSF1R. In addition, this antibody immunoprecipitated human CSF1R and its known single-nucleotide polymorphism variants. AMB-05X potently inhibits CSF1-driven proliferation of both human and cynomolgus monkey primary bone marrow–derived monocyte/macrophage cells in vitro as well as CSF1- and IL-34–driven proliferation of human myelomonocytic AML-5 cells.

AMB-05X does not cross-react with mouse CSF1R. Therefore, a surrogate anti-mouse CSF1R antibody (M279) was developed for use in mouse tumor model studies. Like AMB-05X, M279 potently and specifically inhibited CSF1R-mediated activity in vitro. In vivo, M279 significantly inhibited the growth of a variety of xenograft and syngeneic tumor models, including MDA-MB-231 (human breast adenocarcinoma), Renca (mouse renal cell carcinoma, syngeneic), and NCI-H1650 and NCI-H1975 (human non-small-cell lung carcinomas) tumor models, by 50% to 70% based on tumor volume. In addition, tumor-associated macrophage content in all tumors treated with M279 was significantly lower than in control-treated tumors, as shown by a variety of methods, including immunohistochemistry, flow cytometry, and immunofluorescence.

2.3.2 Pharmacokinetics

Single IV doses of AMB-05X administered to cynomolgus monkeys produced a nonlinear increase in exposure at doses of 0.1 to 5 mg/kg but an approximately dose-proportional increase at doses of 5 to 100 mg/kg. When receptor-mediated clearance had been saturated at higher serum concentrations of AMB-05X ([redacted] µg/mL), the kinetics of AMB-05X became linear. The volume of distribution at steady state for AMB-05X in monkeys was approximately equal to plasma volume, indicating limited extravascular distribution.

The toxicokinetics of repeated IV doses of AMB-05X was assessed in both 4-week and 14-week repeat-dose toxicity studies and did not differ markedly between male and female monkeys. In general, exposure to IV AMB-05X increased approximately dose proportionally in monkeys over the dose range of 10 to 300 mg/kg. No marked (>2-fold) accumulation of AMB-05X was observed after 4 or 13 once-weekly doses in monkeys. During the dosing phase of these studies, AMB-05X–binding ADAs were detected in 1 of 30 animals in the 4-week study and 13 of 35 animals in the 14-week study; during the recovery phase of the 14-week study, ADAs were detected in 8 of 10 animals. In general, ADAs decreased exposure to AMB-05X in these animals. For both studies, high concentrations of AMB-05X in the serum samples may have interfered with detection of ADAs in animals that tested ADA-negative.

2.3.3 Toxicology

In toxicology studies in the cynomolgus monkey, animals received IV AMB-05X at up to 300 mg/kg once-weekly for 4 or 14 weeks. All directly AMB-05X–related findings were attributed to its expected pharmacology of inhibition of macrophages. Additionally, changes related to the acute post-dosing formation of ADA/drug complex (also called circulating immune complexes [CICs]) occurred in some animals in the 14-week study.

Clinical observations attributed to AMB-05X pharmacology consisted of reversible periorbital swelling due to increased extracellular matrix, as observed by light microscopy. Clinical pathology changes included reversible increases in serum ALT, AST, and glutamate dehydrogenase (GLDH) without a light microscopic correlate in the liver and without elevations in sorbitol dehydrogenase (SDH), a liver-specific marker of injury. The increased extracellular matrix and elevated activities of serum enzymes were thought to result from decreased clearance due to inhibition of macrophages (Radi, 2011). Additional AMB-05X–related changes included decreased bone turnover, characterized by elongation of bone growth plates, decreased numbers of osteoclasts, and decreases in serum markers of bone turnover, all of which were reversible. The presence of yeast organisms in the lung and protozoal organisms in the gastrointestinal tract in a few animals (contributing to death in 1 animal) may be incidental or a pharmacologic effect of AMB-05X. Increased neutrophil counts occurred in association with myeloid hyperplasia.

During the last 2 months of the dosing phase in the 14-week study, acute post-dosing sequelae (platelet effects and clinical signs including death) were observed in ADA-positive animals at 10 and 50 mg/kg. The role of ADA/drug complexes in the acute post-dosing findings was confirmed by demonstration of ADA/drug complexes serologically and immunohistochemically. No post-dosing CICs or related effects occurred at 300 mg/kg. Retrospective analyses correlating immunogenicity rates in animals and humans demonstrate low predictive value of nonclinical

immunogenicity rates for human clinical responses (Ponce, 2009). Moreover, for nonclinical species dosed with human or humanized proteins, immunogenicity in animals is generally greater than in humans. For these reasons, the observed adverse effects in ADA-positive monkeys at 10 and 50 mg/kg attributed to the formation of ADA/drug complexes are not considered to be predictive of human clinical risk.

Synovial concentrations of AMB-05X can be extrapolated from the 14-week cynomolgus monkey studies. In these studies, peak serum concentrations over the dosing period were [redacted] mg/mL, which translates to synovial concentrations of [redacted] µg/mL at steady-state (Stepensky, 2012; AmMax modeling; AMB051-20-NHP1 study results).

2.4 Summary of Clinical Data

Refer to the IB for additional information on clinical studies of AMB-05X.

Two clinical studies of IV AMB-05X have been conducted in subjects with advanced solid tumors: a first-in-human monotherapy study and a combination study with pembrolizumab.

2.4.1 Monotherapy Study

The first-in-human study of IV AMB-05X evaluated safety, tolerability, PK, and PD in subjects with advanced solid tumors (Papadopoulos, 2017). The study initially dosed subjects once weekly at 0.5 mg/kg. In subsequent cohorts, the dosing regimen was revised to IV infusion over a 60-minute period every 2 weeks. Escalation of AMB-05X dose was advanced through 1.5, 3, 6, 10, and 20 mg/kg levels.

All 25 subjects (100%) had measurable disease at baseline by local assessment, which supported their enrollment into the study. By central assessment, 21 subjects (84%) had measurable disease at baseline. Per central assessment, 8 subjects (32%) had a best response of stable disease; per local assessment, 1 subject (4.0%) had partial response and 6 subjects (24%) had stable disease (central and local assessments of subject response did not fully overlap). Per central assessment, 1 subject (with stable disease) had a >20% reduction in tumor burden based on RECIST; per local assessment, 1 subject (with partial response) had a 40% reduction in tumor burden. The median for maximum percentage change from baseline in tumor volume was 19.3% (range: -24.0% to 104.8%).

All 25 subjects (100%) had at least 1 TEAE; the most common were nausea and vomiting (12 subjects [48%] each); fatigue and periorbital edema (11 subjects [44%] each); constipation (9 subjects [36%]); and anemia, AST increased, and decreased appetite (8 subjects [32%] each). A total of 18 subjects (72%) had AEs that were at least Grade 3 in severity and 5 (20%) had AEs that were at least Grade 4.

One subject in the 20-mg/kg cohort experienced a nonreversible DLT of Grade 3 bilateral deafness; lack of a baseline audiology exam and the recent receipt of multiple cycles of cisplatin therapy (1 month before first dose of AMB-05X) precluded any meaningful assessment of the progressive aspect of hearing loss.

SAEs were reported for 11 subjects (44%), AEs leading to withdrawal from the study were reported for 4 subjects (16%), and AEs leading to discontinuation of investigational product were

reported for 5 subjects (20%). Fatal AEs were reported for 3 subjects (12%); the events occurred in the setting of progressive disease and were considered not related to treatment with AMB-05X by the investigators.

AEs considered treatment-related by the investigator were reported by 19 subjects (76%). Periorbital edema (without clinical sequelae) was the most common treatment-related AE (11 subjects [44%]); the majority of events resolved and were managed without intervention. AST increased was also a common treatment-related AE (7 subjects [28%]). Seven subjects (28%) had treatment-related AEs that were Grade 3 or higher in severity, and 1 subject (4%) discontinued AMB-05X due to a treatment-related AE (the previously mentioned bilateral deafness DLT). There were no treatment-related serious or fatal AEs.

Macrophages were quantified in skin biopsies as an indicator of pharmacologic effect. In all subjects in the 10-mg/kg and 20-mg/kg dose groups who had available skin biopsy data, macrophage levels were reduced from baseline at Week 5, as indicated by positive staining for CD68 and/or CD163.

2.4.2 Combination Study with Pembrolizumab

The combination study of IV AMB-05X administered with pembrolizumab (Study 20150195) evaluated safety, tolerability, and objective response rate (ORR) in subjects with select advanced solid tumors.

The study was conducted in 2 parts:

- Part 1 (Phase 1b) evaluated the safety of AMB-05X in combination with pembrolizumab using a 6+3 design. The starting dose was AMB-05X 1,400 mg + pembrolizumab 200 mg every 3 weeks. Fifteen subjects were enrolled and received at least 1 dose of AMB-05X + pembrolizumab. The mean (standard deviation [SD]) treatment duration was 0.8 (0.7) months. The ORR was 0%.
- Part 2 (Phase 2) further evaluated safety and tested whether AMB-05X could enhance the antitumor activity observed historically with pembrolizumab alone and/or overcome lack of response to pembrolizumab monotherapy in subjects with select solid tumors. One hundred and one subjects were enrolled and received at least 1 dose of AMB-05X + pembrolizumab. Of these, 90 subjects received AMB-05X 1,100 mg + pembrolizumab 200 mg every 3 weeks, and 11 subjects received AMB-05X 1,400 mg + pembrolizumab 200 mg every 3 weeks. The mean (SD) treatment duration was 1.6 (2.5) months. The ORR was 3.0%.

PK results from a total of 116 subjects were available from the study. Following administration in cycles 1 and 2, AMB-05X exposures increased in an approximately dose-proportional manner over the dose range of 1,100 to 1,400 mg. Over this 1.3-fold increase in dose, mean C_{max} increased 1.4-fold in both cycle 1 and cycle 2, and mean AUC over the dosing interval τ (AUC_τ) increased 1.5-fold in both cycle 1 and cycle 2. Median t_{max} values ranged from 2.0 to 3.0 hours post-dose in cycles 1 and 2. No significant serum accumulation of AMB-05X was observed between cycles 1 and 2; mean accumulation ratio for AUC_τ ranged from 1.25 to 1.27.

