



CLINICAL STUDY PROTOCOL ABC008-IBM-201

Protocol Title: A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Determine the Efficacy and Safety of ABC008 in the Treatment of Subjects with Inclusion Body Myositis

Protocol Number: ABC008-IBM-201

Protocol Phase: II/III

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Sponsor: **Abcuro Inc.**
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PROTOCOL SIGNATURE PAGE – SPONSOR

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Multicenter Study to Determine the Efficacy and Safety of
ABC008 in the Treatment of Subjects with Inclusion Body
Myositis

PROTOCOL NUMBER: ABC008-IBM-201, Amendment 6

[Redacted Signature]

MD

[Redacted Date]
Date

INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice, and all applicable national and local regulations and requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the Institutional Review Board/Independent Ethics Committee.

Institution/Clinic: _____

Principal Investigator:

Print Name

Title

Signature

Date

PROTOCOL SYNOPSIS

Protocol Number: ABC008-IBM-201
EU CT Number: 2022-501925-19-00
Protocol Title: A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Determine the Efficacy and Safety of ABC008 in the Treatment of Subjects with Inclusion Body Myositis
Short Title: A Phase II/III Study of ABC008 to Determine Efficacy and Safety in IBM
Sponsor: Abcuro, Inc.
Study Phase: Phase II/III
Study Sites: Approximately 50 sites in the United States (US), Canada, Europe, and Australia
Objectives: This study is being conducted to determine the efficacy, safety, and tolerability of subcutaneous (SC) dosing of ABC008 in subjects with inclusion body myositis (IBM). Part A (Sentinel Cohort): Primary Objective To determine the safety and tolerability of recurrent dosing of ABC008 in subjects with IBM at two SC dose levels. Note: Efficacy is not a specific objective of Part A (Sentinel Cohort); however, subjects from Part A will be included in the efficacy and safety analyses for the overall study, as described for Part B. Part B (Double-Blind Safety and Efficacy Cohort): Primary Efficacy Objectives To determine the efficacy of ABC008 in IBM at two SC dose levels as measured by IBM Functional Rating Scale (IBMFRS) at Week (W) 76. Key Secondary Efficacy Objectives To determine the efficacy of SC ABC008 in subjects with IBM at W76, as measured using: 1. Manual muscle testing (MMT) 12; 2. Grip strength for the dominant hand by dynamometry; 3. Strength of quadriceps for the dominant leg by dynamometry; 4. Modified Timed Up and Go test (mTUG).
Safety Objectives To determine the safety and tolerability of SC ABC008 in subjects with IBM. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Objectives In subjects with IBM: [REDACTED]

Health-related Quality-of-Life Objectives

To determine the health-related quality of life (HRQoL) related to SC ABC008 in subjects with IBM.

Part C (PD Recovery Cohort):

Primary Objective

To evaluate the PD recovery of the depletion of killer cell lectin-like receptor G1 (KLRG1)+ cells after the end of treatment with SC ABC008 in subjects with IBM.

Study Design:

This is a Phase II/III randomized, double-blind, placebo-controlled, parallel, multicenter study with three parts. Part A is a sentinel safety cohort in which subjects will receive three doses of study drug and the resultant safety and tolerability data will be evaluated by a Data and Safety Monitoring Board (DSMB). With a favorable DSMB review, the study will progress to Part B, with the main purpose of evaluating the efficacy, safety, and tolerability of two dose levels of ABC008 compared with placebo in subjects with IBM. Part C is a PD and safety follow-up to follow recovery of the depletion of KLRG1+ cells.

Part A (Sentinel Cohort) of the study comprises an up to five-week Screening Period, a 76-week Treatment Period (including 20 weeks of sentinel dosing followed by a DSMB review to determine continued dosing through the end of the Treatment Period), and safety follow-up four weeks after the W76 visit (eight weeks after the last dose at W72 in the Treatment Period). Part A will be double-blind and placebo-controlled. Approximately 30 eligible subjects in Part A will be randomized in a 2:2:1 ratio to one of two dose levels of ABC008 or matching placebo. The study drug will be dosed via SC injection every eight weeks (Q8W). After subjects have received three doses of study drug, a DSMB will review the interim safety data for all Part A subjects through at least the W20 visit. Subjects may continue in their assigned groups in a double-blind manner while the DSMB sentinel cohort review is pending. Continued dosing of Part A subjects through W72 will be predicated on a favorable DSMB assessment of safety, as will initiation of enrollment in Part B.

