Protocol AMB-051-01

PROTOCOL TITLE	An Adaptive, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Intra-articular AMB-05X Injections in Subjects with Tenosynovial Giant Cell Tumor of the Knee
PROTOCOL NUMBER	AMB-051-01
IND NUMBER	100835
REGISTRIES	EUDRACT #: 2020-003275-17 ClinicalTrials.gov Identifier: NCT04731675
INVESTIGATIONAL PRODUCT	AMB-05X monoclonal antibody
STUDY DESIGN	Phase 2
INDICATION	Tenosynovial Giant Cell Tumor (TGCT)
SPONSOR	AmMax Bio, Inc. [redacted]
VERSION	2.1
DATE APPROVED	16 August 2021

SPONSOR APPROVAL

Title:	An Adaptive, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Intra-articular AMB-05X Injections in Subjects with Tenosynovial Giant Cell Tumor of the Knee
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Signatures verify the information in this document is accurate and complete.

[redacted]

[redacted]

[redacted]

[redacted]

INVESTIGATOR'S SIGNATURE

Title: An Adaptive, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Intra-articular AMB-05X Injections in Subjects with Tenosynovial Giant Cell Tumor of the Knee

Protocol Number: AMB-051-01

I confirm that I have read this protocol. I will comply with the protocol, statutory requirements as described in the United States Code of Federal Regulations (CFR) 21 Parts 11, 50, 54, 56, and 312, and local requirements in the countries where the study is performed, 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 the ethical principles of the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all study site personnel who participate in the conduct of this clinical study. I will discuss this material with them to ensure they are fully informed regarding the study medication, 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.
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[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
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (drug classification system)
BPI	Brief Pain Inventory
COVID-19	coronavirus disease 2019
CR	complete response
CSF1	colony-stimulating factor 1
CSF1R	colony-stimulating factor 1 receptor
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
FDA	US Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability & Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
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
MRI	magnetic resonance imaging
NRS	numeric rating scale
OR	overall response
PD	pharmacodynamic(s)
PI	principal investigator: the investigator who leads study conduct at an individual study center. Every study center has a principal investigator.
PK	pharmacokinetic(s)
PR	partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
ROM	range of motion
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation

Abbreviation	Definition
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TGCT	tenosynovial giant cell tumor
TVS	tumor volume score
UDS	urine drug screen
ULN	upper limit of normal

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Number	AMB-051-01
Study Title	An Adaptive, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of Intra-articular AMB-05X Injections in Subjects with Tenosynovial Giant Cell Tumor of the Knee
Investigational Product	AMB-05X drug substance is a human monoclonal antibody against the colony-stimulating factor 1 receptor (CSF1R). Study drug is packaged as a [redacted] of [redacted] mL of [redacted] mg/mL in [redacted] mL glass vials.
Development Phase	Phase 2
Duration of Trial	Approximately 28 weeks of participation for each subject. This includes up to 4 weeks for screening, 12 weeks for dosing, and 12 weeks for post-treatment safety and efficacy evaluation.
Study Objective	Obtain safety and efficacy data for the investigational drug AMB-05X in the treatment of tenosynovial giant cell tumor (TGCT)
Primary Outcome Measure	Frequency and severity of reported treatment-emergent adverse events (TEAEs)
Secondary Outcome Measures	1. The 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 1.1) (Eisenhauer, 2009) at Week 12 2. 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 activity 3. Mean change from Baseline in range of motion (ROM) 4. Mean change from Baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function score 5. Mean change from Baseline in Worst Stiffness Numeric Rating Scale (NRS) score 6. Percentage of subjects who respond with a decrease of at least 30% in mean Brief Pain Inventory (BPI) score 7. Mean change from Baseline in BPI 8. Mean change from Baseline in Worst Pain NRS score

	9. EQ-5D-5L Health Assessment 10. Serum and synovial CSF1 levels 11. Serum and synovial AMB-05X levels 12. Serum and synovial anti-AMB-05X antibody levels
Study Design	This is a multicenter study with an adaptive design that will enroll approximately 12 subjects with TGCT of the knee for 12 weeks of multiple-dose, open-label treatment with AMB-05X. The study schema is provided in Section 1.2, and the Schedule of Events is provided in Section 1.3. 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. Clinic visits will occur at Screening (Visit 1, within 4 weeks prior to Baseline); Baseline/Week 0 (Visit 2, when subjects receive their first injection of AMB-05X); Week 2 (Visit 3); Week 4 (Visit 4); Week 6 (Visit 5); Week 8 (Visit 6); Week 10 (Visit 7, when subjects receive their last injection of AMB-05X); Week 12 (Visit 8, end of treatment period and assessment of primary and secondary endpoints); Week 14 (Visit 9, for post-treatment follow-up 2 weeks after completing the treatment period); and Week 24 (Visit 10, for final post-treatment follow-up 12 weeks after completing the treatment period). The study will begin dosing AMB-05X at 150 mg administered via intra-articular injection to the affected knee joint. Subjects will receive an injection of AMB-05X once every 2 weeks for 12 weeks (for 6 treatments total). Safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy assessments will be reviewed by the Sponsor on a continuous, subject-by-subject basis to determine whether the assigned dose is appropriate. Depending on these results, the Sponsor may either decrease the dosage strength to 90 mg or increase the dosage strength to 210 mg in subsequent subjects who enroll. In general, subjects are expected to complete the study at the dose strength which they started the study, unless they experience a clinically significant AE that would warrant a dose reduction. As a general rule, clinically significant AEs include, but are not limited to, any AE considered to be at least possibly related to study drug and severe in intensity or meets the criteria for a SAE. Subjects who are unable to tolerate a dosage strength of 90 mg will be withdrawn from the study. When at least 3 subjects have completed Week 6, a data monitoring committee (DMC) will review the available safety, tolerability, PK, PD, and efficacy data. Study enrollment and conduct may continue unchanged during DMC review. Based on the recommendations of the DMC, the Sponsor may then implement any one of the following adaptive changes without a protocol amendment: • Continuation of enrollment under the existing design, without any changes to the study.

	• Continuation of enrollment with a new dose. Specifically, the DMC may recommend a dose reduction to 90 mg or a dose increase to 210 mg in subsequent subjects. Subjects may not exceed a dose of 210 mg or go below a dose of 90 mg. Subjects who are unable to tolerate a dose of 90 mg will be discontinued from the study. • Discontinuation of further enrollment and/or suspension/termination of the study. Thereafter, the DMC should continue to review available data on a regular basis throughout the study (each time 3 subjects complete study treatment) and provide ongoing recommendations regarding appropriate next steps in study conduct (as outlined above). If a change in dose is made during the study, the DMC will again review the available data when 3 subjects have completed Week 6 at the new dose and provide further recommendations as outlined above.
Dosage and Administration	The study will begin dosing AMB-05X at 150 mg administered via intra-articular injection to the affected knee joint as described in Section 8. Subjects will receive an injection of AMB-05X once every 2 weeks for 12 weeks (for 6 treatments total). A total of 3 dose levels are permitted in this study: 90 mg, 150 mg, and 210 mg. Based on ongoing review of the available safety, PK, PD, and efficacy data, the Sponsor may decrease the dose to 90 mg or increase the dose to 210 mg in subsequent subjects. Study drug will be administered at the study center by qualified study staff. Subjects will remain at the study center for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.
Assessments	**Safety and Tolerability** Safety and tolerability will be assessed on an ongoing basis by monitoring adverse events (AEs) (including any serious AEs [SAEs], AEs leading to withdrawal, injection-site reactions [ISRs], and any other dose-limiting toxicities [DLTs]), physical examinations/vital signs, changes in clinical laboratory values, and ECG results. A DMC composed of qualified medical/clinical representatives will review the clinical data and will provide recommendations to the Sponsor regarding the acceptability of continued enrollment in the study and whether any modifications are warranted. **Efficacy** 1. OR will be centrally assessed from magnetic resonance imaging (MRI) scans using RECIST v1.1 (Eisenhauer, 2009). A CR is defined as disappearance of all tumors, and a PR is defined as at least a 30% decrease in the sum of diameters of target tumors from the baseline sum of diameters.

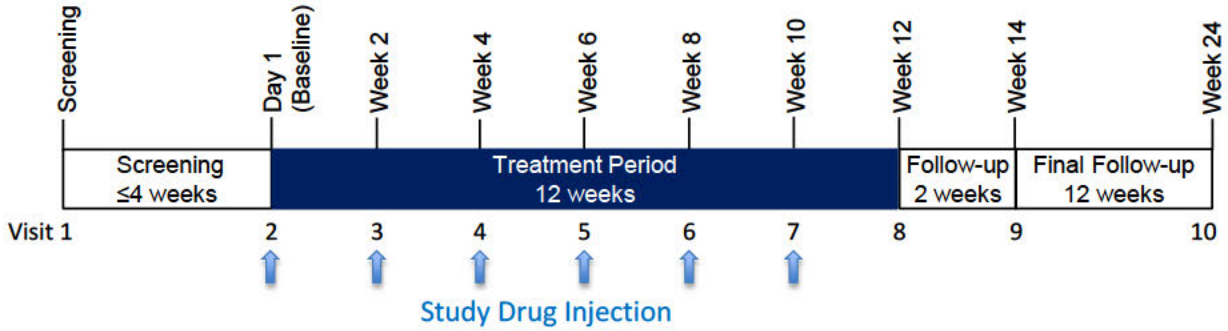
	2. TVS is a semi-quantitative MRI scoring system that describes tumor mass and is based on 10% increments in the estimated volume of the maximally distended synovial cavity or tendon sheath involved. A score of 0 indicates no evidence of tumor; a score of 10 indicates a tumor that is equal in volume 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. 3. ROM of the joint will be assessed by qualified assessors at the clinical site. Measurements will be recorded in degrees. At baseline, the plane of movement with the smallest (worst) relative value will be identified; only this plane will be used for evaluating change in ROM subsequently. 4. The PROMIS Physical Function Scale will be used to assess physical function of the upper and lower limbs. The scale ranges from 1 ('unable to do' or 'cannot do') to 5 ('without any difficulty' or 'not at all'), where higher scores represent better outcomes. 5. The Worst Stiffness NRS is a 1-item, self-administered questionnaire assessing the "worst" stiffness within the last 24 hours. The NRS for this item ranges from 0 (no stiffness) to 10 (stiffness as bad as you can imagine). 6. The Worst Pain NRS is a component of the Brief Pain Inventory assessing the "worst" pain in the last 24 hours. The NRS for this item ranges from 0 (no pain) to 10 (pain as bad as you can imagine). 7. Brief Pain Inventory (BPI) Short Form is a self-administered questionnaire used to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily functioning. The subject is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a scale from 0 to 10. 8. EQ-5D-5L is a widely used quality of life instrument that includes questions in each of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The choices include 5 levels of severity for each domain followed by a general health visual analogue scale (VAS). **Pharmacokinetics/Pharmacodynamics** Serum AMB-05X concentrations will be measured at Week 0 (pre-dose and 2 hours after the first dose), Week 2 (pre-dose [trough]), and Week 10 during steady state (including pre-dose [trough] and 2 hour after the last dose). Synovial AMB-05X concentrations will be measured at Weeks 0, 2, 4, 6, 8, and 10 (all at pre-dose [trough]). Anti-drug antibody analysis will also be performed on select serum and synovial samples.