Safety in Part 1 is summarized as follows:

- All subjects had at least 1 TEAE. The most common AEs were fatigue (66.7%), AST increased (60.0%), periorbital edema (53.3%), decreased appetite and diarrhea (each in 33.3% of subjects), and dyspnea, hypophosphatemia, nausea, and pyrexia (each in 26.7% of subjects).
- A total of 14 subjects (93.3%) had events that were Grade 3 or higher, including 6 subjects (40.0%) who had Grade 4 events and 5 subjects (33.3%) who had fatal (Grade 5) AEs. All of the fatal AEs were considered not related to study treatment.
- Seven subjects (46.7%) had at least 1 SAE, none of which occurred in more than 1 subject.
- TEAEs considered related to AMB-05X were reported in 12 subjects (80.0%). The most common AMB-05X–related AEs were periorbital edema and AST increased (each in 46.7% of subjects) and fatigue (26.7%).
- One subject (14.3%) who received AMB-05X 1,400 mg + pembrolizumab 200 mg had DLTs of autoimmune pancreatitis, autoimmune hepatitis, cholecystitis, and electrolyte imbalance, after which the AMB-05X dose was decreased to 1,100 mg. No subject who received AMB-05X 1,100 mg + pembrolizumab 200 mg had a DLT. No subject had a TEAE leading to discontinuation of investigational product.
- No clinically relevant trends in hematology, serum chemistry, or urinalysis laboratory values were reported.

Safety in Part 2 is summarized as follows:

- All subjects had at least 1 TEAE. The most common AEs were fatigue (53.5%), periorbital edema (39.6%), anemia (37.6%), nausea (29.7%), constipation (28.7%), pyrexia (26.7%), and decreased appetite and rash (each in 25.7% of subjects).
- A total of 99 subjects (98.0%) had events that were Grade 3 or higher, including 68 subjects (67.3%) who had Grade 4 events and 57 subjects (56.4%) who had fatal (Grade 5) events. Of the fatal AEs, only tumor flare and pneumonitis (1 subject each) were considered related to study treatment.
- Seventy-three subjects (72.3%) had at least 1 SAE. The most common SAEs were pyrexia (6.9%) and pneumonia and urinary tract infection (each in 5.0% of subjects).
- TEAEs considered related to AMB-05X were reported in 90 subjects (89.1%). The most common AMB-05X–related AEs were AST increased (53.5%), periorbital edema (38.6%), and fatigue (30.7%).
- Seventeen subjects (16.8%) had a TEAE leading to discontinuation of investigational product. TEAEs leading to discontinuation in >1 subject were periorbital edema and pneumonitis (2 subjects each).
- Six subjects (5.9%) who received AMB-05X 1,100 mg + pembrolizumab 200 mg had DLTs of AST increased (2 subjects) and fatigue, lipase increased, epilepsy, rash generalized, and rash maculo-papular (1 subject each).
- During the study, 4 subjects (4.0%) treated with AMB-05X + pembrolizumab had liver function test results that potentially met the criteria for Hy's Law (ALT or AST > 3 × ULN

and total bilirubin > 2 × ULN and alkaline phosphatase < 2 × ULN). After further evaluation, none of the subjects met the definitive criteria for Hy's Law.

- No clinically relevant trends in hematology, serum chemistry, or urinalysis laboratory values were reported.

3 OBJECTIVES AND ENDPOINTS

The objectives of this study are to evaluate the safety, efficacy, and PK of IV AMB-05X in the treatment of TGCT.

3.1 Primary Endpoint

The primary endpoint is the frequency and severity of reported TEAEs.

3.2 Secondary Endpoints

3.2.1 Efficacy Secondary Endpoints

The following efficacy endpoints will be assessed at Week 12:

- Proportion of subjects who achieve an overall tumor response (OR, which includes both CR and PR) per RECIST v1.1 (Eisenhauer, 2009)
- Proportion of subjects with overall response based on TVS, a TGCT-specific method that calculates tumor volume as a percentage of the estimated maximally distended synovial cavity
- Mean change from Baseline in ROM score
- Mean change from Baseline in the PROMIS Physical Function score
- Mean change from Baseline in Worst Stiffness NRS score
- Percentage of subjects who respond with a decrease of at least 30% in mean BPI score from Baseline
- Mean change from Baseline in BPI score
- Mean change from Baseline in Worst Pain NRS score
- Mean change from Baseline in EQ-5D-5L health assessment

3.2.2 Pharmacokinetic and Pharmacodynamic Secondary Endpoints

- Serum (and optional synovial) AMB-05X levels
- Serum (and optional synovial) AMB-05X–binding ADA levels
- Serum (and optional synovial) CSF1 levels

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, open-label, multiple-dose, dose-escalation study with an adaptive design that will enroll up to approximately 48 subjects with TGCT for 12 weeks of open-label treatment with IV AMB-05X. There will be a screening period of up to 4 weeks, a treatment period of 12 weeks, and a post-treatment follow-up period of 12 weeks. Each subject will receive a dose of AMB-05X every 2 or 4 weeks, for a total of 6 or 3 doses over the 12-week treatment period.

A study schema is provided in Section 1.2, and the Schedule of Events is provided in Section 1.3.

4.1.1 Study Visit Schedule

Study visits will occur at the following times:

- At Screening (Visit 1)
- During the Treatment Period:
  - At Baseline/Day 1 (Visit 2), within 4 weeks after Screening (subjects receive their first dose of AMB-05X)
  - At Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), Week 8 (Visit 6), and Week 10 (Visit 7)
  - At Week 12 (Visit 8) (the end of the Treatment Period and timepoint for assessment of primary and secondary endpoints; no AMB-05X is administered)
- During the Follow-up Period:
  - At Week 14 (Visit 9) and Week 24 (Visit 10)

Refer to Appendix 5 for potential changes to study conduct in the context of COVID-19 (coronavirus disease 2019).

4.1.2 Adaptive Dose Cohorts and Data Monitoring Committee

The study will enroll up to approximately 48 subjects total into up to 6 serial dose cohorts, designated Cohorts A through F. Each cohort will be composed of at least 3 and at most 12 subjects. All subjects, regardless of their dose regimen, will have a study visit every 2 weeks during the treatment period.

Dosing will begin with Cohort A at the following starting dose level and regimen:

- An initial priming dose of 4 mg/kg on Day 1
- Followed by 5 maintenance doses of 2 mg/kg administered every 2 weeks (at Weeks 2, 4, 6, 8, and 10)

The dose levels and regimens for subsequent cohorts will be determined by the Sponsor based on an ongoing analysis of available data from the previous cohort(s). The following range of dose levels and regimens may be implemented in subsequent cohorts without a protocol amendment:

Range of Dose Levels		
	Initial Dose on Day 1	**Maintenance Doses**
Minimum	2 mg/kg	1 mg/kg
Maximum	12 mg/kg	8 mg/kg

Although the minimum and maximum specified for the initial dose are both higher than those specified for maintenance doses, the initial dose does not have to be higher than subsequent maintenance doses. While remaining within the range specified, the initial dose may be the same as the subsequent maintenance doses, or the initial dose may be a higher, priming dose.

Allowable Regimens			
	Frequency	**# Doses**	**Schedule**
Minimum	Every 4 weeks	3 doses	Initial dose on Day 1
			2 maintenance doses, at Weeks 4, 8
Maximum	Every 2 weeks	6 doses	Initial dose on Day 1
			5 maintenance doses, at Weeks 2, 4, 6, 8, 10

Thus, the lowest dose that a cohort could receive would be an initial dose of 2 mg/kg on Day 1, followed by 2 maintenance doses of 1 mg/kg every 4 weeks (at Weeks 4 and 8). The highest dose that a cohort could receive would be an initial dose of 12 mg/kg on Day 1, followed by 5 maintenance doses of 8 mg/kg every 2 weeks (at Weeks 2, 4, 6, 8, and 10).

A Sponsor DMC composed of qualified medical/clinical representatives from the Sponsor will review the available safety, tolerability, PK, PD, and efficacy data on an ongoing basis and provide recommendations regarding appropriate next steps in study conduct. Study enrollment will begin with an initial 3 subjects in Cohort A. The DMC will begin to review study data after the first 3 subjects complete Week 6 and will continue to review data throughout the study (each time 3 additional subjects [from any cohort] complete Week 12). Whenever a new dose is instituted during the study, the DMC will again review the available data once 3 subjects have completed Week 6 at the new dose.

The DMC will pay special attention to any clinically significant AEs. Clinically significant AEs include DLTs, AEs leading to discontinuation, and AESIs, all considered at least possibly related to study drug. A DLT is defined as any Grade 3 or higher AE or SAE considered at least possibly related to study drug. AESIs are defined in Section 7.3.8.2.

Based on the recommendations of the DMC, the Sponsor may implement any of the following decisions without a protocol amendment, in the manner of a 3+3 dose escalation study design:

- If none of the first 3 subjects of a cohort experiences a clinically significant AE after 12 weeks on study drug, the Sponsor may elect to begin enrollment of the next cohort.

- If exactly 1 subject among the first 3 subjects of a cohort experiences a clinically significant AE, an additional 3 subjects will be enrolled into that cohort. If only 1 of the 6 subjects experiences a clinically significant AE, the Sponsor may then elect to proceed with enrollment of the next cohort.
- If exactly 2 subjects among the first 3 subjects of a cohort experience a clinically significant AE, the Sponsor will suspend enrollment in that cohort, and the DMC will make recommendations on next steps, such as suspending further enrollment in that cohort, enrolling another 3 subjects into the cohort, or initiating another cohort at a lower dose.
- If exactly 2 subjects in a 6-subject cohort experience a clinically significant AE, the Sponsor may elect to enroll an additional 3 subjects into that cohort at the same dose. If no additional clinically significant AEs occur, the Sponsor may then elect to proceed with enrollment of the next cohort.
- If ≥3 subjects in a 3- or 6-subject cohort experience a clinically significant AE, the Sponsor will suspend dosing and enrollment in that cohort and/or any further dose escalation in the study. Additional subjects may be enrolled at a lower dose.
- If data from the first 3 subjects in a cohort to complete treatment indicate suboptimal drug exposure and efficacy, and there are no significant safety issues such as clinically significant AEs, the Sponsor may elect to discontinue further enrollment in that cohort and proceed directly to the next cohort.
- If safety permits according to the rules above (ie, if ≤1/3 of the previous subjects in the cohort experience a clinically significant AE), the Sponsor may elect to enroll up to 12 subjects per cohort for more conclusive data.
- Following the rules above, the Sponsor may elect to enroll the subsequent cohort in a staggered / overlapping manner (initiating enrollment in the next cohort while the current cohort is still completing the study or still enrolling) or sequentially (waiting until more complete data are available from the current cohort before initiating the next cohort).
- The Sponsor may discontinue further enrollment and/or suspend/terminate the study (see Section 10.1.7).