Part B (Double-Blind Safety and Efficacy Cohort) of the study comprises an up to five-week Screening Period, a 76-week Treatment Period, and safety follow-up four weeks after the W76 visit (eight weeks after the last dose). The W80 safety follow-up visit may be conducted via phone. Part B will be double-blind and placebo-controlled. Approximately 200 eligible subjects in Part B will be randomized in a 1:1:1 ratio to one of two dose levels of ABC008 or matching placebo. The study drug will be dosed via SC injection Q8W.

In both Part A and Part B, at the W80 visit, subjects will be eligible to enroll in an open-label long-term extension study. If conducted in person, the W80 visit may serve as both the safety follow-up visit for Part A or B of the current study and the Baseline Visit for the long-term extension study.

Subjects who choose not to enroll in the open-label long-term extension study and subjects who prematurely discontinue study drug during Part A or B will progress to Part C (PD Recovery Cohort) for follow-up. If conducted in person, the Part A or B W80 visit may serve as the Baseline Visit for Part C. Part C of the study will consist of adverse event (AE) follow-up monthly, PD assessments and pregnancy testing every three months. The Follow-up Period in Part C will be a minimum of three

months and will continue for each subject until their KLRG1+ cells have recovered. This will be performed by flow cytometry. All subjects entering Part A and B will have baseline flow cytometry performed and subjects entering Part C will have flow cytometry performed every three months until recovery. Once KLRG1+ cell recovery has been documented, an End-of-Study phone call will be conducted to notify the subject and collect any AEs not previously reported.

Efficacy, safety, HRQoL, and HRU assessments will be conducted.

Blood samples will be obtained to evaluate PK, PD, and immunogenicity of ABC008 throughout the study.

Stopping Criteria:

Criteria for premature discontinuation of dosing for individual subjects are detailed in Section 5.4.1.

Any of the following will prompt a safety assessment by the Medical Monitor (MM) in discussion with the Investigator to determine whether dosing may proceed in additional subjects:

- Any treatment-emergent serious adverse event (TESAE);
- Any severe treatment-emergent adverse event (TEAE).

The following will prompt a consultation between the MM and the DSMB to determine whether dosing may proceed in additional subjects:

- $\geq$ two subjects with a serious adverse event from the same Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, unless clearly attributed to underlying disease.
- $\geq$ two subjects with discontinuations due to AEs as detailed in Section 5.4.1, unless clearly attributed to clinical deterioration due to IBM.

Safety will be continuously assessed throughout the study and the Sponsor may stop the study for safety reasons without consulting the DSMB.

Planned Study Duration:

The start of the study will be the date on which the first subject provides informed consent, and the end of the study will be the date of the last subject's last scheduled protocol-directed assessment.

Part A (Sentinel Cohort):

Up to 85 weeks, consisting of an up to five-week Screening Period, a 76-week double-blind Treatment Period, and safety follow-up four weeks after the W76 visit (eight weeks after the last dose at W72 in the Treatment Period). Safety data for all Part A subjects through at least the W20 visit will be reviewed by a DSMB. Subjects will continue in their assigned groups in a double-blind manner while the DSMB sentinel cohort review is pending. Continued dosing of Part A subjects through W72 will be predicated on a favorable DSMB assessment.

Part B (Double-Blind Safety and Efficacy Cohort):

Up to 85 weeks, consisting of an up to five-week Screening Period, a 76-week double-blind Treatment Period, and safety follow-up four weeks after the W76 visit (eight weeks after the last dose at W72 in the Treatment Period).

In both Part A and Part B, at the W80 Follow-up Visit, subjects will be eligible to enroll in an open-label long-term extension study. If conducted in person, the W80 visit may serve as both the safety follow-up visit for Part A or B of the current study and as the Baseline Visit for either the long-term extension study or Part C of this study.