	Serum and synovial fluid CSF1 levels will be analyzed as a biomarker.
Study Population	This study will enroll approximately 12 male and female adult subjects with local or diffuse TGCT of the knee.
Inclusion Criteria	**A subject may be included if ALL of the following criteria are met:** 1. Subject ≥ 18 years 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 Health Insurance Portability and Accountability Act (HIPAA) authorization, if applicable, prior to the conduct of any study specific procedures. 2. A diagnosis of TGCT of the knee joint that has been histologically confirmed either by a pathologist at the treating institution or by a central pathologist. If not previously confirmed, biopsy with histological confirmation is required. 3. Measurable disease of at least 1 cm based on RECIST v1.1, assessed from MRI scans by a central radiologist. Subjects with one knee joint involvement only, and only limited posterior extra-articular nodular TGCT lesions as assessed by central radiologist and tumor review committee. 4. Stable prescription of analgesic regimen during the 2 weeks before Baseline 5. Negative urine drug screen (UDS) at Screening and Baseline 6. Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline. 7. Agrees to follow contraception guidelines (see Section 5.3) 8. Adequate hematologic, hepatic, and renal function, at Screening Visit defined by: • Absolute neutrophil count ≥ 1.5×10^9/L • Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 1.5 × upper limit of normal (ULN) • Hemoglobin > 10 g/dL • Total bilirubin ≤ 1.5 × ULN • Platelet count ≥ 100×10^9/L • Serum creatinine ≤ 1.5 × ULN 9. Willing and able to complete the Brief Pain Inventory (BPI), Worst Stiffness NRS item, PROMIS Physical Function Scale, EQ-5D-5L, and other self-assessment instruments throughout the study

Exclusion Criteria	**A subject will be excluded if ANY of the following criteria is met:** 1. Prior investigational drug use within 4 weeks or 5 half-lives (whichever is longer) before Baseline 2. Use of pexidartinib, any other oral tyrosine kinase inhibitors (e.g., imatinib or nilotinib), or any biologic treatment targeting CSF1 or CSF1R within 3 months before Baseline 3. History of extensive or reconstructive knee surgery, except for prior diagnostic synovectomy, which is not exclusionary if at least 3 months prior to Baseline 4. Active cancer (either currently or within 1 year before Baseline) that requires therapy (e.g., surgery, chemotherapy, or radiation therapy), with the exception of 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 6. Hepatitis C virus (HCV) or hepatitis B virus (HBV) or known active or chronic infection with human immunodeficiency virus (HIV) 7. Known active tuberculosis 8. 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 his or her results 9. Women who are breastfeeding 10. A screening Fridericia-corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women) 11. MRI contraindications (e.g., pacemaker, loose metallic implants) 12. History of hypersensitivity to any ingredient of the study drug 13. History of drug or alcohol abuse within 3 months before the first dose of study drug 14. 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 or interfere with interpretation of study results and, in the Investigator's opinion, make the subject inappropriate for this study 15. Subjects who, in the Investigator's opinion, should not participate in the study for any reason, including if there is a question about their ability to comply with study requirements
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 approximately 12 subjects 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 treatment using descriptive statistics. **Safety Analyses** Safety analyses will include all subjects who received 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 recorded 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 treatment group. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to study drug. 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 concentration data will be summarized by collection time. PK parameters will be deduced where possible by WinNonlin analysis.

1.2. Study Schema



1.3. Schedule of Events

	Screening	Treatment Period							Follow-up	
Study Visit	**V1 Screening**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8/ET**	**V9**	**V10**
Study Week	**≤4 weeks before**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**24**
Study Day	**Baseline**	**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									
Confirmation of eligibility	X	X								
Physical exam	X	X			X			X	X	X
Weight and height[1]	X	X	X	X	X	X	X	X	X	X
Vital signs[2]	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X			X			X		
Pregnancy test[3]	X	X		X		X		X		
Urine drug screen	X	X								
Clinical laboratory tests[4]	X	X			X			X		X
HBV, HCV, HIV, TB	X									
Serum PK samples[5]		X	X				X			
Serum CSF1[5]		X	X				X			
Serum anti-AMB-05X antibody[5]		X					X			
Synovial PK samples[6]		X	X	X	X	X	X			
Synovial CSF1[6]		X	X	X	X	X	X			
Synovial anti-AMB-05X antibody[6]		X		X			X			

[1] Height is collected only at the Screening.
[2] 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.
[3] For females of childbearing potential, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at subsequent visits indicated.
[4] Clinical laboratory tests to include chemistry, hematology, and urinalysis
[5] Serum samples will be collected for measurement of AMB-05X concentrations pre-dose and 2 hours post-dose at Week 0, pre-dose at Week 2, and pre-dose and 2 hours post-dose at Week 10.
Serum CSF1 levels will be measured at the same timepoints.
Serum anti-AMB-05X antibody will be measured in the pre-dose samples at Week 0 and Week 10.
[6] Synovial fluid (2 mL) will be collected pre-dose at Weeks 0, 2, 4, 6, 8, and 10 for AMB-05X PK measurements, and for CSF1. Synovial anti-AMB-05X antibody will be measured in the pre-dose samples at Week 0 and Week 4, and at Week 10.

	Screening	Treatment Period							Follow-up	
Study Visit	**V1 Screening**	**V2 Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8/ET**	**V9**	**V10**
Study Week	**≤4 weeks before**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**24**
Study Day	**Baseline**	**1**	**15 ± 2**	**29 ± 2**	**43 ± 3**	**57 ± 3**	**71 ± 3**	**85 ± 3**	**99 ± 3**	**169 ±7**
MRI[7]	X				X			X		X
Tumor assessment	X				X			X		X
Tumor biopsy[8]	X									
Worst Stiffness NRS	X	X			X			X	X	X
Physical Function Scale (PROMIS)	X	X			X			X		X
BPI	X	X			X			X		X
EQ-5D-5L	X	X			X			X		X
Joint ROM	X	X			X			X	X	X
Study drug injection		X	X	X	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.

[7] MRIs will be assessed by a central reader.

[8] Tumor biopsy will be performed for subjects at Screening who do not have histologically confirmed TGCT. Any required biopsies should be performed after MRI review of the tumor by the central reader.

2. INTRODUCTION

2.1. Tenosynovial Giant Cell Tumor

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 (Staals, 2016; de Saint Aubain Somerhausen, 2013).

TGCTs are caused by the abnormal expression of colony-stimulating factor 1 (CSF1) as a result of genomic mutations (balanced translocations) at the CSF1 gene locus of chromosome 1p13 (West, 2006; Cupp, 2007). This translocation results in the dysregulation of CSF1 and COL6A3.8 CSF1 (Ohjimi,1996; Mertens, 1993) leading to excessive production of CSF1. CSF1 acts at the CSF1 receptor (CSF1R) resulting in 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 (de Saint Aubain Somerhausen, 2013; West, 2006; Cupp, 2007). Although TGCTs are nonmetastatic in nature, they can develop into locally destructive lesions causing significant local tissue injury, loss of joint function, and impaired quality of life (West, 2006).

The annual incidence of TGCT is estimated to be ~43 cases per 1 million individuals, with approximately 40,000 new cases per year in the US and Europe combined (Ehrenstein, 2017; Mastboom, 2017). 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 66–80%), followed by the ankle, elbow, shoulder, wrist/hand, and hip (Murphey, 2008).

TGCT most commonly affects individuals between 20-50 years of age and 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, leading to eventual loss of joint function, impaired quality of life, and severe morbidity (Tap, 2019; Giustini, 2018).

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 (Mastboom, 2017; Staals, 2016; Brahmi, 2016; Palmerini, 2015). 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 their use is limited due to late sequela (Benner, 2020).

Persistent disease can cause cartilage destruction and bone erosion, in addition to functional limitations from long-term pain, swelling, and limitations to range-of-motion. Joint replacement or even amputation might be necessary in these cases (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).

In late 2019, pexidartinib, an oral small molecule tyrosine-kinase inhibitor with activity against CSF1R was approved by the US Food and Drug Administration for the treatment of adult

patients with symptomatic TGCT with severe morbidity/functional limitations, not amenable to surgery (Turalio™ US FDA Package Insert, 2019). 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 remains a concern among patients treated with pexidartinib (Tap, 2019; Gelderblom, 2020).