4.1.3 Subject Dose Reduction

Enrolled subjects will begin treatment at the planned dose levels for their assigned cohorts. The Investigator may exercise his/her clinical judgment and consider a reduction in an individual subject's maintenance dose (eg, from 2 mg/kg to 1 mg/kg, 4 mg/kg to 2 mg/kg, or 8 mg/kg to 4 mg/kg) for subjects who experience a DLT. Before implementing a dose reduction for a subject, the Investigator should contact the Medical Monitor to discuss the case. Subjects who are unable to tolerate the lowest dose level specified in Section 4.1.2 will have study drug discontinued.

4.2 Justification for Dose

The proposed starting dose level for Cohort A is an initial priming dose of 4 mg/kg IV, followed by 5 maintenance doses of 2 mg/kg IV every 2 weeks thereafter, for a total of 6 doses over 12 weeks. This dose level is well supported by a 14-week Good Laboratory Practice (GLP)

toxicology study with QD IV dosing in cynomolgus monkeys (see Section 2.3) and by the first-in-human and pembrolizumab-combination clinical studies of IV AMB-05X (see Section 2.4).

Figure 1 shows simulated AMB-05X concentrations in serum and synovial fluid for the Cohort A starting dose level. The projected serum drug levels are modeled from published Phase 1 data (Papadopoulos, 2017). The extrapolated synovial fluid partitioning is based on published results with other antibodies (Stepensky, 2012 and AmMax internal data). The Cohort A starting dose level should yield serum and tissue AMB-05X concentrations previously shown to be safe and achieve steady-state drug levels by the end of the treatment period. The projected synovial AMB-05X concentrations achieve a target estimated level for efficacy (indicated by the y-axis arrow).

Figure 1. Simulated Serum and Synovial Fluid AMB-05X Concentrations for the Cohort A Starting Dose Level

4.3 End of Study Definition

A subject is considered to have completed study treatment if the subject has completed all 12 weeks of the Treatment Period.

A subject is considered to have completed the study if the subject has completed all study visits, including visits during the Follow-up Period.

The end of the study is defined as the date of the last study visit of the last subject in the study.

4.4 Subject Early Termination

Subjects may choose to discontinue study drug or withdraw from study participation at any time, for any reason, specified or unspecified, without prejudice. The Investigator and/or Sponsor may also discontinue a subject's study drug or withdraw the subject from the study at any time. The

Investigator will discontinue a subject's study drug if the Investigator concludes that continuation would be detrimental to the subject's safety or well-being.

Reasons for premature discontinuation of study drug / withdrawal from the study may include:

- Pregnancy
- Adverse event
- Death
- Physician decision
- Subject decision
- Lack of efficacy
- Protocol violation
- Study termination by the Sponsor
- Lost to follow-up
- Other, to be specified

If ET occurs for any reason, the Investigator must make every effort to determine the primary reason for the ET and record this information on the eCRF. The Investigator will also schedule ET procedures for a subject who terminates early but does not withdraw consent for study participation (see Section 8.11). ET procedures consist of Visit 8 (Week 12), Visit 9 (Week 14), and Visit 10 (Week 24) (whichever visits the subject has yet to complete at the time of ET). Subjects who discontinue study drug as the result of an AE will also be followed according to Section 7.3.4. Subjects who withdraw consent will be considered withdrawn from further study participation.

If a subject fails to appear for study visits without stating an intention to withdraw, the site must make every effort to regain contact with the subject, including making 3 telephone calls to the subject and, if necessary, sending a registered letter to the subject's last known mailing address. Attempts to contact the subject will be documented in the subject's site file. If the subject continues to be unreachable, the subject will be considered lost to follow-up and thus withdrawn from the study.

5 STUDY POPULATION

This study will enroll up to approximately 48 adult subjects with local or diffuse TGCT in the United States and Europe.

5.1 Inclusion Criteria

A subject may be included in this study if ALL of the following criteria are met.

1. Male or female ≥18 years of age.
2. Able to communicate well with study staff and understand and comply with the requirements of the study. Reads and voluntarily signs the ICF and the HIPAA authorization (if applicable) before the conduct of any study-specific procedures.
3. TGCT that has been histologically confirmed by a pathologist. If the diagnosis has not been previously histologically confirmed, biopsy with histological confirmation is required before enrollment.
4. Measurable disease as defined by RECIST v1.1 (except with a minimum size of 2 cm), assessed from MRI scans by a central radiologist.
5. If subject uses prescription analgesic, subject must be on a stable prescription analgesic regimen during the 2 weeks before Baseline.
6. Agrees to follow contraception guidelines (see Section 5.3).
7. Adequate hematologic, hepatic, and renal function at Screening, defined by:
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - AST and ALT ≤ 1.5 × ULN
   - Hemoglobin > 10 g/dL
   - Total bilirubin ≤ 1.5 × ULN (elevated bilirubin secondary to a known, relatively benign condition [eg, Gilbert's syndrome] is not exclusionary)
   - Platelet count ≥ 100×10^9/L
   - Serum creatinine ≤ 1.5 × ULN
8. Willing and able to complete the PROMIS Physical Function Scale, Worst Stiffness NRS, BPI, and EQ-5D-5L throughout the study.

5.2 Exclusion Criteria

A subject will be excluded if ANY of the following criteria is met.

1. Use of any investigational drug within 4 weeks or 5 half-lives (whichever is longer) before Baseline.
2. Use of pexidartinib, any other oral tyrosine kinase inhibitor (eg, imatinib or nilotinib), or any biologic treatment targeting CSF1 or CSF1R within 3 months before Baseline.

3. Current or prior radiotherapy within 3 months before Baseline
4. Current or prior active cancer within 3 years before Baseline that requires/required therapy (eg, surgery, chemotherapy, or radiation therapy), except adequately treated basal or squamous cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix or breast, or prostate carcinoma not requiring treatment apart from active surveillance.
5. Known metastatic TGCT or malignant transformation of diffuse-type TGCT.
6. Any history of complex or reconstructive surgery on the affected joint (eg, involving plates, screws, or metal implants).
7. HCV or HBV or known active or chronic infection with HIV.
8. Known active TB.
9. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the Investigator's opinion, would likely interfere with the subject's study participation or the interpretation of the subject's results.
10. A woman who is pregnant or breastfeeding. For women of childbearing potential, a positive pregnancy test at either Screening or Baseline will be exclusionary.
11. A screening QTcF ≥450 ms (men) or ≥470 ms (women)
12. MRI contraindications (eg, pacemaker, loose metallic implants)
13. History of hypersensitivity to any ingredient in the study drug.
14. History of drug or alcohol abuse within 3 months before Baseline.
15. Has any other severe acute or chronic medical or psychiatric condition or clinically significant laboratory abnormality that may increase the risk associated with study participation/treatment, interfere with interpretation of study results, or, in the Investigator's opinion, make the subject inappropriate for this study.
16. A person who is held in detention as the result of a judicial or official decision or who is in a subordinate relationship to the Sponsor or Investigator.
17. A subject who, in the opinion of the Investigator, should not participate in this study for any reason, including instances where the subject's stability or ability to comply with study requirements is in question.

5.3 Contraception Guidelines

Subjects must agree to adhere to the following contraception guidelines (Heads of Medicines Agencies, 2014) throughout the study and for 90 days after the last dose of study drug.

5.3.1 Contraception Guidelines for Female Subjects

A female enrolling in this study must meet ONE of the following contraceptive criteria:

1. She is not a female of childbearing potential because of one of the following:
    a. She is postmenopausal.

A postmenopausal state is defined as having no menses for at least 1 year without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, a single FSH measurement is insufficient to establish a postmenopausal state without at least 1 year of amenorrhea.

b. She is permanently sterile by hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

2. She is totally abstinent from heterosexual intercourse as her preferred and usual lifestyle (abstinent on a long-term and persistent basis). Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods) and withdrawal are not acceptable. Subjects who practice total abstinence must use another method of contraception if they become sexually active.
3. Any male sexual partner is vasectomized and has received medical confirmation of the surgical success.
4. She agrees to use one of the following highly effective contraceptive methods:
    a. Combined hormonal contraception (containing estrogen and progestogen) associated with inhibition of ovulation: oral, intravaginal, or transdermal
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
    c. Intrauterine device (IUD)
    d. Intrauterine hormone-releasing system (IUS)
    e. Bilateral tubal occlusion
5. Where allowed by local laws and regulations, a double-barrier contraceptive method—specifically, female subject use of cap, diaphragm, or sponge with spermicide AND male partner use of condom—is acceptable.

5.3.2 Contraception Guidelines for Male Subjects

A male enrolling in this study must meet ONE of the following contraceptive criteria:

1. He is not a fertile male because he is permanently sterile by bilateral orchiectomy.
2. He is totally abstinent from heterosexual intercourse as his preferred and usual lifestyle (abstinent on a long-term and persistent basis). Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods) and withdrawal are not acceptable. Subjects who practice total abstinence must use another method of contraception if they become sexually active.
3. He is vasectomized and has received medical confirmation of the surgical success.
4. He agrees to use a male condom AND his female partner, if she is a female of childbearing potential, uses one of the following highly effective contraceptive methods:

a. Combined hormonal contraception (containing estrogen and progestogen) associated with inhibition of ovulation: oral, intravaginal, or transdermal
b. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
c. IUD
d. IUS
e. Bilateral tubal occlusion

5. Where allowed by local laws and regulations, a double-barrier contraceptive method—specifically, male subject use of condom AND female partner of childbearing potential use of cap, diaphragm, or sponge with spermicide—is acceptable.

6 STUDY INTERVENTION

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

AMB-05X drug substance is a human monoclonal antibody against CSF1R.