Part C (PD Recovery Cohort):

At least three months; duration of Follow-up Period to be determined for each subject based upon recovery of KLRG1+ cells. Subjects will continue to have AE follow-up monthly, PD assessments and pregnancy testing every three months until KLRG1+ recovery.

Planned Number of Subjects:

Part A (Sentinel Cohort):

For Part A, it is planned to screen approximately 40 subjects in order to obtain approximately 30 enrolled subjects.

For this sentinel cohort, eligible subjects will be randomized in a 2:2:1 ratio to one of two dose levels of ABC008 (approximately 12 subjects each) or matching placebo (six subjects).

Part B (Double-Blind Safety and Efficacy Cohort):

For Part B, it is planned to screen approximately 250 subjects in order to obtain approximately 201 additional enrolled subjects.

For Part B, eligible subjects will be randomized in a 1:1:1 ratio to one of two dose levels of ABC008 or matching placebo. Each group will enroll approximately 67 subjects.

Total enrollment for the study (Parts A and B) is planned to be approximately 231 subjects (79 subjects in each of the ABC008 groups and 73 subjects in the placebo group).

Inclusion Criteria:

For both Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort), the following inclusion criteria must be met for a subject to be eligible for inclusion in the study. Eligibility criteria for this study should be assessed only after signing of informed consent for this study. All data from Screening and all data except for central laboratory results from Baseline (Day 1) Visit should be used to confirm subject eligibility.

1. Adult males and females age ≥ 40 years at the time of the first dose of study medication;
2. Able to read, understand, and provide signed informed consent prior to the performance of any study-related procedures;
3. Willing and able to comply with the requirements of the protocol, including traveling to the site for study-related assessments and SC injections, and using electronically administered diaries and questionnaires;
4. Weight ≥ 40 and ≤ 150 kg;
5. Diagnosis of either clinico-pathologically defined IBM, clinically defined IBM, or probable IBM according to the European Neuromuscular Centre (ENMC) IBM 2011 research diagnostic criteria ([Rose et al., 2013](#)), modified to allow inclusion of subjects age ≥ 40 years with documented IBM. Documented histopathology results must be available prior to Baseline (Day 1) to confirm eligibility;
6. As required to complete the mTUG test, able to arise from a standard armchair (described in Section 6.2.6), with use of their arms but without support from another person or device (e.g., cane, walking stick), at Screening and Baseline (Day 1);
7. As required to complete the mTUG test, able to walk three meters, turn around, walk back to the chair, and sit down, with or without an assistive device. Once arisen from the chair, subject may use any walking device but cannot be supported by another person, furniture, or a wall;
8. Agree to adhere to relevant local guidelines regarding minimizing exposure to severe acute respiratory syndrome coronavirus 2 from the first Screening Visit until End-of-Treatment (EOT)/Early Termination visit (ETV);
9. Negative coronavirus disease 2019 (COVID-19) test results within 48 hours before Baseline (Day 1) (polymerase chain reaction [PCR] or rapid antigen testing as per local guidance);
10. Agree (to the best of their knowledge), to avoid contact with any person suspected or known to have an infectious disease of which they are at risk of contracting from the first Screening Visit until the EOT/ETV;

11. Women of childbearing potential (WOCBP) and male subjects with female partners who are WOCBP (based on gender assignment at birth) must agree to use highly effective (<1% failure rate) contraception (as detailed in Section 7.6.4) for at least 30 days prior to the first dose of study medication, during the study, and for 180 days following EOT/ETV.
12. Male subjects (based on gender assignment at birth) must refrain from sperm donation for the duration of the study and for 180 days after EOT/ETV;
13. WOCBP (based on gender assignment at birth) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).

Exclusion Criteria:

For both Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort), a subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study. Eligibility criteria for this study should be assessed only after signing of informed consent for this study. All data from Screening and all data except for central laboratory results from Baseline (Day 1) Visit should be used to confirm subject eligibility.