The viability of CSF1R inhibition as treatment modality was further established in an early-stage clinical trial in TGCT patients evaluating emactuzumab, a monoclonal antibody that targets CSF1R (Cassier, 2015). Following systemic (IV) administration, 86% of patients 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, the localized nature of the disease, and prior clinical validation of CSF1R as an effective treatment target, AmMax Bio, Inc. is developing AMB-05X, a human monoclonal antibody inhibiting the CSF1R, as a direct, local injectable 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 c-fms (CSF1R). It potently blocks both CSF1- and IL-34–mediated proliferation of growth factor–dependent human myelomonocytic cells in vitro and also effectively interacts with the monkey receptor but not other species such as rodents.

2.3. Summary of Nonclinical Data

2.3.1. Pharmacology

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

AMB-05X inhibits CSF1-induced phosphorylation of human c-fms. In addition, this antibody caused immunoprecipitation of human c-fms and its known single nucleotide polymorphism (SNP) 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 c-fms. Therefore, a surrogate anti-mouse c-fms antibody, M279, was developed and tested for activity to be used in nonclinical tumor model studies in mice. This antibody, in an analogous manner to AMB-05X, potently and specifically inhibits c-fms-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, TAM content in all tumors treated with M279 compared with control-treated was shown to be significantly decreased by a variety of methods, including immunohistochemistry (IHC), flow cytometry, and immunofluorescence.

2.3.2. Pharmacokinetics

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

Toxicokinetics (TK) of AMB-05X, as assessed in both the 4-week and 14-week repeat-dose toxicity studies, did not differ markedly between male and female monkeys. In general, exposure to 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, treatment-associated anti-AMB-05X-binding antibodies (ADAs) in monkeys administered AMB-05X 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 the exposure of 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 the in vivo toxicology studies in the cynomolgus monkey, animals received up to 300 mg/kg, IV, weekly for 4 or 14 weeks. In the 4-week and in both 14-week studies, all direct AMB-05X-related findings were attributed to the 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 on 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 are considered 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 and decreased number of osteoclasts, and decreases in serum markers of bone turnover, both 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 GLP cynomolgus monkey studies with repeat-administration AMB-820 (AMB-05X) for 14-weeks. In these studies, peak serum concentrations over the dosing period were [redacted] mg/mL which would translate to [redacted] µg/mL steady-state synovial fluid concentrations (Stepensky, 2012; AmMax modeling; AMB051-20-NHP1 study results).

2.3.4. Non-Human Primate Intra-articular Administration of AMB-05X

The clinical formulation of AMB-05X was sequentially injected at two dose levels into the knees of 4 normal male 6-10 kg cynomolgus monkeys (AMB051-20-NHP1 CRL-Reno). On Day 1, anesthetized animals received a dose of 1.5 mg/kg (a human-equivalent dose of ~100 mg), 0.035 mL/kg and a time-course of serum sampling was performed over the following week and the injected knee was sampled for synovial drug levels on Day 8. Three weeks after the first IA administration, the protocol called for injection of the other knee at 5 mg/kg ([redacted] mL/kg of the [redacted]/mL AMB-05X formulation), but the animals were inadvertently dosed at ~0.04 mL/kg again and hence, ~2.5 mg/kg or a human equivalent of ~160 mg. Serum sampling was performed at various time points over a two-week period and synovial drug levels were analyzed one- and two-weeks post dosing. Clinical observations and animal mobility were assessed daily and knee range-of-motion testing was performed on both knees (i.e. with and without AMB-05X dosing) was performed on Days 2 and 7 of each dosing cycle. Food consumption and body weights were additionally monitored. Regardless of the administered dose or time point of examination, there were no observations of abnormal behavior, mobility, or altered knee range of motion measurements. AMB-05X drug levels were generally consistent with modeled projections and was generally linear between the two dose levels. For example, at the [redacted] mg/kg IA dose, the serum AMB-05X C_{max} was [redacted] µg/mL (mean ± SD) and declined to [redacted] µg/mL over the week following dosing. Following the second dosing interval (~2.5 mg/kg), two of four animals had serum and synovial drug levels approximately linearly increased from the 1.5 mg/kg dose and 2 had very low synovial and systemic exposures, potentially related to ADA and currently under investigation. Serum AUC_{last} values averaged [redacted] µg·hr/mL at [redacted] mg/kg and [redacted] µg·hr/mL at [redacted] mg/kg (for the two animals with substantial exposures). The knee synovial fluid AMB-05X concentration 7 days post-dose was [redacted] µg/mL ([redacted] nM) for both dose levels.

2.3.5. Clinical Safety Extrapolation

The projected human synovial fluid concentrations are projected to be [redacted] µg/mL ([redacted] nM) throughout a 2-week intra-articular dosing regimen of 150 mg (or greater). This synovial concentration is well above a projected effective concentration. From a systemic exposure perspective, as described above, intra-articular dosing of cynomolgus monkey knees at or above the clinical regimen appeared safe and well-tolerated. Importantly and as anticipated, serum

exposures remained very low - significantly below that associated with any transaminase elevations in Amgen's Phase 1/2 monotherapy study in patients with advanced solid tumors (Papadopoulos, 2017). As reported, no transaminase elevations or other AEs of concern were observed at an exposure of [redacted] µg·hr/mL (1.5 mg/kg IV) and limited AST elevation or other AEs were observed at [redacted] µg·hr/mL (3 mg/kg IV). Systemic exposures in the 14-week i.v. monkey GLP toxicology wherein findings through 300 mg/kg were related to exaggerated pharmacology far exceeded anticipated systemic exposures in the pending clinical trial. Thus, nonclinical and prior clinical study results support the 12-week intra-articular dosing trial as designed.

2.4. Summary of Clinical Data

2.4.1. Clinical Studies of AMB-05X

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

2.4.1.1. Monotherapy Study

The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of IV infusion of AMB-05X were evaluated in a first-in-human study in subjects with advanced solid tumors (Papadopoulos, 2017). The initial study design was based on weekly IV infusions of AMB-05X at a starting dose of 0.5 mg/kg. In subsequent cohorts, the dosing regimen was revised to IV infusion over a 60-minute period Q2W. Escalation of AMB-05X dose was advanced through the 1.5, 3, 6, 10, and 20 mg/kg levels.

All 25 subjects (100%) had measurable disease at baseline by local assessment, supporting enrollment in the study. Per 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 (the readings of subject response did not fully overlap in central versus local assessments). Per central assessment, 1 subject (with stable disease) had a > 20% reduction in tumor burden per Response Evaluation Criteria in Solid Tumors (RECIST); per local assessment, 1 subject (with partial response) had a 40% reduction in tumor burden. The maximum percentage change from baseline in tumor volume was a median of 19.32% (range: -24.0% to 104.8%).

All 25 subjects (100%) had at least 1 treatment-emergent adverse event; 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 adverse events that were at least Grade 3 in severity and 5 (20%) had adverse events that were at least Grade 4.

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

Serious adverse events were reported for 11 subjects (44%), adverse events leading to study discontinuation were reported for 4 subjects (16%), and adverse events leading to withdrawal from investigational product were reported for 5 subjects (20%). Fatal adverse events 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.

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

Macrophages were quantitated on 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, reductions from baseline in macrophages, as indicated by positive staining for CD68 and/or CD163, were observed at week 5.

2.4.1.2. Combination Study with Pembrolizumab

The primary objective of Study 20150195 was to evaluate the safety, tolerability, and objective response rate (ORR) of AMB-05X administered in combination with pembrolizumab in subjects with select advanced solid tumors.

This 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 1400 mg AMB-05X plus 200 mg pembrolizumab every 3 weeks (Q3W). Part 2 (phase 2) further evaluated the 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.

A total of 15 subjects were enrolled in part 1 of the study, all of whom received ≥ 1 dose of AMB-05X and pembrolizumab. Subjects were treated with AMB-05X and pembrolizumab for a mean (SD) of 0.8 (0.7) months. In part 2 of the study, 101 subjects were enrolled all of whom received ≥ 1 dose of AMB-05X and pembrolizumab. Ninety (90) subjects received AMB-05X 1100 mg every 3 weeks plus pembrolizumab 200 mg every 3 weeks and 11 subjects received AMB-05X 1400 mg every 3 weeks plus pembrolizumab 200 mg every 3 weeks. Subjects were treated with AMB-05X and pembrolizumab for a mean (SD) of 1.6 (2.5) months.

The objective response rate was 0% in Part 1 and 3.0% in Part 2.

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 1100 to 1400 mg. Mean C_{max} and mean AUC over the dosing interval τ (AUC_{τ}) increased by 1.4- and 1.5-fold, respectively, in cycle 1 and 1.4-fold and 1.5-fold, respectively, in cycle 2, for a 1.3-fold increase in dose. Median time to reach C_{max} (t_{max}) values ranged from 2.0 to 3.0 hours postdose in cycles 1 and 2. No significant serum accumulation of

AMB-05X was observed in subjects between cycles 1 and 2 with mean accumulation ratio for AUC_{τ} ranging from 1.25 to 1.27.

In Part 1, one subject (14.3%) in the AMB-05X 1400 mg plus pembrolizumab 200 mg group had dose-limiting toxicities (DLTs) of autoimmune pancreatitis, autoimmune hepatitis, cholecystitis, and electrolyte imbalance, after which the AMB-05X dose was decreased to 1100 mg. No subject in the AMB-05X 1100 mg plus pembrolizumab 200 mg group had a DLT. All subjects had ≥1 TEAE. The most common adverse events were fatigue (66.7%), aspartate aminotransferase 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, including 6 subjects (40.0%) who had Grade 4 events and 5 subjects (33.3%) who had fatal (Grade 5) adverse events. All of the fatal (Grade 5) adverse events were not considered related to study treatment. Seven subjects (46.7%) had ≥1 SAEs, none of which occurred in more than 1 subject. Adverse events considered treatment-related to AMB-05X were reported in 12 subjects (80.0%). The most common AMB-05X–related adverse events were periorbital edema and aspartate aminotransferase increased (each in 46.7% of subjects) and fatigue (26.7%). No subject had a TEAE leading to withdrawal of investigational product. No clinically relevant trends in hematology, serum chemistry, or urinalysis laboratory values were reported.