The drug product is a sterile, clear, colorless to slightly yellow liquid containing drug substance at a concentration of [redacted] mg/mL. Drug product is packaged in [redacted] mL glass vials, each containing a deliverable volume of [redacted] mL.

Additional information about the physical, chemical, and pharmaceutical properties of AMB-05X is provided in the IB.

6.1.2 Dosing and Administration

Dosing will begin with Cohort A with an initial priming dose of 4 mg/kg on Day 1 followed by 5 maintenance doses of 2 mg/kg administered every 2 weeks (at Weeks 2, 4, 6, 8, and 10), for a total of 6 doses over the 12-week treatment period.

The allowable range of dose levels and regimens for subsequent cohorts is provided in Section 4.1.2. Subjects in subsequent cohorts will receive study drug either every 2 weeks or every 4 weeks. The Sponsor will determine the dose levels and regimens for subsequent cohorts within the allowable range based on an ongoing analysis of available data from the previous cohort(s), as described in Section 4.1.2.

Study drug will be administered via IV infusion at the study center by qualified study staff. The temperatures and times specified in this section must be strictly adhered to. Failure to follow these instructions may lead to denaturation and inactivation of the study drug.

Calculating Volume of Study Drug Needed for Each Subject

The volume of study drug (and thus the number of study drug vials) needed for each subject will be calculated based on the subject's weight according to the following equation:

Volume of study drug needed for subject (in mL) =

X mg/kg dose × subject's body weight in kg ÷ [redacted] mg/mL drug concentration

Each vial will deliver [redacted] mL (or [redacted] mg) of study drug. The appropriate number of vials (based on the volume of study drug needed) will be thawed.

[redacted] Study Drug

Study drug vials should be [redacted]

[redacted] Study Drug for Administration

[redacted] Carefully check vials for damage (eg, cracks). During inspection, vials should be free of any external moisture or condensation. If necessary, wipe the vial with a clean lint-free wipe to remove moisture. Quarantine damaged vials and report the compromised investigational product to the Sponsor. The Sponsor will provide further instructions for destruction and reporting.

[redacted]

Withdraw the calculated volume of study drug needed for the subject. Study drug will be diluted with normal saline and administered as instructed in the pharmacy manual. Unused study drug in opened and dispensed vials should not be used for subsequent dosing. Subjects will remain at the study center for at least 60 minutes after dosing to allow monitoring for any adverse reactions, including any infusion-site reactions.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Study drug must be received at the study center by a person designated by the study team. Site personnel must maintain an accurate drug accountability record of the receipt and dispensing of study drug. The Site Monitor will verify study drug accountability during monitoring visits.

Site personnel must administer study drug only to individuals enrolled in the study. Administration of study drug must be recorded in the subject's source documents, the eCRF, and the study drug inventory log.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Study drug is formulated as a [redacted] mg/mL drug substance in a solution of [redacted] Study drug appears as a [redacted]. Drug product is packaged in sterile [redacted]-mL glass vials each containing a deliverable volume of [redacted] mL.

Study drug labels will be printed in the local language of the study center and will comply with the legal requirements of the country where the study center is located.

6.2.3 Product Storage and Stability

Study drug must be handled and stored safely and properly in a secure location that only the Investigator and designated staff can access.

Upon receipt, study drug kits must be stored in compliance with the labeled storage conditions [redacted]. The storage, [redacted] temperatures and times specified here and in Section 6.1.2 must be strictly adhered to. Failure to follow these instructions may lead to denaturation and inactivation of the study drug. Study drug vials should not be [redacted].

Storage conditions must be adequately monitored, and appropriate temperature logs maintained as source data. Any excursion in storage temperature should be recorded and reported to the Sponsor to ensure study drug is suitable for administration. Refer to the pharmacy manual for detailed information regarding storage and temperature constraints.

6.2.4 Disposal

Any leftover study drug in opened vials will be disposed of onsite according to the study center's standard operating procedures; glass vials will be retained for accountability.

After receiving written authorization from the Sponsor or its designee, the site will either send unused and empty vials of study drug to the address provided at the time of authorization for destruction or, with specific approval from the Sponsor, destroy the unused and empty vials of study drug onsite according to the study center's standard operating procedures. The study staff must provide a drug destruction certificate to the Sponsor or its designee.

6.3 Measures to Minimize Bias: Randomization and Blinding

If there is concurrent enrollment of multiple cohorts, subjects will be randomized to a cohort via the interactive web response system (IWRS). There is no blinding except for the blinding of the central radiologist to a subject's dose.

6.4 Study Intervention Compliance

Study drug will be administered by qualified study staff at the study center.

6.5 Concomitant Therapy

A subject's concomitant medications will be reviewed during the screening period. Subjects should be instructed to notify the study center about any new medications they start taking or any medications they stop taking. All medications administered from the time the ICF is signed through a subject's last study visit must be recorded on the Concomitant Medications eCRF. Any significant non-drug therapies (including physical therapy and blood transfusions) will be recorded on the Concomitant Procedures eCRF.

Subjects who use a prescription analgesic must be on a stable regimen of prescription analgesic during the 2 weeks before Baseline and should make every effort to maintain a stable regimen of prescription analgesic during the study, so as not to confound the measurement of pain in this study.

Use of any other investigational drug is prohibited within 4 weeks or 5 half-lives (whichever is longer) before Baseline and during the study.

Use of pexidartinib, any other oral tyrosine kinase inhibitor (eg, imatinib or nilotinib), or any biologic treatment targeting CSF1 or CSF1R is prohibited within 3 months before Baseline and during the study.

MRI contraindications (eg, pacemaker, loose metallic implants) are prohibited during the study.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Screening Procedures

7.1.1 Subject ID

Each subject screened will be assigned a unique 6-digit Subject ID via the interactive web response system (IWRS). The Subject ID will consist of a 3-digit center number (101, 201, etc) and a 3-digit subject number that starts with 001 for each site. Thus, if the center number is 101, the Subject IDs assigned to subjects at that center will be 101-001, 101-002, 101-003, etc.

7.1.2 Demographics and Medical History

Demographic data and a complete medical history with review of body systems will be documented for all subjects during the screening period. Any change in the subject's condition or health status between consent and the first dose of study drug will be captured as medical history. Any AE that occurs between consent and the first dose of study drug will be recorded but will not be considered treatment emergent.

7.1.3 Height

Height will be measured at Screening only.

7.1.4 Tumor Biopsy

For subjects whose TGCT diagnosis has not been previously histologically confirmed, a tumor biopsy will be performed during the screening period after a central radiologist has reviewed the subject's screening MRI scan.

7.2 Safety Assessments

Safety will be evaluated using the following assessments:

- Reported AEs (see Section 7.3) and concomitant medications (see Section 6.5)
- Body weight
- Vital signs
- Physical examination
- ECG
- Pregnancy tests
- Clinical laboratory tests
- Tolerability assessment

7.2.1 Vital Signs

Vital signs, including blood pressure (systolic and diastolic, in mmHg), body temperature (in °C), heart rate (in beats per minute), and respiratory rate (in breaths per minute) will be recorded with the subject in a sitting position after having rested for 5 minutes.

7.2.2 Physical Examination

A full physical exam will include, but not be limited to, an examination of general appearance, skin, HEENT (head, eyes, ears, nose, throat), lungs, heart, abdomen, back, lymph nodes, extremities, and basic nervous system evaluation.

Information about the physical examination must be present in the source documentation at the study center. Significant findings that are present before the first dose of study drug must be included on the medical history / current medical conditions page of the eCRF. Significant findings made after the first dose of study drug that meet the definition of an AE must be recorded on the AE page of the eCRF.

7.2.3 Electrocardiogram

Standard 12-lead ECGs will be performed, and the following ECG parameters will be measured: heart rate, RR, PR, QRS, and QTcF. The Subject ID, the subject's age, the date and actual time of the tracing, and the study code must appear on each page of the tracing. Tracings will be dated, signed, and interpreted by a qualified physician. The overall interpretation will be collected with a Yes / No statement about whether any clinically significant abnormalities are present that need to be specified further in the source document and eCRF. Original ECG tracings, appropriately signed, will be archived at study centers.

7.2.4 Pregnancy Tests

For women of childbearing potential, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at all other visits specified in the Schedule of Events and at the discretion of the Investigator (eg, for a subject with irregular menses). The results of the serum pregnancy test at Screening and the urine pregnancy test at Visit 2 (Baseline) must be received before a subject may be enrolled.

7.2.5 Clinical Laboratory Tests

Table 1 shows the clinical laboratory parameters to be evaluated during the study. Blood samples will be drawn for chemistry and hematology. Urine samples will be collected for urinalysis. Details on sample collection and processing will be described in the laboratory manual.

Table 1. Clinical Laboratory Parameters

Hematology	Platelet count Mean platelet volume (MPV) Red blood cell (RBC) count Red cell distribution width (RDW) Hematocrit Hemoglobin Mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV)

	Reticulocytes White blood cell (WBC) count (total and differential)	
Chemistry (including lipids)	Alanine transaminase (ALT)	Globulin
	Albumin	Glucose (non-fasting)
	Alkaline phosphatase (ALP)	High-density lipoprotein (HDL)
	Aspartate transaminase (AST)	Lactate dehydrogenase (LDH)
	Bilirubin (total, direct, indirect)	Low-density lipoprotein (LDL)
	Blood urea nitrogen (BUN)	Magnesium
	Carbon dioxide (CO_2)	Phosphorus
	Calcium	Potassium
	Chloride	Sodium
	Cholesterol	Total protein
	Creatinine	Triglycerides
	Gamma-glutamyl transferase (GGT)	Uric acid
Routine Urinalysis	Color, visual color, turbidity, glucose, bilirubin, ketones, specific gravity, blood, pH, protein, acidified protein, urobilinogen, nitrite, leukocyte esterase Microscopic examination if indicated: urine WBC, urine RBC, bacteria, oval fat bodies, squamous epithelial cells, renal tubular epithelial cells, transitional epithelial cells, yeast, mucus, sperm, dysmorphic RBC	

7.3 Adverse Events and Serious Adverse Events

7.3.1 Definition of Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality.

An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. An overdose with symptoms should be recorded as an AE.

A worsening of previous illness or condition from baseline while participating in the study is also considered an AE.