1. Any other form of myositis or myopathy other than IBM, e.g., metabolic or drug-induced myopathy, drug-induced myositis, anti-synthetase syndrome, polymyositis or dermatomyositis, cancer-associated myositis (myositis diagnosed within three years, either before or after), myositis in overlap with another autoimmune disease (e.g., systemic lupus, systemic sclerosis, rheumatoid arthritis), or muscular dystrophy;
2. Any condition, e.g., severe degenerative arthritis with limited range of motion, which precludes the ability to quantitate muscle strength or perform functional assessments (e.g., mTUG), in the Investigator's opinion;
3. Presence of another autoimmune or autoinflammatory disease which, in the view of the Principal Investigator or MM, may impact the subject's ability to perform study procedures such that it would confound clinical assessment. Examples include rheumatoid arthritis, psoriatic arthritis, axial spondyloarthropathy, inflammatory bowel disease, systemic lupus erythematosus. Subjects with Sjogren's syndrome, T-cell large granular lymphocyte leukemia (T-LGLL), or well-controlled thyroid disease are permitted;
4. Receipt of any of the following treatments within the following time frames before Screening (or as otherwise specified):
 - a. Intravenous or intramuscular corticosteroids: four weeks;
 - b. Oral prednisone (or prednisone equivalent) >7.5 mg/day at Screening;
 - c. Use of nonbiologic immunosuppressants (e.g., cyclosporine, mycophenolate mofetil or sodium, azathioprine, methotrexate, sirolimus, Janus kinase inhibitors): 12 weeks;
 - d. Intra-articular therapies, such as corticosteroids or hyaluronic acid preparations: four weeks;
 - e. Intravenous, intramuscular, or SC immunoglobulin (IVIG, IMIG, or SCIG): 12 weeks;
 - f. Cytokine, integrin, or activin antagonists or selective co-stimulation modulators, including, but not limited to, interleukin (IL)-1, IL-6, IL-17, IL-12/23, IL-23, interferon, integrin, and tumor necrosis factor α antagonists, abatacept, bimagrumab: 12 weeks;
 - g. Cell-depleting or modulating therapies (e.g., alemtuzumab, antithymocyte globulin, atacicept, belimumab, obinutuzumab, ocrelizumab, ofatumumab, rituximab, sipilizumab): 12 months;
 - h. Use of chemotherapeutic regimens or other cytotoxic therapies, e.g., cyclophosphamide, doxorubicin or hydroxyrubicin, vincristine, and prednisone; purine analogs, alkylating agents: 24 weeks;
 - i. Other immunomodulatory biologics: 12 weeks or five half-lives, whichever is longer;