In Part 2, 6 subjects (5.9%) who received AMB-05X 1100 mg plus pembrolizumab 200 mg had DLTs of aspartate aminotransferase increased (2 subjects) and fatigue, lipase increased, epilepsy, rash generalized, and rash maculo-papular (1 subject each). All subjects (100.0%) had ≥1 TEAA. The most common adverse events 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, including 68 subjects (67.3%) who had Grade 4 events and 57 subjects (56.4%) who had fatal (Grade 5) adverse events. Of the fatal (Grade 5) adverse events, only tumor flare and pneumonitis (1 subject each) were considered related to study treatment. Seventy-three subjects (72.3%) had ≥1 or more SAEs. The most common SAEs were pyrexia (6.9%) and pneumonia and urinary tract infection (each in 5.0% of subjects). TEAEs considered treatment-related to AMB-05X were reported in 90 subjects (89.1%) and 86 subjects (85.1%), respectively. The most common AMB-05X–related adverse events were aspartate aminotransferase increased (53.5%), periorbital edema (38.6%), and fatigue (30.7%). Seventeen subjects (16.8%) had a treatment-emergent adverse event leading to withdrawal of investigational product. The only treatment-emergent adverse events leading to withdrawal reported in more than 1 subject were periorbital edema and pneumonitis (2 subjects each). During the study, 4 subjects (4.0%) treated with AMB-05X and pembrolizumab had liver function test results that potentially met the criteria of Hy's Law (ALT or AST > 3 x ULN and total bilirubin> 2 x ULN and alkaline phosphatase < 2 x 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.

2.4.2. Intra-articular Administration of Antibodies in Clinical Studies

There are multiple reports of the intra-articular administration of antibodies, typically into the knee for arthritic conditions, at doses ranging 10-600 mg (more commonly 100-150 mg) which

have been generally well-tolerated (Evans, 2014; Wang, 2018). Notably, there is also a case report for 100 mg bevacizumab (Avastin^{R}, anti-VEGF) administered monthly for 1 year intra-articular to the knee of a GCT patient with no adverse local nor systemic effects (Nissen, 2014).

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives of this study are to evaluate the safety and efficacy of AB-05X post intra-articular injection of 150 mg biweekly for up to 12 weeks in the treatment of TGCT.

3.1. Primary Endpoint

The primary outcome measure is the frequency and severity of reported TEAEs.

3.2. Secondary Endpoints

1. The 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) at Week 12
2. 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 activity
3. Mean change from Baseline in ROM score
4. Mean change from Baseline in the PROMIS Physical Function score
5. Mean change from Baseline in Worst Stiffness NRS score
6. Percentage of subjects who respond with a decrease of at least 30% in mean BPI score
7. Mean change from Baseline in BPI
8. Mean change from Baseline in Worst Pain NRS score
9. EQ-5D-5L Health Assessment
10. Serum and synovial CSF1 levels
11. Serum and synovial AMB-05X levels
12. Serum and synovial anti-AMB-05X antibody levels

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 2, multicenter study with an adaptive design that will enroll approximately 12 subjects with TGCT of the knee for 12 weeks of multiple-dose, open-label treatment with AMB-05X.

The study schema is provided in Section 1.2, and the Schedule of Events is provided in Section 1.3. The subject will sign an informed consent prior to any study screening activities. 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. Clinic visits will occur at Screening (Visit 1; within 4 weeks prior to Baseline); Baseline/Week 0 (Visit 2; when subjects receive their first injection of AMB-05X); Week 2 (Visit 3); Week 4 (Visit 4); Week 6 (Visit 5); Week 8 (Visit 6); Week 10 (Visit 7, when subjects receive their last injection of AMB-05X); Week 12 (Visit 8, end of treatment period and assessment of primary and secondary efficacy endpoints); Week 14 (Visit 9, for post-treatment follow-up 2 weeks after completing the treatment period); and Week 24 (Visit 10, for final post-treatment follow-up 12 weeks after completing the treatment period).

The study will begin dosing AMB-05X at 150 mg administered via intra-articular injection to the affected knee joint. Subjects will receive an injection of AMB-05X once every 2 weeks for 12 weeks (for 6 treatments total).

Tumor assessment via centrally read MRI will be performed at Screening and Weeks 6, 12, and 24. Worst pain NRS, worst stiffness NRS, PROMIS, BPI, and joint ROM will be evaluated periodically throughout the study.

Safety will be characterized, including reported AEs and SAEs and changes in physical examinations, vital signs, clinical laboratory studies (including pregnancy testing for females of childbearing potential), and ECGs.

For PK, serum AMB-05X concentrations will be measured at Week 0 (pre-dose and 2 hours after first dose), Week 2 (pre-dose [trough]), and Week 10 during steady state (including pre-dose [trough] and 2 hours after the last dose). Synovial AMB-05X concentrations will be measured at pre-dose at Weeks 0, 2, 4, 6, 8, and 10.

For PD, serum CSF1 levels will be measured at Week 0 (including pre-dose and 2 hours after first dose), Week 2 (pre-dose [trough]), and Week 10 during steady state (including pre-dose [trough] and 2 hours after the last dose). Synovial CSF1 levels will be measured at pre-dose at Weeks 0, 2, 4, 6, 8, and 10.

Serum anti-AMB-05X antibody levels will be measured pre-dose at Week 0 and Week 10. Synovial anti-AMB-05X antibody levels will be measured pre-dose at Weeks 0, 4, and 10.

Safety, PK, PD, and efficacy assessments will be reviewed by the Sponsor on a continuous, subject-by-subject basis to determine whether the assigned dose is appropriate. Depending on these results, the Sponsor may either decrease the dosage strength to 90 mg or increase the dosage strength to 210 mg in subsequent subjects who enroll. In general, subjects are expected to complete the study at the dose strength which they started the study, unless they experience a clinically significant AE that would warrant a dose reduction. As a general rule, clinically

significant AEs include, but are not limited to, any AE considered to be at least possibly related to study drug and severe in intensity or meets the criteria for a SAE. Subjects who are unable to tolerate a dosage strength of 90 mg will be withdrawn from the study

When at least 3 subjects have completed Week 6, a data monitoring committee (DMC) will review the available safety, tolerability, PK, PD, and efficacy data. Study enrollment and conduct may continue unchanged during DMC review. Based on the recommendations of the DMC, the Sponsor may then implement any one of the following adaptive changes without a protocol amendment:

- Continuation of enrollment under the existing design, without any changes to the study.
- Continuation of enrollment with a new dose or dose frequency criteria. Specifically, the DMC may recommend a dose reduction to 90 mg or a dose increase to 210 mg in subsequent subjects. Subjects may not exceed a dose of 210 mg or go below a dose of 90 mg. Subjects who are unable to tolerate a dose of 90 mg will be discontinued from the study.
- Discontinuation of further enrollment and/or suspension/termination of the study

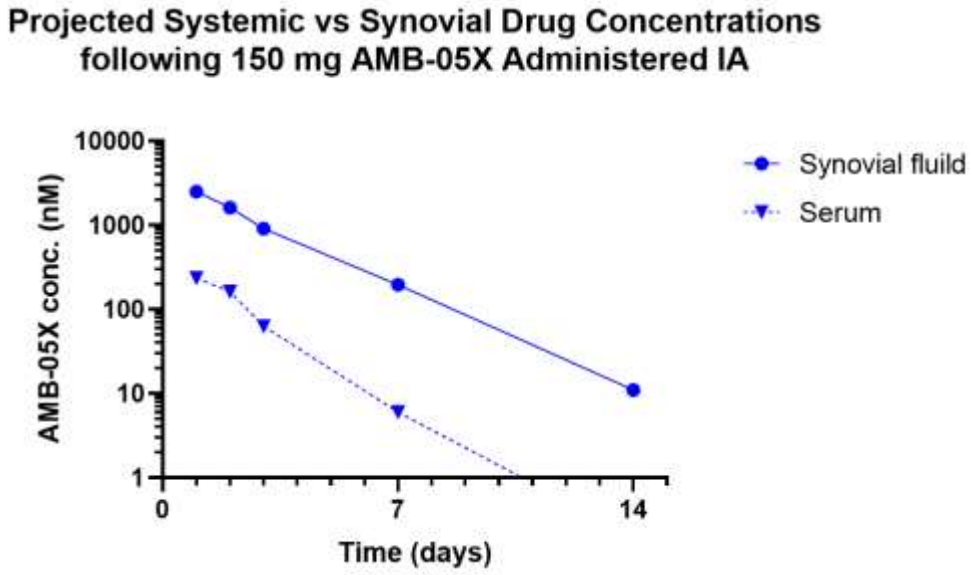
Thereafter, the DMC should continue to review available data on a regular basis throughout the study (each time 3 subjects complete study treatment) and provide ongoing recommendations regarding appropriate next steps in study conduct (as outlined above). If a change in dose is made during the study, the DMC will again review the available data when 3 subjects have completed Week 6 at the new dose and provide further recommendations as outlined above.

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

4.2. Rationale for Dose Regimen and Duration of Treatment

While AMB-05X has not been administered into the joints of TGCT patients, monoclonal antibodies (mAbs) have been used as intra-articular therapies at doses ranging from 10 to 600 mg, albeit more commonly at 100 to 150 mg in adults (Wang, 2018; Evans, 2014; NCT01160822). Moreover, another anti-CSF1R mAb has demonstrated preliminary efficacy administered systemically to TGCT patients (Cassier, 2015) thus supporting the class approach.

There is limited data in the literature on the synovial and systemic pharmacokinetics of antibodies following intra-articular administration, but based on the cynomolgus monkey results described above, published systemic PK with this mAb (Papadopoulos, 2017), and some published relevant modeling data (Stepensky, 2012), a projection of serum and synovial AMB-05X concentrations vs time following a first administration of 150 mg intra-articular is described in the figure below:



The estimated systemic exposure is consistent with safe and well-tolerated regimens from the prior Phase 1 study and the synovial fluid concentrations are projected to remain well above an effective level throughout the 12-week, bimonthly dosing period.