7.3.2 Definition of Serious Adverse Event

An SAE is any event that meets any of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event. An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. 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.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

7.3.3 Classification of an Adverse Event

7.3.3.1 Severity

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the AE page of the subject's eCRF. Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (CTCAE 2017), summarized here:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
- **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: Death related to AE.

7.3.3.2 Relationship to Study Drug

The Investigator must assess the relationship of each AE to the study drug according to the categories defined below and record it on the AE page of the subject's eCRF.

- **Definitely related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably related**: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly related**: There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the study drug). However, other factors may have contributed to the event (eg, 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.
- **Unlikely to be related**: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the study drug) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the participant's clinical condition, other concomitant treatments).
- **Not related**: The AE is completely independent of study drug 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.

This assessment will help the Sponsor to determine whether an AE might be a suspected adverse reaction. A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

The Investigator may change the causality assessment at any time based on new accumulated information. An AE with causal relationship not initially determined will require follow-up to assign causality.

7.3.3.3 Expectedness

An unexpected AE or unexpected, suspected adverse reaction refers to an event or reaction that is not listed in the Reference Safety Information section of the most recent version of the IB at the time of the event or is not listed at the specificity or severity that has been observed. The Sponsor will be responsible for determining whether an AE is expected or unexpected.

7.3.4 Time Period and Frequency for Event Assessment and Follow-up

AEs will be recorded from the time the ICF is signed until the subject completes the last study visit or withdraws from the study.

AEs will be assessed at each study visit, and subjects should be encouraged to contact the study center to report any AEs at their onset. Study staff will elicit information about AEs using nonspecific questions such as "Have you experienced any change in your health status since your last visit?" Subjects will also be monitored closely for the development of an AE.

Any AE or clinically significant abnormality of ECG, physical examination finding, or clinical laboratory measurement that occurs during the study should be followed until no further medical intervention is warranted (eg, it resolves, becomes medically stable, or is assessed as chronic) or until the subject is lost to follow-up. AE follow-up must comply with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

7.3.5 Adverse Event Reporting

Information about AEs will be recorded on the AE page of the subject's eCRF. When known, the diagnosis (rather than individual symptoms) should be entered as the event term in the eCRF. For example, an upper respiratory infection with symptoms of cough, rhinitis, and sneezing should be recorded as upper respiratory infection. When the diagnosis is unclear, key symptoms may be entered separately, and the Investigator should obtain appropriate tests to establish a diagnosis, if possible. After a diagnosis is determined, the eCRF event term should be updated.

For each AE, the onset date, seriousness, severity (Section 7.3.3.1), relationship to study drug (causality) (Section 7.3.3.2), action taken, outcome, and date of resolution (or continuing) will be recorded. The Investigator must make a causality assessment for each AE.

7.3.6 Serious Adverse Event Reporting and Follow-up

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria and to do so in an expedited manner. Specifically, suspected, unexpected serious adverse reactions (SUSARs) are subject to expedited safety reporting requirements. The Sponsor will report SUSARs to the appropriate authorities within the timelines and format required by local regulations. The Sponsor will also inform all participating investigators of SUSARs and any new safety risks.

Therefore, study centers must report all SAEs, including death, due to any cause, that occur from the time the ICF is signed until the subject completes the last study visit or withdraws from the study, to the Sponsor or its designee within 24 hours of the study center staff learning of its occurrence. When reporting an SAE, all relevant seriousness criteria should be recorded, and relationship to study drug should be assigned at the time of initial report, as this is required to determine regulatory reporting.

The Investigator must also report applicable SAEs to the Institutional Review Board (IRB) / Independent Ethics Committees (IEC) according to the requirements of the IRB/IEC. The Sponsor will provide the Investigator with information on SUSARs from other study centers or other studies conducted with the study drug to provide to IRBs/IECs.

The Investigator is expected to institute appropriate diagnostic and therapeutic measures necessary to treat and promote resolution of the SAE. Any medications or procedures used to treat the SAE must be recorded on the appropriate pages of the subject's eCRF. The Investigator must determine whether the seriousness of the event warrants discontinuation of study drug.

The Investigator is expected to proactively follow up on the SAE with the subject at subsequent visits/contacts and to report follow-up information on the SAE to the Sponsor or its designee. All SAEs will be followed until no further medical intervention is warranted (eg, the event resolves, becomes medically stable, or is assessed as chronic) or until the subject is lost to follow-up.

The Sponsor or designee may contact the study center to solicit additional information or to follow up on the event. If requested, medical records (such as laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates) should be sent to the Sponsor or its designee after redacting all information that personally identifies the subject or hospital staff (per the European General Data Protection Regulation).

After a subject's last study visit, the Investigator is not obligated to actively seek AEs or SAEs. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study drug or to study participation, the Investigator must notify the Sponsor or designee within 24 hours of learning of the event.

7.3.7 Reporting of Pregnancy

Any pregnancy in a female subject or in the female partner of a male subject that occurs from the time the subject signs an ICF until a subject's last study visit must be reported to the Sponsor or its designee within 24 hours of study center staff learning of its occurrence. A pregnant female subject will be immediately discontinued from study drug.

The subject or pregnant partner should provide consent and then will be followed throughout the course of the pregnancy. Pregnancy follow-up information, including the status and health of the mother and the child and the outcome of the pregnancy, will be reported to the Sponsor or its designee. Any premature termination of the pregnancy will be reported. Any complication of the pregnancy affecting either the mother or the fetus that meets seriousness criteria will be reported as an SAE. A planned elective termination of the pregnancy will not be considered an SAE.

7.3.8 Clinically Significant Adverse Events

Clinically significant AEs include DLTs, AEs leading to discontinuation, and AESIs, all considered at least possibly related to study drug. The DMC will pay special attention to the occurrence of clinically significant AEs in their recommendations regarding continuation or suspension of dosing or enrollment, cohort expansion, initiation of a new dose cohort, and dose selection.

7.3.8.1 Dose-Limiting Toxicity

A DLT is defined as any Grade 3 or higher AE or SAE considered at least possibly related to study drug. For subjects who experience a DLT, the Investigator may exercise his/her clinical judgment and consider a reduction in an individual subject's maintenance dose (eg, from

2 mg/kg to 1 mg/kg, 4 mg/kg to 2 mg/kg, or 8 mg/kg to 4 mg/kg). Before implementing a dose reduction for a subject, the Investigator should contact the Medical Monitor to discuss the case. Subjects who are unable to tolerate the lowest dose level specified in Section 4.1.2 will have study drug discontinued.

7.3.8.2 Adverse Events of Special Interest

AESIs for this study will include the following:

- Any events of liver toxicity, including elevations in liver enzymes (ALP, ALT, AST, bilirubin)
- Any periorbital edema or facial edema
- Grade 2 or higher: infections, nausea, vomiting, diarrhea
- Any infusion reactions
- Any neutropenia, anemia, or thrombocytopenia

All AESIs will be captured on an AESI report form. The DMC will pay special attention to AESIs considered at least possibly related to study drug.

7.4 Efficacy Assessments

Efficacy will be evaluated using the following assessments:

- MRI and central radiologist assessment of tumors based on RECIST v1.1 and TVS
- Clinician evaluation of ROM in the affected joint
- PRO instruments of PROMIS Physical Function Scale, Worst Stiffness NRS, BPI Short Form (including the Worst Pain NRS item), and EQ-5D-5L

7.4.1 Tumor Assessments

7.4.1.1 MRI

MRI procedures will be detailed in a separate MRI manual. MRI scans will be evaluated centrally by an independent radiologist blinded to a subject's dose. MRI scans will be assessed for tumor response based on RECIST v1.1 (Section 7.4.1.2) and based on TVS (Section 7.4.1.3).

7.4.1.2 Response Based on RECIST v1.1

OR will be centrally assessed from MRI scans using RECIST v1.1 and will include CR and PR (Eisenhauer, 2009). A CR is defined as disappearance of all tumors. A PR is defined as at least a 30% decrease in the sum of diameters of target tumors from the baseline sum of diameters.

7.4.1.3 Response Based on Tumor Volume Score

Quantification of tumor volume in TGCT is complicated by the irregular shape of the tumor and heterogeneous contrast between the tumor and its surrounding structures, which make it challenging to delineate tumor boundaries. TVS is a semi-quantitative scoring method for MRIs developed specifically for assessing TGCT (Tap, 2015). TVS draws from existing MRI scoring methods commonly used in arthritis (the Rheumatoid Arthritis MRI Score and the Whole Organ MRI Score) and from existing radiological experience in assessing changes in tumor volume and

patterns of distension of synovial cavities. TVS calculates tumor volume as a percentage of the estimated volume of the maximally distended synovial cavity or tendon sheath and provides a score in 10% increments. A score of 0 indicates no evidence of tumor; a score of 10 indicates a tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath.

Tumor outcomes based on TVS will be classified according to the following:

- Complete response (CR): lesion is completely gone
- Partial response (PR): ≥50% decrease in TVS relative to Baseline
- Progressive disease (PD): ≥30% increase in TVS relative to the lowest score during the study
- Stable disease (SD): does not meet any of the other classifications

Tumor response based on TVS is defined as CR or PR. The overall number of responses and the number of subjects with and without disease progression will be assessed.

7.4.2 Joint Range of Motion

ROM of the affected joint will be assessed by qualified assessors at the study center and recorded in degrees. At Baseline, the plane of movement with the smallest (worst) relative ROM will be identified; only this plane will be used for evaluating change in ROM subsequently.

7.4.3 PROMIS Physical Function Scale

The PROMIS Physical Function Scale provided in Appendix 1 is a 10-question PRO instrument that will be used to assess physical functioning based on use of the upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back) and on instrumental activities of daily living. Five questions address the degree to which the subject's health limits certain physical activities, and subjects select a response to each question that ranges from 1 ("cannot do") to 5 ("not at all"). Five questions address the degree to which the subject is able to perform certain physical activities, and subjects select a response to each question that ranges from 1 ("cannot do") to 5 ("without any difficulty").

7.4.4 Worst Stiffness Numeric Rating Scale

The Worst Stiffness NRS provided in Appendix 2 is a single-item PRO instrument designed to assess "worst" stiffness at the site of the tumor. The instrument uses an 11-point NRS that ranges from 0 ("no stiffness") to 10 ("stiffness as bad as you can imagine"). Subjects are asked to recall their "worst" stiffness at the site of the tumor in the last 24 hours.