- j. Transfusion with blood, packed red blood cells, or platelets or treatment with plasmapheresis or plasma exchange: six weeks;
 - k. Anabolic steroids: four weeks;
 - l. Growth hormone: four weeks;
 - m. Physiologic supplementation with testosterone permitted provided dose stable for four weeks before Screening and expected to stay stable during the study;
 - n. Therapies associated with neuromuscular side effects including antimalarial drugs (e.g., chloroquine, hydroxychloroquine), colchicine, cholesterol-lowering drugs (e.g., statins) except if on stable dose for at least 12 weeks, and without impact on assessment of IBM progression.
5. Initiation of an exercise or a physical therapy regimen within four weeks of Screening. Any exercise or physical therapy regimen initiated prior to the Screening Visit must have been stable for at least four weeks prior to Screening;
6. Subject has had recent serious or ongoing infection, or risk for serious infection, including but not limited to:
- a. Acute or chronic infection defined as any infection requiring oral antibiotic, antifungal, or antiviral (antimicrobial) therapy within two weeks of Baseline (Day 1);
 - b. Hospitalization or receipt of a course of systemic (intravenous or intramuscular) antimicrobial therapy for infection within 24 weeks prior to Screening;
 - c. Symptomatic COVID-19 infection at Screening. In the setting of a positive COVID-19 test within two days of Baseline (Day 1), subject may be retested one additional time as long as they are within the study screening window;
 - d. Symptomatic herpes zoster or herpes simplex infection (oral herpes simplex virus lesions permitted) within 12 weeks prior to Screening or during the Screening Period. Chronic antiviral therapy with e.g., valacyclovir permitted;
 - e. History of severe and/or disseminated viral infections, and/or opportunistic infections within 12 months of Screening;
 - f. Seropositivity for or active infection by human immunodeficiency virus (HIV);
 - g. Active, chronic, or history of hepatitis B virus or hepatitis C virus (HCV) infection (hepatitis B core antibody or surface antigen positive, or HCV antibody positive with reflex HCV ribonucleic acid [RNA] positive at Screening; subjects who have received curative therapy for HCV are permitted if therapy was completed at least 24 weeks prior to Screening and subject is HCV RNA negative);
 - h. Known active or untreated latent tuberculosis (TB) within 12 weeks prior to or at Screening and/or positive QuantiFERON®-TB Gold Plus and/or positive T-SPOT®.TB tests at Screening. Subjects with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines are allowed if no history of re-exposure to TB since treated. Intermediate or borderline test results require a repeat test to confirm negative status or medical evaluation to rule out a concern for TB disease. T-SPOT.TB may be performed locally, or QuantiFERON-TB Gold Plus test may be performed locally or centrally at site's discretion;
 - i. Receipt of a live attenuated vaccine within 30 days or a non-live vaccine within 14 days of first dose;
 - j. Primary immunodeficiency (unless otherwise considered, in the opinion of the Investigator and MM, to confer a clinically insignificant infection risk, such as deficiency in immunoglobulin (Ig) A, Components of the Complement System, innate immunity (C1q, C2, or C4) without a history of recurrent infections [three or more infections in one year requiring antimicrobial therapy]);

- k. History of recurrent infections (three or more infections requiring antimicrobial therapy in the 12 months prior to Screening);
- 7. Any of the following laboratory values at Screening:
 - a. Estimated glomerular filtration rate <30 mL/min by the Chronic Kidney Disease Epidemiology Collaboration equation;
 - b. Hemoglobin <10 g/dL;
 - c. White blood cell count $<3.0 \times 10^9$ /L;
 - d. Absolute neutrophil count $<1.5 \times 10^9$ /L ($1500/\text{mm}^3$);
 - e. Platelet count $<100 \times 10^9$ /L;
 - f. Serum aspartate aminotransferase or serum alanine aminotransferase $>3 \times$ the upper limit of normal (ULN) unless considered consistent with muscle origin;
 - g. Total bilirubin $>2 \times$ ULN ($3 \times$ ULN for subjects with documented Gilbert's syndrome).
- 8. Presence of New York Heart Association Class III or IV heart failure, or uncontrolled blood pressure (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg at rest);
- 9. Mean (based on triplicate measurements) QT interval corrected using Fridericia's formula >450 msec for males or >470 msec for females on screening electrocardiograms (ECGs), and/or clinically significant ECG findings at Screening as per Investigator assessment (subjects with non-clinically significant bundle branch block are permitted);
- 10. Major surgery within 12 weeks before Screening, major surgery planned during the study period, or any surgery planned during the study period that would require corticosteroid therapy and/or could confound the results of the study, put the subject at undue risk, or interfere with protocol adherence;
- 11. Clinical evidence of significant unstable or uncontrolled diseases (e.g., cardiac [including congestive heart failure, angina, or recent (<6 months prior to Screening) myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring systemic corticosteroid therapy, pulmonary hypertension, or interstitial lung disease], hematologic, gastrointestinal, endocrinologic [e.g., hypothyroidism, diabetes], hepatic, renal, neurological, infectious, psychiatric [e.g., severe depression]) that, in the opinion of the Investigator or Sponsor, could confound the results of the study, put the subject at undue risk, or interfere with protocol adherence;
- 12. Evidence of current or previous clinically significant disease, medical condition (including abnormal laboratory values), or finding in the medical examination that in the Investigator's or Sponsor's opinion would compromise the safety of the subject or the ability to interpret the data;
- 13. Any active or suspected malignancy including myeloproliferative or lymphoproliferative disorder or history of documented malignancy within the last five years before Screening. Subjects with T-LGLL or appropriately excised and cured cervical carcinoma *in situ*, basal or squamous cell carcinoma of the skin are permitted;
- 14. Clinically significant abnormality in kappa/lambda ratio or evidence of monoclonal protein (M protein) indicating possible monoclonal gammopathy of undetermined significance or smoldering myeloma;
- 15. Alcohol abuse or drug abuse in the last one year prior to Screening in the opinion of the Investigator;
- 16. Columbia Suicide Severity Rating Scale score of 4 or 5 on the suicidal ideation items, intent in the last 6 months prior to randomization, or any "yes" on the Suicidal Behavior item that is related to suicidal behaviors or attempts occurring during the past two years;
- 17. Women who are pregnant, lactating, or discontinued lactation less than 12 weeks prior to Screening, or who plan to become pregnant or initiate lactation during the study;