4.3. Number of Subjects

This study will enroll approximately 12 male and female adult subjects with local or diffuse TGCT.

4.4. Treatment Assignment

This is an open-label study. Subjects will be initially assigned to receive 150 mg administered via intra-articular injection to the affected knee joint. Subjects will receive an injection of AMB-05X once every 2 weeks for 12 weeks (for 6 treatments total). The Sponsor may decrease the dose to 90 mg or increase the dose to 210 mg in subsequent subjects based on its ongoing review of the available data.

4.5. Subject and Study Early Termination

4.5.1. 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 required for that subject, including the last follow-up visit.

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

4.5.2. Subject Early Termination

Subjects can choose to discontinue study participation at any time, for any reason, specified or unspecified, without prejudice. Subjects may be considered withdrawn and subject to ET procedures if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The Investigator will terminate a subject's study participation if the subject withdraws consent, the subject becomes pregnant, or the Investigator concludes that continuation would be detrimental to the subject's safety or well-being.

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.

If ET occurs for any reason, the Investigator must make every effort to determine the primary reason for a subject's early withdrawal from the study and record this information on the electronic case report form (eCRF).

All subjects who receive study drug after enrollment at Visit 2 and discontinue prior to Visit 8 should complete the procedures for Visit 8/ET and Visit 9 follow-up. Subjects who discontinue after Visit 8 should complete the procedures for Visit 9 follow-up. All subjects who complete study treatment should be encouraged to return for Visit 10 (12 weeks post-treatment).

Reasons a subject may terminate participation early include:

- Adverse event
- Death
- Protocol violation
- Physician decision
- Withdrawal of consent by the subject
- Study terminated by Sponsor
- Lost to follow-up
- Lack of efficacy
- Other, to be specified

4.5.3. Study Premature Termination

This study may be stopped prematurely, that is, before completion as defined in this protocol, by AmMax or a controlling regulatory authority if new information arises that suggests continuing the study may pose an undue risk to subject safety or well-being.

AmMax will review emerging safety data to identify safety and tolerability signals. These data include AEs and their associated frequency and severity, TEAEs, SAEs, suspected unexpected serious adverse reactions, 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.

5. SELECTION OF SUBJECTS

This study will enroll approximately 12 qualified subjects ≥ 18 years old with TGCT of the knee. The study will enroll subjects at approximately 10 investigative sites in the United States and Europe.

5.1. Subject Inclusion Criteria

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

1. Subject ≥ 18 years 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 Health Insurance Portability and Accountability Act (HIPAA) authorization, if applicable, prior to the conduct of any study-specific procedures.
2. A diagnosis of TGCT of the knee joint that has been histologically confirmed either by a pathologist at the treating institution or by a central pathologist. If not previously confirmed, biopsy with histological confirmation is required.
3. Measurable disease of at least 1 cm and based on RECIST v1.1 (Eisenhauer, 2009) assessed from MRI scans by a central radiologist. Subjects with one knee joint involvement only, and only limited posterior extra-articular nodular TGCT lesions as assessed by central radiologist and tumor review committee.
4. Stable prescription of analgesic regimen during the 2 weeks before Baseline
5. Negative urine drug screen (UDS) at Screening and Baseline
6. Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline
7. Agrees to follow contraception guidelines (see Section 5.3)
8. Adequate hematologic, hepatic, and renal function, at Screening visit, defined by:
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - AST or ALT ≤ 1.5 × ULN
   - Hemoglobin > 10 g/dL
   - Total bilirubin ≤ 1.5 × ULN
   - Platelet count ≥ 100×10^9/L
   - Serum creatinine ≤ 1.5 × ULN
9. Willing and able to complete the BPI, Worst Stiffness NRS item, PROMIS Physical Function Scale, EQ-5D-5L, and other self-assessment instruments throughout the study

5.2. Subject Exclusion Criteria

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

1. Prior investigational drug use within 4 weeks or 5 half-lives (whichever is longer) before Baseline

2. Use of pexidartinib, any other oral tyrosine kinase inhibitors (e.g., imatinib or nilotinib), or any biologic treatment targeting CSF1 or CSF1R within 3 months before Baseline
3. History of extensive or reconstructive knee surgery, except for prior diagnostic synovectomy, which is not exclusionary if at least 3 months prior to Baseline
4. Active cancer (either currently or within 1 year before Baseline) that requires therapy (e.g., surgery, chemotherapy, or radiation therapy), with the exception of 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
6. HCV or HBV or known active or chronic infection with HIV
7. Known active tuberculosis
8. 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 his or her results
9. Women who are breastfeeding
10. A screening Fridericia-corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women)
11. MRI contraindications (e.g., pacemaker, loose metallic implants)
12. History of hypersensitivity to any ingredient of the study drug
13. History of drug or alcohol abuse within 3 months before the first dose of study drug
14. 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 or interfere with interpretation of study results and, in the Investigator's opinion, make the subject inappropriate for this study
15. Subjects who, in the Investigator's opinion, should not participate in the study for any reason, including if there is a question about their ability to comply with study requirements

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) and agrees to remain abstinent throughout the study and for 90 days after the last dose of study drug. Periodic abstinence (e.g., 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. She has only 1 male sexual partner, that partner is vasectomized, and the vasectomized partner has received medical assessment 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 of one of the following:
   a. He is in Tanner Stage 1 (preadolescent).
   b. 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) and agrees to remain abstinent throughout the study and for 90 days after the last dose of study drug. Periodic abstinence (e.g., 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 assessment 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. ASSESSMENTS BY STUDY VISIT

Section 1.3 provides the Schedule of Events for this study. Visits should be planned according to the schedule to ensure subjects receive 12 weeks of treatment and 12 weeks of follow-up.

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

6.1. Visit 1 / Screening

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

- Assign a Subject ID. Each subject will be assigned a 6-digit Subject ID that consists of a 3-digit number representing the study site and a 3-digit subject number, sequential within each study site.
  - Thus, if the center number is 101, Subject IDs will be assigned as 101-001, 101-002, 101-003, etc., in ascending order. If the center number is 202, the Subject IDs will be 202-001, 202-002, 202-003, etc., in ascending order.
- Collect demographic information and take medical history.
- Record all concomitant medications, including dose amount and dosing frequency, taken within 4 weeks prior to Screening.
- 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 (including height and weight).
- Perform a 12-lead ECG.
- Collect blood samples for clinical laboratory tests (chemistry and hematology), HBV, HCV, HIV, TB (QuantiFERON), and serum pregnancy test for females of childbearing potential.
- Collect a urine sample for urinalysis and urine drug screen.
- Perform MRI.
- Tumor assessment.
- Tumor biopsy for subjects who do not have histologically confirmed TGCT. Any required biopsies should be performed after MRI review of the tumor by the central reader.
- Perform the following clinical assessments:
  - Worst stiffness NRS
  - PROMIS Physical Function Scale
  - BPI
  - EQ-5D-5L
  - Joint ROM
- Review results and confirm eligibility.

Individuals who successfully complete Screening procedures and meet all eligibility criteria may be enrolled in the study. These subjects 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 subject who does not meet study eligibility criteria, capture screen failure information, report screen failure status, and record any changes in concomitant medications and AEs since Screening.

6.2. Visit 2 / Baseline (Day 1, Week 0)

6.2.1. Visit 2 – Pre-dose Procedures

Confirm that subject meets all inclusion/exclusion criteria, then complete the following procedures prior to administration of first dose of study drug:

- Perform a urine pregnancy test for female subjects of childbearing potential.
  - Any subject with a positive result will be recorded as a screen failure.
- Collect a urine sample for urinalysis and urine drug screen.
- Update any changes in concomitant medications since Visit 1 (Screening).
- Record any AEs that may have occurred since the subject signed the ICF. AEs that occur before the first application of study drug will be recorded as such to distinguish them from TEAEs.
- Conduct a full physical exam and document any changes since the previous visit.
- 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.
- Perform a 12-lead ECG.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect serum samples prior to dosing for measurement of AMB-05X concentration, CSF1 levels, and anti-AMB-05X antibodies.
- Collect synovial fluid for measurement of AMB-05X concentration, CSF1 levels, and anti-AMB-05X antibodies.
- Perform the following clinical assessments:
  - Worst stiffness NRS
  - PROMIS Physical Function Scale
  - BPI
  - EQ-5D-5L
  - Joint ROM

6.2.2. Visit 2 – Dosing and Post-dose Procedures

- Inject study drug.

- Observe subject for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.
- Collect serum samples for measurement of AMB-05X concentration and CSF1 levels at 2 hours post-dose.

6.3. Visit 3 (Week 2 ± 2 Days)

Complete the following procedures during the visit:

- Record any changes in concomitant medications since the previous visit.
- Record any AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Obtain weight.
- Collect serum samples prior to dosing for measurement of AMB-05X concentration and CSF1 levels.
- Collect synovial fluid for measurement of AMB-05X concentration and CSF1 levels prior to study drug injection.
- Inject study drug.
- Observe subject for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.

6.4. Visit 4 (Week 4 ± 2 Days)

Complete the following procedures during the visit:

- Perform a urine pregnancy test for female subjects of childbearing potential.
- Record any changes in concomitant medications since the previous visit.
- Record any AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Obtain weight.
- Collect synovial fluid for measurement of AMB-05X concentration, CSF1 levels, and anti-AMB-05X antibodies prior to study drug injection.
- Inject study drug.
- Observe subject for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.

6.5. Visit 5 (Week 6 ± 3 days)

Complete the following procedures during the visit:

- Record any changes in concomitant medications since the previous visit.