7.4.5 Brief Pain Inventory Short Form and Worst Pain Numeric Rating Scale

The BPI Short Form provided in Appendix 3 is a PRO instrument used to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily functioning (Cleeland, 1994). Subjects list current pain treatments and rate on a scale from 0 to 10 their worst, least, average, and current pain intensity; how much relief current pain treatments provide; and the degree to which pain interferes with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

The Worst Pain NRS is an item in the BPI that assesses a subject's "worst" pain in the last 24 hours. The 11-point NRS for this item ranges from 0 ("no pain") to 10 ("pain as bad as you can imagine").

7.4.6 EQ-5D-5L

The EQ-5D-5L assessment provided in Appendix 4 is a widely used PRO quality-of-life instrument developed by the EuroQol Group that consists of 2 pages: the EQ-5D descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and subjects select one of 5 levels (statements describing severity) that most accurately describes their health state for each dimension. The VAS records the subject's self-rated general health on a vertical VAS.

7.5 Pharmacokinetic and Pharmacodynamic Assessments

Serum will be collected and optional synovial fluid may be collected to assess AMB-05X, CSF1, and anti–AMB-05X antibody at the visits indicated in the Schedule of Events.

Serum AMB-05X and CSF1 concentrations will be measured at the following visits:

- Day 1, Week 4, and Week 8: before dosing and within 15 minutes after the end of infusion
- Weeks 2 and 6:
  - If the subject will receive study drug at the visit, collect the serum sample before dosing.
  - If the subject will not receive study drug at the visit, collect the serum sample at any time during the visit.
- Week 10:
  - If the subject will receive study drug at this visit, collect serum samples before dosing and within 15 minutes after the end of infusion.
  - If the subject will not receive study drug at this visit, collect a serum sample at any time during the visit.
- Weeks 12, 14, and 24: at any time during the visit

Synovial AMB-05X and CSF1 concentrations may be measured pre-dose at Day 1 and pre-dose at the visit associated with the last dose of study drug for each subject (Week 8 or Week 10) as an optional assessment.

ADA levels against AMB-05X will be measured from pre-dose serum samples and any synovial samples collected at Day 1, at Week 4, at the visit associated with the last dose of study drug for each subject (Week 8 or Week 10), and at Week 14.

Actual dosing and sampling times will be accurately recorded on the eCRF.

7.6 Blood Sampling

Blood samples will be taken by direct venipuncture. Blood sampling volumes will be limited by the most stringent regulations applicable to a particular site or region. Details on sample collection and processing will be described in a separate laboratory manual.

8 ASSESSMENTS BY STUDY VISIT

The Schedule of Events for this study is provided in Section 1.3.

Refer to Appendix 5 for potential changes to study conduct in the context of COVID-19, including the possibility of remote visits.

8.1 Visit 1 / Screening

After the subject provides signed consent and HIPAA authorization (if applicable), complete the following procedures. If necessary, screening assessments may be performed at more than 1 visit during the 4-week screening period.

- Obtain a 6-digit Subject ID from IWRS.
- Collect demographic information and take medical history.
- Record all concomitant medications, including dose amount and dosing frequency, taken within 4 weeks before Screening.
- Obtain height and weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Conduct a full physical examination.
- Perform a 12-lead ECG.
- Evaluate ROM of the affected joint.
- Administer the following PRO instruments:
  - PROMIS Physical Function Scale
  - Worst Stiffness NRS
  - BPI Short Form
  - EQ-5D-5L
- Collect a urine sample for urinalysis.
- Collect blood samples for HBV, HCV, HIV, TB (QuantiFERON), serum pregnancy test for females of childbearing potential, and clinical laboratory tests (chemistry and hematology).
- Perform MRI. A central radiologist will evaluate MRI scans to assess tumors.
- For subjects whose TGCT diagnosis has not been previously histologically confirmed, a tumor biopsy will be performed during the screening period after the central radiologist has reviewed the subject's screening MRI scan.
- Once test results are obtained, check inclusion/exclusion criteria.

Individuals who successfully complete screening procedures and meet all eligibility criteria will be notified and scheduled for Visit 2 (Baseline). The interval between Visit 1 (Screening) and Visit 2 (Baseline) should not exceed 4 weeks.

For any individual who does not meet eligibility criteria, capture screen failure information, contact IWRS to report screen failure status, and record any changes in concomitant medications and AEs since Screening.

8.2 Visit 2 / Baseline (Day 1)

Approximately 16 to 24 hours before scheduled study drug administration, set up the appropriate number of study drug vials to thaw in the refrigerator according to Section 6.1.2.

8.2.1 Pre-dose Procedures

- Collect a urine sample for a urine pregnancy test for females of childbearing potential and for urinalysis.
- Update any changes in concomitant medications since Visit 1 (Screening).
- Record any AEs that may have occurred since the ICF was signed. AEs that occur before the first dose of study drug will be recorded as such to distinguish them from TEAEs.
- Once test results are obtained, check inclusion/exclusion criteria.
  - Individuals who do not meet eligibility criteria (eg, females of childbearing potential with a positive pregnancy test) will be recorded as screen failures.

If the subject met all inclusion and no exclusion criteria, complete the following procedures:

- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Conduct a full physical examination and document any changes since the previous visit.
- Perform a 12-lead ECG.
- Evaluate ROM of the affected joint.
- Administer the following PRO instruments:
  - PROMIS Physical Function Scale
  - Worst Stiffness NRS
  - BPI Short Form
  - EQ-5D-5L
- Collect blood samples for clinical laboratory tests (chemistry and hematology) and serum PK, CSF1, and anti–AMB-05X antibody (pre-dose sample).
- Optional assessment: collect synovial fluid for PK, CSF1, and anti–AMB-05X antibody.

8.2.2 First Dose and Post-dose Procedures

- Administer study drug via IV infusion.
- Collect blood samples for serum PK and CSF1 within 15 minutes after the end of infusion.
- Monitor the subject for at least 60 minutes post-dose for any adverse reactions, including any infusion-site reactions.

- Schedule the subject for Visit 3 (Week 2).
- Contact IWRS to record the visit.

8.3 Visit 3 (Week 2 ± 2 Days)

If the subject is on an every-2-weeks study drug regimen, set up the appropriate number of study drug vials to thaw in the refrigerator approximately 16 to 24 hours before scheduled study drug administration and according to Section 6.1.2.

For all subjects, complete the following procedures during the visit:

- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Collect a urine sample for urinalysis.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect blood samples for serum PK and CSF1 (before study drug administration, if applicable for the subject).
- Schedule the next visit with the subject.
- Contact IWRS to record the visit.

If the subject is on an every-2-weeks study drug regimen, administer study drug via IV infusion. Monitor the subject for at least 60 minutes post-dose for any adverse reactions, including any infusion-site reactions.

8.4 Visit 4 (Week 4 ± 2 Days)

Set up the appropriate number of study drug vials to thaw in the refrigerator approximately 16 to 24 hours before scheduled study drug administration and according to Section 6.1.2.

Complete the following procedures during the visit:

- Collect a urine sample for a urine pregnancy test for female subjects of childbearing potential and for urinalysis.
  - Any subject with a positive pregnancy test result must complete ET procedures and will be recorded as ET.
- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.

- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect pre-dose blood samples for serum PK, CSF1, and anti–AMB-05X antibody.
- Administer study drug via IV infusion.
- Collect post-dose blood samples for serum PK and CSF1 within 15 minutes after the end of infusion.
- Monitor the subject for at least 60 minutes post-dose for any adverse reactions, including any infusion-site reactions.
- Schedule the next visit with the subject.
- Contact IWRS to record the visit.

8.5 Visit 5 (Week 6 ± 3 Days)

If the subject is on an every-2-weeks study drug regimen, set up the appropriate number of study drug vials to thaw in the refrigerator approximately 16 to 24 hours before scheduled study drug administration and according to Section 6.1.2.

For all subjects, complete the following procedures during the visit:

- Collect a urine sample for urinalysis.
- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Conduct a full physical examination and document any changes since the previous physical exam.
- Perform a 12-lead ECG.
- Evaluate ROM of the affected joint.
- Administer the following PRO instruments:
  - PROMIS Physical Function Scale
  - Worst Stiffness NRS
  - BPI Short Form
  - EQ-5D-5L
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect blood samples for serum PK and CSF1 (before study drug administration, if applicable for the subject).
- Perform MRI. A central radiologist will evaluate MRI scans to assess tumors.

- Schedule the next visit with the subject.
- Contact IWRS to record the visit.

If the subject is on an every-2-weeks study drug regimen, administer study drug via IV infusion. Monitor the subject for at least 60 minutes post-dose for any adverse reactions, including any infusion-site reactions.

8.6 Visit 6 (Week 8 ± 3 Days)

Set up the appropriate number of study drug vials to thaw in the refrigerator approximately 16 to 24 hours before scheduled study drug administration and according to Section 6.1.2.

Complete the following procedures during the visit:

- Collect a urine sample for a urine pregnancy test for female subjects of childbearing potential and for urinalysis.
  - Any subject with a positive pregnancy test result must complete ET procedures and will be recorded as ET.
- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect pre-dose blood samples for serum PK and CSF1 (and anti–AMB-05X antibody, if the subject will be receiving the last dose of study drug at this visit).
- Optional assessment: If the subject will be receiving the **last** dose of study drug at this visit, collect pre-dose synovial fluid for PK, CSF1, and anti–AMB-05X antibody.
- Administer study drug via IV infusion to the affected joint.
- Collect post-dose blood samples for serum PK and CSF1 within 15 minutes after the end of infusion.
- Monitor the subject for at least 60 minutes post-dose for any adverse reactions, including any infusion-site reactions.
- Schedule the next visit with the subject.
- Contact IWRS to record the visit.

8.7 Visit 7 (Week 10 ± 3 Days)

If the subject is on an every-2-weeks study drug regimen, set up the appropriate number of study drug vials to thaw in the refrigerator approximately 16 to 24 hours before scheduled study drug administration and according to Section 6.1.2.

For all subjects, complete the following procedures during the visit:

- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Collect a urine sample for urinalysis.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect blood samples for serum PK and CSF1 (before study drug administration, if applicable for the subject).
- Schedule the next visit with the subject.
- Contact IWRS to record the visit.