18. Participation in another investigational drug study within 30 days prior to Screening (or five times the half-life of the drug, whichever is longer);
19. Has known hypersensitivity to ABC008, any component of the formulation of ABC008, or history of anaphylaxis to any prior monoclonal antibody (mAb) therapy;
20. Unable to comply with the protocol in the Investigator's or Sponsor's opinion;
21. For subjects in France only: Persons under court protection, persons not affiliated to a social security system, or protected adults (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1).

Test Product:

ABC008 (anti-KLRG1 afucosylated humanized IgG1) drug product is supplied as a sterile liquid with no preservatives for SC administration at a concentration of [REDACTED] mg/mL. The test product is provided as a single use vial comprised of [REDACTED] mg/mL (1 mL) of ABC008 formulated with [REDACTED] and [REDACTED]

Dose and Dose Frequency

For both Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort) of the study:

Arm 1: 0.5 mg/kg ABC008 SC Q8W starting at Day 1.

Arm 2: 2.0 mg/kg ABC008 SC Q8W starting at Day 1.

The last dose of study medication will be at W72 (assuming a favorable DSMB assessment of the Part A safety data through at least W20 [following dosing at Day 1, W8, and W16]).

Subjects will not be dosed during Part C (PD Recovery Cohort).

Mode of Administration: SC injection.

ABC008 is packaged in [REDACTED]

Control Product:

Placebo is supplied as a solution comprised of [REDACTED] and [REDACTED], which does not contain the active ABC008 component.

Dose and Dose Frequency

For both Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort) of the study:

Arm 3: Placebo Q8W starting at Day 1.

The last dose of study medication will be at W72 (assuming a favorable DSMB assessment of the Part A safety data through at least W20 [following dosing at Day 1, W8, and W16]).

Subjects will not be dosed during Part C (PD Recovery Cohort).

Mode of Administration: SC injection.

Placebo is packaged in [REDACTED]

Endpoints:

Part A (Sentinel Cohort):

Primary Endpoint

The primary endpoint for Part A of the study will be safety, as assessed by the incidence, type, and severity of TEAEs.

Secondary Endpoints

1. Incidence, type, and severity of TESAEs;
2. Incidence, type, and severity of TEAEs with onset within 24 hours from the start of any of study medication administration;
3. Incidence of TEAEs leading to study medication or study discontinuation;

4. Clinically significant changes in standard laboratory parameters, vital signs, and ECGs;
5. Adverse events of special interest (AESIs):
 - a. Injection site reactions;
 - b. Systemic injection reactions (e.g., hypersensitivity, systemic inflammatory response);
 - c. Infection, including but not limited to, reactivation of latent herpes viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV), herpes simplex virus (HSV) types 1 or 2, or varicella zoster virus (VZV).

Note: Safety is the primary objective of Part A; however, subjects from Part A will be included in the efficacy and safety analyses for the overall study, as described for Part B below.

Part B (Double-Blind Safety and Efficacy Cohort):

Primary Efficacy Endpoint

The primary endpoint for the study will be mean change from Baseline (Day 1) in IBMFRS at W76.