- Record any AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Conduct a full physical exam and document any changes since the previous visit.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Obtain weight.
- Perform a 12-lead ECG.
- Collect a urine sample for urinalysis.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Collect synovial fluid for measurement of AMB-05X concentration and CSF1 levels prior to study drug injection.
- Perform MRI.
- Tumor assessment.
- Perform the following clinical assessments:
  - Worst stiffness NRS
  - PROMIS Physical Function Scale
  - BPI
  - EQ-5D-5L
  - Joint ROM
- Inject study drug.
- Observe subject for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.

6.6. Visit 6 (Week 8 ± 3 days)

- Perform a urine pregnancy test for female subjects of childbearing potential.
- Record any changes in concomitant medications since the previous visit.
- Record any AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Obtain weight.
- Collect synovial fluid for measurement of AMB-05X concentration and CSF1 levels prior to study drug injection.
- Inject study drug.
- Observe subject for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.

6.7. Visit 7 (Week 10 ± 3 days)

- Record any changes in concomitant medications since the previous visit.
- Record any AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Obtain weight.
- Collect serum samples prior to dosing for measurement of AMB-05X concentration and CSF1 levels.
- Collect synovial fluid for measurement of AMB-05X concentration, CSF1 levels, and anti-AMB-05X antibodies prior to study drug injection.
- Inject study drug.
- Observe subject for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.
- Collect serum samples 2 hours post-dosing for measurement of AMB-05X concentration and CSF1 levels.

6.8. Visit 8 (Week 12 ± 3 days) or Early Termination

- Perform a urine pregnancy test for female subjects of childbearing potential.
- Record any changes in concomitant medications since the previous visit.
- Record any AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Conduct a full physical exam and document any changes since the previous visit.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Obtain weight.
- Perform a 12-lead ECG.
- Collect a urine sample for urinalysis.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Perform MRI.
- Tumor assessment.
- Perform the following clinical assessments:
  - Worst stiffness NRS
  - PROMIS Physical Function Scale
  - BPI
  - EQ-5D-5L
  - Joint ROM

6.9. Visit 9 (Week 14 ± 3 days)

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

6.10. Visit 10 (Week 24 ± 7 days)

- Record any changes in concomitant medications since the previous visit.
- Record any AEs that may have occurred since the previous visit and follow up on the status of any existing AEs.
- Conduct a full physical exam and document any changes since the previous visit.
- Measure vital signs (blood pressure, heart rate, temperature, and respiratory rate) with the subject in a sitting position after having rested for 5 minutes.
- Obtain weight.
- Collect a urine sample for urinalysis.
- Collect blood samples for clinical laboratory tests (chemistry and hematology).
- Perform MRI.
- Tumor assessment.
- Perform the following clinical assessments:
  - Worst stiffness NRS
  - PROMIS Physical Function Scale
  - BPI
  - EQ-5D-5L
  - Joint ROM

6.11. Early Termination Procedures

A subject who terminates from the study prior to Visit 8 should return to the site to complete the procedures for Visit 8/ET and Visit 9 follow-up. A subject who terminates from the study after Visit 8 should return to the site to complete the procedures for Visit 9 follow-up. All subjects who complete study treatment should be encouraged to return for Visit 10 (12 weeks post-treatment). Study personnel should make every effort to conduct all protocol-specified procedures to complete the study. Every effort should also be made to obtain a final MRI.

7. TREATMENT OF SUBJECTS

7.1. Description of Study Drug

Refer to Section 8.1 for information on the study drug.

7.2. Concomitant Medications

A review of concomitant medications will be conducted during the screening period.

The Investigator should instruct the subject to notify the study site about any new medications he/she takes after the start of the study or any medications they have stopped using.

All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered from the time the ICF is signed through Visit 10 or ET must be listed on the Concomitant Medications/Therapy eCRF.

7.3. Prohibited and Permitted Treatment

The following treatments are prohibited:

- Prior investigational drug use within 4 weeks or 5 half-lives (whichever is longer) before Baseline
- Use of pexidartinib, any other oral tyrosine kinase inhibitor (e.g., imatinib or nilotinib), or any biologic treatment targeting CSF1 or CSF1R within 3 months before Baseline and for the duration of the study

7.4. Treatment Compliance

Subject compliance with study treatment will be monitored by site staff administering study drug injections.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Study Drug, Labeling, Packaging, and Dispensing

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

Study drug is packaged as a [redacted] of [redacted] mL of [redacted] mg/mL in [redacted] mL glass vials. AMB-05X vials will be stored [redacted] °C until use.

8.2. Study Drug Storage

Study drugs must be received at the study site by a person designated by the study team, handled and stored safely and properly, and kept in a secured location that only the Investigator and designated staff can access.

Upon receipt, AMB-05X should be stored between [redacted] °C protected from light and according to the storage and expiration (where required) information provided on the label in the original container.

Storage conditions must be adequately monitored, and appropriate temperature logs maintained as source data.

8.3. Study Drug Administration

After confirmation of enrollment eligibility at Visit 2 (Baseline), subjects will be enrolled into the study and receive the first dose of study drug.

The study will begin dosing AMB-05X at 150 mg administered via intra-articular injection to the affected joint. Based on ongoing review of the available safety, PK, PD, and efficacy data, the Sponsor may decrease the dose to 90 mg or increase the dose to 210 mg in subsequent subjects. A separate Study Drug Administration Instructions will be provided with detailed study drug administration procedures.

A single vial will be removed from the kit [redacted] prior to administration. [redacted], diluted with [redacted] mL normal saline (0.9% NaCl solution), and mixed gently prior to injection. AMB-05X must be administered within [redacted] hours from the beginning of the warming procedure. For a dose of 150 mg, a total of [redacted] mL of the diluted solution will be withdrawn from the vial in a sterile syringe and administered via an intra-articular injection to the affected knee joint. For a dose of 210 mg, [redacted] mL of the diluted solution will be withdrawn, and for a dose of 90 mg, [redacted] mL of the diluted solution will be withdrawn.

Eligible subjects will receive the intra-articular injection of AMB-05X to the affected knee joint once every 2 weeks for 12 weeks (for 6 treatments total). The Sponsor may change the dose based on its own ongoing review or periodic DMC review of available data (each time 3 new subjects complete study treatment).

Study drug will be administered at the study center by qualified study staff. Subjects will remain at the study center for a minimum of 90 minutes after dosing to monitor for any adverse reactions, including any injection-site reactions.

8.4. Study Drug Accountability

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.

8.5. Study Drug Handling and Disposal

Only after receiving written authorization by AmMax or its designee, the Investigator will send all unused and empty vials of study drug to the address provided at the time of authorization for destruction.

With specific approval from AmMax, unused and empty vials of study drug may be destroyed at the site, following the standard operating procedures at the study site. The study staff must provide a drug destruction certificate to AmMax or its designee.

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. Screening Assessments

9.1.1. Demographic and Medical History

A complete medical history and review of body systems along with demographic data will be documented for all subjects during the screening period. All data up to the time of enrollment will also be recorded in the eCRF.

Any AE or change in the subject's condition or health status occurring after consent but prior to the first application of study drug will be recorded but not considered treatment emergent.

9.1.2. Tumor Biopsy

Tumor biopsy will be performed for subjects at Screening who do not have histologically confirmed TGCT. Any required biopsies should be performed after MRI review of the tumor by the central reader.

Tumor biopsy will be done via needle aspiration under CT or ultrasound guidance.

9.2. Efficacy Assessments

9.2.1. Tumor Assessment

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

9.2.2. MRI

A separate MRI Manual will be provided detailing MRI procedures. MRIs will be read and evaluated by a central independent blinded reader for assessment of tumor response.

TVS is a semi-quantitative MRI scoring system that describes tumor mass and is based on 10% increments in the estimated volume of the maximally distended synovial cavity or tendon sheath involved. 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.

9.3. Clinical Outcome Assessments

Clinical outcome assessments will include Worst Pain NRS, Worst Stiffness NRS, PROMIS Physical Function Scale, BPI, and evaluation of joint ROM.

9.3.1. Worst Stiffness NRS

This is a single item self-administered questionnaire designed to assess "worst" stiffness at the site of the tumor. This instrument uses an 11-point NRS, ranging from 0 ("no stiffness") to 10

("worst stiffness imaginable") (see Appendix 1). Subjects will be asked to recall their "worst" stiffness at the site of the tumor in the past 24 hours. Subjects will complete this assessment at Screening, Baseline (Week 0), Week 6, Week 12, and Week 14/ET.

9.3.2. PROMIS

The PROMIS Physical Function Scale will be used to assess physical function of the upper and lower limbs (see Appendix 2). The scale ranges from 1 ('unable to do' or 'cannot do') to 5 ('without any difficulty' or 'not at all'), where higher scores represent better outcomes.

9.3.3. BPI

The BPI Short Form is a self-administered questionnaire used to evaluate the severity of a subject's pain and the impact of this pain on the subject's daily functioning (see Appendix 3). The subject is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a scale from 0-10.

9.3.4. EQ-5D-5L Health Assessment

The EQ-5D-5L assessment is a widely used quality of life instrument that includes questions in each of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The choices include 5 levels of severity for each domain followed by a general health VAS (see Appendix 4).

9.3.5. ROM

ROM of the joint will be assessed by qualified assessors at the clinical site. Measurements will be recorded in degrees. At baseline, the plane of movement with the smallest (worst) relative value will be identified; only this plane will be used for evaluating change in ROM subsequently.

9.4. Pharmacokinetic/Pharmacodynamic Assessments

Serum AMB-05X concentrations will be measured at Week 0 (pre-dose and 2 hours after the first dose), Week 2 (pre-dose [trough]), and Week 10 during steady state (including pre-dose [trough] and 2 hour after the last dose). Synovial AMB-05X concentrations will be measured pre-dose at Weeks 0, 2, 4, 6, 8, and 10.

Serum CSF1 levels will be measured at Week 0 (including pre-dose and 2 hours after first dose), Week 2 (pre-dose [trough]), and Week 10 during steady state (including pre-dose [trough] and 2 hours after the last dose). Synovial CSF1 levels will be measured pre-dose at Weeks 0, 2, 4, 6, 8, and 10. CSF1 will be measured by ELISA analysis.