If the subject is on an every-2-weeks study drug regimen (and thus will be receiving the **last** dose of study drug at this visit):

- Collect a pre-dose blood sample for serum anti–AMB-05X antibody.
- Optional assessment: collect synovial fluid for PK, CSF1, and anti–AMB-05X antibody.
- Administer study drug via IV infusion.
- Collect post-dose blood samples for serum PK and CSF1 within 15 minutes after the end of infusion.
- Monitor the subject for at least 60 minutes post-dose for any adverse reactions, including any infusion-site reactions.

8.8 Visit 8 (Week 12 ± 3 Days) or Early Termination

Complete the following procedures during the visit:

- Collect a urine sample for a urine pregnancy test for female subjects of childbearing potential and for urinalysis.
- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Conduct a full physical examination and document any changes since the previous physical exam.
- Perform a 12-lead ECG.
- Evaluate ROM of the affected joint.

- Administer the following PRO instruments:
  - PROMIS Physical Function Scale
  - Worst Stiffness NRS
  - BPI Short Form
  - EQ-5D-5L
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect blood samples for serum PK and CSF1.
- Perform MRI. A central radiologist will evaluate MRI scans to assess tumors.
- Schedule the next visit with the subject.
- Contact IWRS to record the visit.

8.9 Follow-up Visit 9 (Week 14 ± 3 Days)

- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with subject in a sitting position after having rested for 5 minutes.
- Conduct a full physical examination and document any changes since the previous visit.
- Evaluate ROM of the affected joint.
- Administer the Worst Stiffness NRS.
- Collect a urine sample for a urine pregnancy test for female subjects of childbearing potential and for urinalysis.
- Collect blood samples for clinical laboratory (chemistry and hematology).
- Collect blood samples for serum PK, CSF1, and anti–AMB-05X antibody.
- Schedule the next visit with the subject.
- Contact IWRS to record the visit.

8.10 Follow-up Visit 10 (Week 24 ± 7 Days)

- Record any changes in concomitant medications since the previous visit.
- Record any new AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Obtain weight.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Conduct a full physical examination and document any changes since the previous visit.

- Evaluate ROM of the affected joint.
- Administer the following PRO instruments:
  - PROMIS Physical Function Scale
  - Worst Stiffness NRS
  - BPI Short Form
  - EQ-5D-5L
- Collect a urine sample for a urine pregnancy test for female subjects of childbearing potential and for urinalysis.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect blood samples for serum PK and CSF1.
- Perform MRI. A central radiologist will evaluate MRI scans to assess tumors.
- Contact IWRS to record the visit.

8.11 Early Termination Procedures

A subject who terminates early from the study and does not withdraw consent for study participation will be asked to complete Visit 8 (Week 12) (Section 8.8), Visit 9 (Week 14) (Section 8.9), and Visit 10 (Week 24) (Section 8.10) (whichever visits the subject has yet to complete at the time of ET). Study personnel will make every effort to conduct all protocol-specified procedures to complete the study, including a final MRI.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

Based on prior Phase 1 experience and an anticipated treatment effect with AMB-05X in this population, the sample size of 3 to 12 subjects per cohort is anticipated to provide sufficient data for PK/PD analysis and an estimate of safety, tolerability, and efficacy.

9.2 Populations for Analyses

Safety Population: This population will include all subjects who receive at least 1 dose of study drug. The Safety Population will be used for analysis of safety data.

Modified Intent-To-Treat (mITT) Population: This population will include all subjects who receive at least 1 dose of study drug and have both baseline and post-baseline data for at least 1 efficacy endpoint. The mITT Population will be the primary analysis population for efficacy analysis.

Per-Protocol Population (PP): This population will include subjects in the mITT Population who complete the study and do not have protocol deviations that could significantly affect the interpretation of the endpoints. The PP Population will be identified before database lock. The PP Population may be used for sensitivity analyses of efficacy endpoints.

9.3 Statistical Analyses

9.3.1 General Approach

All study data will be summarized by dose cohort and overall using descriptive statistics. Data from all investigational centers will be pooled for analyses. Unless otherwise specified, descriptive statistics for numeric data (eg, age, weight) will include the number of subjects with data to be summarized (n), mean, SD, median, minimum, and maximum. Categorical/qualitative data (eg, sex, race) will be presented using absolute and relative frequency counts and percentages. All summaries, statistical analyses, and individual subject data listings will be completed using SAS software (SAS Institute, Inc; Cary, North Carolina) Version 9.3 or later.

A detailed statistical analysis plan will be finalized before the first DMC meeting and will be provided separately.

9.3.2 Handling Missing Data

All available data will be presented as descriptive summaries or listings. Missing data will not be imputed.

9.3.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the Safety Population.

9.3.4 Safety Analyses

Safety analyses will include all subjects who receive at least 1 dose of study drug.

The number of subjects exposed to study drug and the duration of exposure will be summarized.

All AEs reported will be listed, documenting severity, start and stop date and time, possible relationship to study drug, action taken, and outcome. TEAEs are defined as AEs that occur after the first dose of study drug. Verbatim terms will be mapped to PTs and related SOCs using MedDRA. PTs and SOCs will be tabulated by dose cohort and overall. All reported AEs will be summarized by the number of subjects reporting each AE, SOC, PT, severity, and relationship to study drug. Multiple occurrences of an AE will be counted only once per subject per SOC and PT in summary tables.

The following will be summarized by SOC, PT, and dose cohort:

- Incidence of all TEAEs
- Incidence of all TEAEs by maximum severity (severe, moderate, and mild) specified by investigators
- Incidence of TEAEs related to study drug as determined by investigators
- Incidence of serious TEAEs
- Incidence of TEAEs leading to early discontinuation/withdrawal from the study

Safety labs (including hematology, chemistry, and urinalysis), vital signs, and ECGs will be tabulated using descriptive statistics. Abnormal/out-of-range findings and changes from pre-dose to post-dose will be listed by subject. Safety labs will be displayed graphically. Shift tables will be provided for all laboratory variables. For ECG parameters, heart rate, RR, PR, QRS, and QTcF will be summarized.

Concomitant medication usage will be summarized. The World Health Organization Drug Dictionary will be used to classify concomitant medications by therapeutic class and generic name based on ATC (Anatomical Therapeutic Chemical) code level 3. A subject will only be counted once in each unique ATC class and generic name if the subject uses multiple drugs.

9.3.5 Efficacy Analyses

Efficacy endpoints will be summarized using descriptive statistics and 95% confidence intervals. Exploratory hypotheses testing may be conducted using a significance level of 0.05 without adjustment for multiplicity.

9.3.6 Pharmacokinetic Analyses

AMB-05X concentrations will be summarized by dose, regimen, and nominal collection time. If warranted, a population PK analysis may be conducted using data from the current study and relevant data from other clinical studies. In addition, an exposure-response analysis may be attempted using the population approach.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Administrative Procedures

10.1.1 Ethics Review

The protocol and the ICF must be reviewed and approved by a properly constituted IRB/IEC and/or national competent authority before study start. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC and/or national competent authority must be given to the Sponsor or its designee before study start.

Before study start, the Investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with the specified documents and with all of the instructions and procedures found in this protocol. The Investigator agrees to provide access to all relevant data and records to the Sponsor's monitors, auditors, and quality assurance representatives; IRBs/IECs; and regulatory authorities, as required.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

At the completion of the study, the Investigator must provide the Sponsor a copy of the final conduct report that was submitted to their IRB/IEC, including a review of AEs, as described by Code of Federal Regulations (CFR) Title 21 Part 312.64.

10.1.2 Good Clinical Practice

This study will be conducted in accordance with principles of GCP as promulgated by the ICH, the US FDA, and applicable local regulations. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of human subjects are protected under current ethical principles and that the clinical study data are credible.

Current GCP standards may be found in ICH Guidance E6 (R2) (Good Clinical Practice: Consolidated Guidance). This guidance describes the principles of GCP and the obligations of the IRB/IEC, the Investigator, and the Sponsor in conducting this study in accordance with those principles.

10.1.3 Informed Consent

A complete description of the study is to be presented to each potential study subject, and a signed and dated (and, where required, witnessed) ICF that has been approved by the IRB/IEC will be obtained before any study-specific procedures are performed.

The subject must be able to communicate well with study staff, understand and comply with the requirements of the study, and read and voluntarily sign the ICF and the HIPAA authorization, if applicable, before the conduct of any study-specific procedures. All reasonable efforts should be taken by the study staff to ensure that the subject is able to comprehend what participation means. All consent documents will be provided in the subject's native language and in a form the subject is able to comprehend.

Females of childbearing potential must be informed that being on the study drug may involve unknown risks to a fetus if pregnancy were to occur during the study and agree to adhere to the contraception requirement. Male participants must be informed of potential risks to the fetus of a partner if conception were to occur during the study and agree to adhere to the contraception requirement. If there is any concern that the participant will not reliably comply, the participant will not be entered into the study.

The process of obtaining informed consent must be documented in the subject source documents. The Principal Investigator must maintain the original signed ICF. A copy of the signed ICF will be given to the subject.

All consent documents and procedures must comply with national laws, respective regulations, and IRBs/IECs relevant to the country where the subject participates. The Sponsor will provide Investigators with a proposed ICF that complies with ICH GCP guidelines and regulatory requirements and that the Sponsor considers appropriate for this study. The Sponsor must agree to any Investigator-suggested changes to the proposed ICF before the ICF is submitted to the IRB/IEC, and a copy of the approved ICF must be provided to the Sponsor's monitor after IRB/IEC approval.

10.1.4 Subject Confidentiality

In order to maintain subject privacy, all eCRFs, study drug accountability records, and study reports and communications will use the 6-digit assigned Subject ID. The Investigator will grant the monitor and auditor from the Sponsor or its designee and any regulatory authority access to the subject's original medical records to verify data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by applicable laws and regulations. The Sponsor will comply with the requirements of US HIPAA regulations and the European General Data Protection Regulation.

10.1.5 Protocol Deviation

Investigators will apply due diligence to avoid a protocol deviation. Unless there is a safety concern, there should be no deviation from the study protocol. In the event of a safety concern, the Investigator/designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from or a change to the protocol to eliminate an immediate hazard to subjects without prior IRB/IEC or regulatory authority approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reason for protocol deviation to the Sponsor or its designee and to the IRB/IEC (if required).