Serum anti-AMB-05X antibody levels will be measured pre-dose at Week 0 and at Week 10. Synovial anti-AMB-05X antibody levels will be measured pre-dose at Weeks 0, 4, and 10.

9.5. Safety Assessments

Safety and tolerability will be assessed on an ongoing basis by monitoring adverse events (AEs) (including any serious AEs [SAEs], AEs leading to withdrawal, injection-site reactions [ISRs], and any other dose-limiting toxicities [DLTs]), physical examinations/vital signs, changes in clinical laboratory values, and ECG results.

A DMC composed of qualified medical/clinical representatives will review the clinical data each time 3 new subjects complete treatment. The DMC will provide recommendations to the Sponsor regarding the acceptability of continued enrollment in the study and whether any modifications are warranted.

Safety will be assessed with the following parameters:

- Reported AEs (see Section 9.6) and concomitant medications (see Section 7.2)
- Vital signs (including body weight, blood pressure, heart rate, temperature, and respiratory rate)
- Physical examination
- ECG
- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- Pregnancy test

9.5.1. 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.

9.5.2. 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 site. Significant findings that are present prior to the start of study drug must be included in the medical history / current medical conditions page of the eCRF.

Significant findings made after the start of study drug that meet the definition of an AE must be recorded on the AE page of the eCRF.

9.5.3. Electrocardiogram

Standard 12-lead ECGs will be performed. The Subject ID and the subject's initials or date of birth (as permitted by applicable practice), 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 sites.

9.5.4. Clinical Laboratory Tests

Blood samples will be drawn for chemistry and hematology. Urine samples will be collected for urinalysis and urine drug screen. Details on sample collection and processing will be described in the laboratory manual.

9.5.5. Pregnancy Tests

For each female of childbearing potential, a serum pregnancy test will be performed at Visit 1 (Screening) and a urine pregnancy test will be performed at visits specified in the Schedule of Events and at the discretion of the Investigator (e.g., for a subject with irregular menses).

The result 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 during Visit 2.

9.6. Adverse Events and Serious Adverse Events

9.6.1. 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 (e.g., 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 (e.g., 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.

9.6.2. 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 SAEs when, based upon appropriate medical judgment, the event may jeopardize the subject or 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.

9.6.3. Classification of an Adverse Event

9.6.3.1. 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 assessed according to the following scale:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.6.3.2. 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 (e.g., the event occurred within a reasonable time after administration of the study drug). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after

discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **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 (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related**: The AE is completely independent of study 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 '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.

9.6.3.3. 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 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.

9.6.4. 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 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 (e.g., 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.

9.6.5. 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 9.6.3.1), relationship to study drug (causality) (Section 9.6.3.2), action taken, outcome, and date of resolution (or continuing) will be recorded. The Investigator must make a causality assessment for each AE.

9.6.6. Serious Adverse Event Reporting and Follow-up

Any SAE, including death, due to any cause, that occurs from the time the ICF is signed until 4 weeks after a subject's last dose of study drug must be reported to the Sponsor or its designee within 24 hours of the study center staff learning of its occurrence.

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria and to do so in an expedited fashion. Specifically, suspected, unexpected serious adverse reactions (SUSARs) are subject to expedited safety reporting requirements. The Sponsor will report applicable SAEs to the appropriate authorities within the timelines and format required by local regulations. Therefore, the Sponsor must be notified of any SAE that occurs after informed consent is obtained within 24 hours of the study center staff learning of its occurrence.

An SAE Form must be completed and reported via email at saereporting@egeeninc.com. All SAEs must be recorded on the AE page of the eCRF, marking the event as serious within the form. 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.

SAEs must also be reported to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) according to the requirements of the IRB/IEC.

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. All SAEs will be followed until no further medical intervention is warranted (e.g., the event resolves, becomes medically stable, or is assessed as chronic) or until the subject is lost to follow-up. Follow-up information on the SAE will also be reported using the AE eCRF.

The Sponsor or designee may contact the study center to solicit additional information or 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 emailed to the safety inbox after redacting all information that personally identifies the subject or hospital staff (per the European Global Data Protection Regulation).

After 4 weeks after a subject's last dose of study drug, 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.

9.7. Pregnancy

Any pregnancy in a female subject or in the partner of a male subject that occurs from the time the subject signs an ICF until 90 days after the final application of study drug must be reported to AmMax or its designee within 24 hours of learning of its occurrence. A pregnant female subject will be immediately discontinued from study drug.

The subject or pregnant partner should provide consent and be followed throughout the course of the pregnancy. Pregnancy follow-up information, including the outcome of the pregnancy, should be reported to AmMax or its designee.

9.8. Pharmacokinetic Assessments

Serum and synovial fluid will be collected from all subjects to assess AMB-05X concentrations and anti-drug antibody formation at the visits indicated in the Schedule of Events.

9.9. Blood and Synovial Fluid Sampling

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

Synovial fluid (2 mL) will be collected from the affected joint prior to injection of study drug at Weeks 0, 2, 4, 6, 8, and 10. The expected total sampling volume over the course of the study is up to 12 mL.

10. STATISTICS

10.1. General Considerations

All study data will be summarized by treatment using descriptive statistics. Unless otherwise specified, descriptive statistics for numeric data (e.g., age, weight) will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical/qualitative data (e.g., sex, race) will be presented using absolute and relative frequency counts and percentages. All summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.3 or later of SAS software (SAS Institute, Inc., Cary, North Carolina).

A detailed final SAP will be provided separately. The SAP will be finalized prior to the first DMC meeting.

10.2. Sample Size Determination

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

10.3. 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.

10.4. Pharmacokinetic Analysis

AMB-05X concentration data will be summarized by collection time. PK parameters will be deduced where possible by WinNonlin analysis.

10.5. Safety Analyses

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

The number of subjects exposed to each treatment group 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 recorded after first dose of study drug. Verbatim terms will be mapped to Preferred Terms (PTs) and related System Organ Classes (SOCs) using Medical Dictionary for Regulatory Activities (MedDRA). PTs and SOCs will be tabulated by treatment group. All reported AEs will be summarized by the number of subjects reporting AEs, 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 TEAEs will be summarized by SOC, PT, and treatment group:

- Incidence of all TEAEs
- Incidence of all TEAEs by maximum severity (severe, moderate, and mild) specified by investigators

- Incidence of TEAEs related to the study drug as determined by the investigators
- Incidence of serious TEAEs
- Incidence of TEAEs leading to early discontinuation withdrawn from study

Safety labs (including hematology, chemistry, and urinalysis) 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 in all laboratory variables will be provided.

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. For ECG parameters, heart rate, RR, PR, QRS, and QT corrected with Fridericia's formula (QTcF) will be summarized by treatment group.

Concomitant medication usage will be summarized by treatment group. 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.

11. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

11.1. Source Documents

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 (i.e., original records or certified copies).

Source documents and the eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source document/eCRF. The source document/eCRF 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 sign and date at the end of the source document/eCRF to endorse the recorded data.

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

11.2. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of AmMax will visit the investigational study 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 AmMax or its representatives. This will be documented in a Clinical Study Agreement between AmMax and the investigator.

During the study, a monitor from AmMax or representative will have regular contacts with the investigational site, for the following:

- 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 in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms 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 (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to AmMax.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to AmMax and those SAEs that met criteria for reporting have been forwarded to the IRB.

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

11.3. Audits and Inspections

Authorized representatives of AmMax, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board 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 a AmMax audit or inspection 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, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

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

12. ADMINISTRATIVE PROCEDURES

12.1. Ethics Review

The protocol and the ICF must be reviewed and approved by a properly constituted IRB/IEC before study start.

A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC and/or national competent authorities must be given to AmMax or designee before study initiation.

Prior to study start, the investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to AmMax monitors, auditors, AmMax' Quality Assurance representatives, IRBs/IECs/REBs, and regulatory authorities as required.

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

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

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

12.2. Good Clinical Practice

This study will be conducted in accordance with principles of GCP as promulgated by the ICH, the FDA and applicable local regulations. Good Clinical Practice 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 CGP 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 AmMax in conducting this study in accordance with those principles.

12.3. Written Informed Consent

A complete description of the study is to be presented to each potential study subject and a signed and dated (and witnessed, where required by law or regulation) 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 ICF and the HIPAA authorization, if applicable, prior to the conduct of any study-specific procedures.

All consent documents and procedures must comply with national laws, respective regulations, and IRBs/ECs relevant to the country where the subject participates.

All reasonable efforts should be taken by the study staff to ensure the subject is able to comprehend what participation means. All consent/assent documents will be provided in the subject's native language and in a form the subject is able to comprehend. Whenever possible, written informed consent should be sought from the subject as soon as he/she becomes capable of comprehending the scope of the study.

The process of obtaining informed consent must be documented in the subject source documents.

AmMax will provide to investigators in a separate document a proposed ICF that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by AmMax before submission to the IRB/IEC, and a copy of the approved version must be provided to the AmMax monitor after IRB/IEC approval.

Females of childbearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirement for the duration of the study. If there is any concern the subject will not reliably comply, they should not be entered in the study.

Male subjects must be informed of potential risks to the fetus of a partner if conception occurs during the study period.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

12.4. 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 AmMax or its designee and any regulatory authority access to the subject's original medical records for verification of 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 the applicable laws and regulations.

AmMax will comply with the requirements of the US HIPPA regulations, and the EU General Data Protection Regulation.

12.5. Protocol Deviation

Investigators will apply due diligence to avoid a protocol deviation. Unless there is a safety concern, there should be no deviations 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 AmMax or its designee and to the IRB/IEC (if required).

12.6. Protocol Amendment

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

12.7. Protocol Termination

AmMax has the right to terminate this study and remove all study material from the site at any time for medical or administrative reasons. AmMax will endeavor to give adequate notice to allow safe withdrawal of subjects from the study.