10.1.6 Protocol Amendment

All amendments to the protocol must be documented in writing; reviewed and approved by the Sponsor, the controlling regulatory authority, and each Investigator; and submitted to the IRB/IEC for approval before implementation.

If the protocol amendment substantially alters the study design or potential risk to the subject, new written informed consent for continued participation in the study must be obtained from each subject who is affected by the change.

10.1.7 Study Termination

This multicenter study as a whole or conduct of the study at any particular study site(s), whichever is applicable, may be terminated prematurely for the following reasons:

- The controlling regulatory authority terminates the study in the applicable region.
- The competent IRB/IEC for a particular study site does not approve the study or irrevocably withdraws its approval of the study.
- It is reasonable to conclude that terminating the study would be in the interests of the health of the study subjects.

  For example, the study may be terminated if new information arises that suggests continuing the study may pose an undue risk to subject safety or well-being. The Sponsor will review emerging safety data to identify safety and tolerability signals. These data include AEs and their associated frequency and severity, TEAEs, SAEs, SUSARs, and clinically significant changes in laboratory results, ECGs, vital signs, and physical examinations. New nonclinical safety data will also be assessed and considered in decisions on termination.
- In the event of a negative development in the benefit/risk profile, it is not possible to increase the amount of insurance coverage accordingly.
- It becomes clear that continuation of the study cannot serve any scientific purpose, and this is confirmed by the IRB/IEC that approved the study.
- The Sponsor or the particular study site is declared insolvent, has had a petition for bankruptcy filed against it, or is dissolved as a legal entity.
- The principal investigator of a study site is no longer capable of performing the tasks of the principal investigator, and no replacement acceptable to both the Sponsor and the site can be found within a reasonable period.
- The Sponsor or the particular study site fails to comply with the obligations arising from their clinical trial agreement and, provided this failure can be remedied, does not remedy the noncompliance within 30 days of receiving a written request from the other party to comply, unless failure to comply is not in reasonable proportion to the premature termination of the study.
- Circumstances beyond the control of the Sponsor or the particular study site render study continuation unreasonable.

If the study is terminated, the Sponsor will endeavor to provide adequate notice and clear guidance on study termination procedures to support the safe withdrawal of subjects from the study.

10.2 Data Handling and Recordkeeping

10.2.1 Source Documents and Electronic Case Report Forms

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (ie, original records or certified copies).

Study center staff will collect and record source data for the study in source documents and transcribe them into eCRFs, which use fully validated software that conforms to 21 CFR Part 11 requirements. Site staff will not be given access to the electronic data capture system until they have been trained.

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source documents / eCRFs. The source documents / eCRFs should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status. The Investigator must electronically sign the completed eCRFs to endorse the recorded data.

The Investigator will retain all completed source documents. The Sponsor will retain the eCRF archive and audit trail for all investigative sites. A site-specific eCRF archive and audit trail will be provided to each Investigator at the close of the study.

10.2.2 Retention of Records

Subject records, source documents, monitoring visit logs, eCRFs, inventories of investigational product, regulatory documents, and other correspondence pertaining to the study must be kept in the appropriate study files at the site.

The Investigator will maintain all study records according to ICH GCP and applicable local regulatory requirements. Records will be retained for as long as mandated by applicable local regulatory requirements and for at least 2 years after the last marketing application approval or at least 2 years after formal discontinuation of clinical development of the investigational product. The essential documents should be retained for longer than 2 years if required by applicable regulatory requirements or by an agreement with the Sponsor.

If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

10.3 Study Oversight

10.3.1 Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or its representative will have regular contact with the investigational site to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded on the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm that AEs and SAEs have been properly documented on eCRFs, that any SAEs have been forwarded to the Sponsor or its designee, and that those SAEs that met criteria for reporting have been forwarded to the IRB/IEC

The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records related to study conduct.

The monitor will be available between visits if the Investigator(s) or other staff need information or advice.

10.3.2 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator agrees to allow the auditor direct access to all relevant documents and to allocate his or her time, and that of site personnel, to the auditor to discuss findings and any relevant issues. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.

The purpose of an audit or inspection by the Sponsor is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements.

Other regulatory agencies may also conduct similar auditing procedures. The Investigator should immediately notify the Sponsor's study monitor of any upcoming regulatory inspection.

10.4 Publication Policy

The Sponsor acknowledges the importance of public disclosure of study results.

10.4.1 Clinical Trial Database

The Sponsor will post key design elements of this protocol in a publicly accessible database such as clinicaltrials.gov. In addition, within 12 months after study completion and after finalization of the study report, the Sponsor will post the results of this study in a publicly accessible database of clinical trial results.

10.4.2 Publishing Study Results

The Sponsor anticipates that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. After study completion, the Sponsor shall form a Publications Committee comprising the Investigators participating in the study and representatives from the Sponsor to oversee the initial publication of overall study results, which will reflect the experience of all participating study centers. Authorship shall be determined in accordance with generally accepted academic standards.

Individual Investigators who wish to publish or publicly disclose study results must wait until after the Sponsor's initial publication of overall study results to do so, provided the Sponsor does so within 12 months after study completion/termination. Subsequently, individual Investigators may publish results from the study, either in part or in full, in compliance with their agreement with the Sponsor. Investigators will provide proposed manuscripts to the Sponsor at least 90 days before submission of the manuscript to a publisher so that the Sponsor may review and respond or so that the Sponsor has the opportunity to file patent applications. Similarly, the Sponsor will provide any Sponsor-prepared manuscript to Investigators for review at least 30 days before submission to a publisher.

Before the Sponsor publicly discloses information from the study, provided the Sponsor does so before 12 months after study completion/termination, the Investigator agrees not to publicly disclose such information in any way without prior written permission from the Sponsor, as such disclosure would constitute violation of the Sponsor's confidentiality restrictions and a detriment to the Sponsor's intellectual property rights.

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APPENDIX 1. PROMIS PHYSICAL FUNCTION SCALE

PROMIS® Item Bank v2.0 – Physical Function – Short Form 10a

Physical Function – Short Form 10a

Please respond to each question or statement by marking one box per row.

		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36r1	Does your health now limit you in walking more than a mile (1.6 km)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Cannot do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45r1	Are you able to sit on and get up from the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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APPENDIX 2. WORST STIFFNESS NUMERIC RATING SCALE

The following question asks about stiffness at the site of your tumor. Please rate your stiffness by checking the one number that best describes your stiffness at its WORST in the last 24 hours.

0 is no stiffness and 10 is stiffness as bad as you can imagine.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

APPENDIX 3. BRIEF PAIN INVENTORY SHORT FORM

BRIEF PAIN INVENTORY

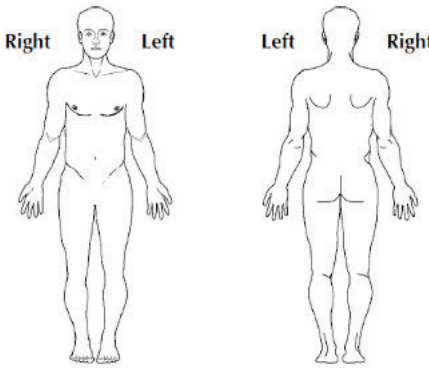
Date_____/_____/_____ Time:_____

Name:_____ _____ _____
Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its WORST in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its LEAST in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the AVERAGE.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

_____

_____

8) In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that shows how much RELIEF you have received.

0%	10	20	30	40	50	60	70	80	90	100%
No relief										Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

APPENDIX 4. EQ-5D-5L

Figure 1 / UK (English) EQ-5D-5L Paper Self-Complete (sample version)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

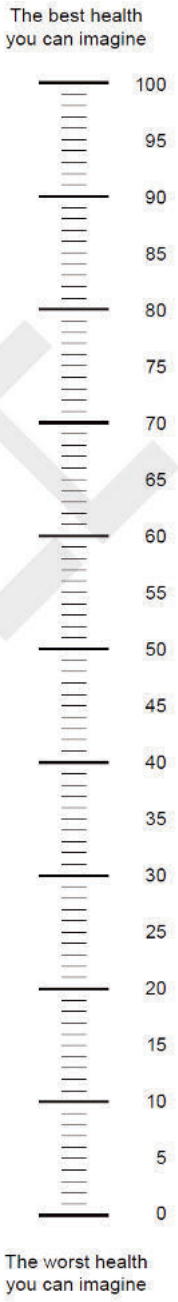
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 5. COVID-19 CONTINGENCY PLAN

COVID-19 Risk Mitigation

To mitigate any risk of COVID-19 infection that might be associated with study participation, study conduct will be modified in the following ways in regions with COVID-19–related shelter-in-place orders, shutdown of clinical trial sites, or other restrictions that would prevent subjects from going to study centers.

- The study will not screen or enroll new subjects in such regions.
- If enrollment has already begun in a region and such restrictions are issued, remote study visits consisting of a combination of home health visits and telemedicine may be conducted in place of certain in-clinic visits.
- The Investigator must consult with the Medical Monitor to determine the best course of action, particularly for situations not delineated here or for further clarification.

If clinic visits are no longer possible, activities that can only be performed in the clinic will not be conducted. Once COVID-19–related restrictions are lifted, sites should attempt to conduct any missed study activities via an unscheduled visit.

If a subject or a member of the subject's household is suspected or confirmed to have COVID-19, only telemedicine activities can proceed. Once the subject or member of his/her household no longer has suspected or confirmed COVID-19, missed study activities should be conducted as an unscheduled visit via home health nurse visit or clinic visit, as the situation allows.

Subject Disposition in the Event of COVID-19 Infection

If a subject is suspected or confirmed to have COVID-19, the Investigator will consider AE and SAE guidelines (Section 7.3) and work with the subject and Medical Monitor to assess safety and determine whether it is in the best interest of the subject to discontinue study drug / withdraw from the study or to continue study drug. If a subject discontinues study drug / withdraws from the study because of COVID-19, the reason for early termination will be captured as such.

Regulatory and Study Oversight Considerations

If onsite monitoring visits are not possible because of COVID-19, remote monitoring may occur, if allowed by local and federal laws and regulations. Home healthcare staff will transfer any source documents collected at a home health visit to the trial site as soon as the situation allows. If a protocol deviation is the result of COVID-19–related circumstances, this information should be captured.