13. DATA HANDLING AND RECORDKEEPING

13.1. Case Report Forms

The study site staff should collect and record data for the study in the source documents, and transcribe into the Electronic Case Report Forms (eCRF) which uses fully validated software that conforms to 21 CFR Part 11 requirements. Site staff will not be given access to the EDC system until they have been trained.

The Investigator must ensure that complete data for the clinical study are collected and accurately documented in the appropriate sections of the eCRF and adequately supported by appropriate source documentation. In addition, it is the Investigator's responsibility to provide electronic signatures where requested indicating concurrence with data in the eCRF.

Data should be entered into the eCRF within three (3) working days of each visit.

13.2. Inspection of Records

AmMax or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. 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 relative to study conduct.

13.3. Retention of Records

Records of subjects, source documents, monitoring visit logs, eCRFs, inventories of study 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. At a minimum, records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable local regulatory requirements. However, the essential documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with AmMax.

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.

14. PUBLICATION POLICY

14.1. Clinical Trial Database

AmMax will post key design elements of this protocol in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be posted in a publicly accessible database of clinical trial results and may be submitted for publication.

14.2. Publishing Study Results

All information from the study will be regarded as confidential. The Investigator agrees not to publicly disclose such information in any way without prior written permission from AmMax.

AmMax must be notified of and be allowed to review and approve any potential publication of the results, either in part or in total, including articles in journals or newspapers, oral presentations, or abstracts, by the Investigator(s) or their representative(s), within a reasonable time frame. Study results cannot be published in violation of AmMax confidentiality restrictions or to the detriment of AmMax's intellectual property rights.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Committee comprising the Investigators participating in the study and representatives from the Sponsor will be formed to oversee the publication of study results, which will reflect the experience of all participating study centers.

Subsequently, individual Investigators may publish results from the study in compliance with their agreement with AmMax. A pre-publication manuscript is to be provided to AmMax at least 90 days prior to submission of the manuscript to a publisher. Similarly, AmMax will provide any AmMax-prepared manuscript to Investigators for review at least 30 days prior to submission to a publisher.

15. LIST OF REFERENCES

Benner B, Good L, Quiroga D, et al. Pexidartinib, a novel small molecule CSF-1R inhibitor is use for tenosynovial giant cell tumor: a systemiatic review of pre-clinical and clinical development. *Drug Des Devel Therapy.* 2020:14;1693-1704.

Brahmi M, Vinceneux A, Cassier PA. Current systemic treatment options for tenosynovial giant cell tumor/pigmented villonodular synovitis: targeting the CSF1/CSF1R Axis. *Curr Treat Options Oncol.* 2016;17(2):10.

Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. *Lancet Oncol.* 2015;16(8):949-956.

Cupp JS, Miller MA, Montgomery KD, et al. Translocation and expression of CSF1 in pigmented villonodular synovitis, tenosynovial giant cell tumor, rheumatoid arthritis and other reactive synovitides. *Am J Surg Pathol.* 2007;31(6):970-976.

de Saint Aubain Somerhausen N, van de Rijn M. Tenosynovial giant cell tumor: localized type / diffuse type. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, eds. *World Health Organization Classification of Tumours of Soft Tissue and Bone*. 4th ed. IARC Press; 2013:100-103.

Ehrenstein V, Andersen SL, Qazi I, et al. Tenosynovial giant cell tumor: incidence, prevalence, patient characteristics, and recurrence. A registry-based cohort study in Denmark. *J Rheumatol.* 2017;44(10):1476-1483.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

Evans CH, Kraus VB, Setton LA. Progress in intra-articular therapy. *Nat Rev Rheumatol*. 2014;10(1):11-22.

Gelderblom H, van de Sande M. Pexidartinib: first approved systemic therapy for patients with tenosynovial giant cell tumor. *Future Oncol*. 2020;16(29):2345-2356.

Giustini N, Bernthal NM, Bukata SV, Singh AS. Tenosynovial giant cell tumor: case report of a patient effectively treated with pexidartinib (PLX3397) and review of the literature. *Clin Sarcoma Res.* 2018;8:14.

Granowitz S, D'Antonio J, Mankin HL. The pathogenesis and long-term end results of pigmented villonodular synovitis. *Clin Orthop Relat Res*. 1976;(114):335-351.

Heads of Medicines Agencies. Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2014. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Mastboom MJL, Verspoor FGM, Verschoor AJ, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. *Acta Orthop.* 2017;88(6):688-694.

Mertens F, Orndal C, Mandahl N, et al. Chromosome aberrations in tenosynovial giant cell tumors and nontumorous synovial tissue. *Genes Chromosomes Cancer.* 1993;6:212-217.

Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: radiologic-pathologic correlation. *Radiographics.* 2008;28(5):1493-1518.

Nissen MJ, Boucher A, Brulhart L, Menetrey J, Gabay C. Efficacy of intra-articular bevacizumab for relapsing diffuse-type giant cell tumour. *Ann Rheum Dis*. 2014;73(5):947-948.

Ohjimi Y, Iwasaki H, Ishiguro M, et al. Short arm of chromosome 1 aberration recurrently found in pigmented villonodular synovitis. *Cancer Genet Cytogenet.* 1996;90:80-85.

Ostuni R, Kratochvill F, Murray PJ, Natoli G. Macrophages and cancer: from mechanisms to therapeutic implications. *Trends Immunol*. 2015;36(4):229-239.

Palmerini E, Staals EL, Maki RG, et al. Tenosynovial giant cell tumour/pigmented villonodular synovitis: outcome of 294 patients before the era of kinase inhibitors. *Eur J Cancer.* 2015;51(2):210-217.

Papadopoulos KP, Gluck L, Martin LP, et al. First-in-human study of AMG 820, a monoclonal anti-colony-stimulating factor 1 receptor antibody, in patients with advanced solid tumors. *Clin Cancer Res.* 2017;23(19):5703-5710.

Ponce R, Abad L, Amaravadi L, et al. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. *Regul Toxicol Pharmacol*. 2009;54(2):164-182.

Radi ZA, Koza-Taylor PH, Bell RR, et al. Increased serum enzyme levels associated with Kuppfer cell reduction with no signs of hepatic or skeletal muscle injury. *Am J Pathol*. 2011;179(1):240-247.

Staals EL, Ferrari S, Donati DM, Palmerini E. Diffuse-type tenosynovial giant cell tumour: current treatment concepts and future perspectives. *Eur J Cancer.* 2016;63:34-40.

Stepensky D. Local versus systemic anti-tumor necrosis factor-α effects of adalimumab in rheumatoid arthritis: pharmacokinetic modelling analysis of interaction between a soluble target and a drug. *Clin Pharmacokinet*. 2012;51(7):443-455.

Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet.* 2019;394(10197):478-487.

Turalio [package insert]. Daiichi Sankyo, Inc; 2020.

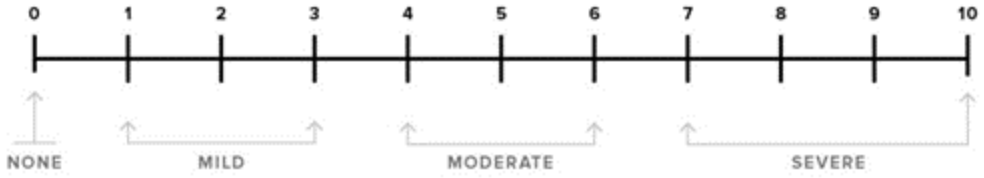
Verspoor F, van der Geest I, Vegt E, Veth R, van der Graaf WT, Schreuder B. Pigmented villonodular synovitis: current concepts about diagnosis and management. *Future Oncol.* 2013;9:1515-1531.

Wang J. Efficacy and safety of adalimumab by intra-articular injection for moderate to severe knee osteoarthritis: An open-label randomized controlled trial. *J Int Med Res.* 2018;46:326-334.

West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *Proc Natl Acad Sci USA.* 2006;103(3):690-695.

Appendix 1. Worst Stiffness NRS

Stiffness of the affected joint will be assessed using a self-administered NRS to assess the "worst" stiffness in the last 24 hours. The NRS for this item ranges from 0 (no stiffness) to 10 (stiffness as bad as you can imagine).



Appendix 2. 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

28 March 2017
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Appendix 3. BPI (Short Form)

BRIEF PAIN INVENTORY

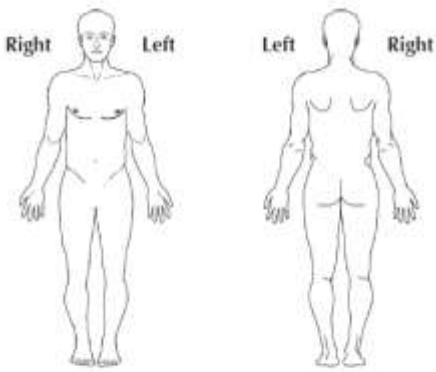
Date_____/_____/_____ Time:_____

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 Assessment

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

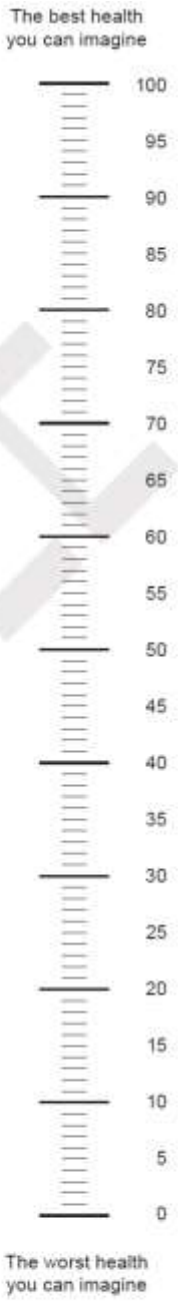
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

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 sites.

- 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 categorized as in-clinic–only activities will not be conducted. Once COVID-19–related restrictions are lifted, sites should attempt to conduct any missed in-clinic–only 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 9.6) 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.