Key Secondary Efficacy Endpoints

The following key secondary endpoints will be analyzed in a sequential manner:

1. Mean change from Baseline (Day 1) in MMT 12 at W76;
2. Mean change from Baseline (Day 1) in hand grip strength for the dominant hand by dynamometry at W76;
3. Mean change from Baseline (Day 1) in quadriceps strength for the dominant leg by dynamometry at W76;
4. Mean change from Baseline (Day 1) in mTUG at W76.

Safety Endpoints

1. Incidence, nature, and severity of TEAEs;
2. Incidence, nature, and severity of TESAEs;
3. Incidence, nature, and severity of TEAEs with onset within 24 hours from the start of any of study medication administration;
4. Incidence of TEAEs leading to study medication or study discontinuation;
5. Changes in standard laboratory parameters, vital signs, and ECGs;
6. AESIs:
 - a. Injection site reactions;
 - b. Systemic injection reactions (e.g., hypersensitivity, systemic inflammatory response);
 - c. Infection, including but not limited to, reactivation of latent herpes viruses such as EBV, CMV, HHV, HSV-1 or -2, or VZV.

Pharmacokinetic Endpoints

Serum concentration and PK parameters, when feasible, of ABC008.

HRQoL Endpoints:

1. Mean change from Baseline (Day 1) in Study Short Form 36-item Health Survey Version 2 (SF-36v2) physical component summary (PCS) score, mental component summary (MCS) score, and individual domain scores at W76;
2. Mean change from Baseline (Day 1) in the EuroQol 5 Dimension, 5 Level, Quality-of-Life Questionnaire (EQ-5D-5L) at W76.

Part C (PD Recovery Cohort):

The endpoint for Part C of the study will be PD recovery as assessed by the time from EOT/ETV to recovery of KLRG1+ cells.

Sample Size and Planned Statistical Analysis:

Sample Size Calculation

In total, approximately 231 subjects will be administered study medication in Parts A and B (79 subjects in each of the ABC008 arms and 73 subjects in the placebo arm). This sample size provides overall power of at least 90% for the primary efficacy analysis at an overall one-sided 2.5% level if the true effect size at each ABC008 dose is 0.5448 for IBMFRS at 76 weeks. In addition, 15% of the subjects are expected to be lost to follow-up by the end of the 76-week Treatment Period.

General Statistical Methodology

A summary of key statistical methods and considerations is presented below. A detailed description of key reporting and analytic methods, including modifications to the methods described below, will be provided in the Statistical Analysis Plan (SAP). Procedures outlined in the SAP will supersede protocol-specified statistical methods in the event of divergence.

Analysis Sets:

The following analysis sets will be defined for Parts A and B:

- Enrolled Analysis Set (ES): Includes all subjects screened and enrolled into the study irrespective of whether they received study drug. This set will be used to summarize subject disposition.
- Safety Analysis Set (SS): Includes all subjects who received at least one dose of study drug with at least one safety assessment after dosing. The analyses using this set will be based upon the actual treatment assignment. This set will be used to summarize demographics and baseline characteristics, protocol deviations, study drug exposure, and safety information (e.g., AEs, laboratory results, vital signs, and ECG measurements).
- Full Analysis Set (FAS): Includes all subjects in the ES randomized to receive the study drug. The analyses using this set will be based upon the randomized treatment assignment. The FAS will be used to evaluate efficacy measures.
- Per Protocol Analysis Set (PPS): Includes all subjects in the FAS who completed the Treatment Period without an important protocol deviation that may impact efficacy assessment. Protocol deviations will be reviewed in a blinded fashion prior to the database lock to assess which subjects meet criteria for an important protocol deviation for exclusion from the PPS analyses. The analyses using this set will be based upon the actual treatment assignment. Select efficacy assessments may be evaluated using the PPS.
- PK Analysis Set: Includes all subjects in the SS with at least one postbaseline time point with valid ABC008 concentration data.
- PD Analysis Set (PDS): Includes all subjects in the SS with at least one postbaseline time point with valid PD assessments.

In addition, the following analysis set will be used in Part C:

- PD Part C Analysis Set will include all subjects in the PDS with valid PD assessments in Part C. The treatment assignments in this analysis set will be based on the original assignments in the PDS.

Data Analysis

The final analysis will rely on the totality of the data from Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort).

Efficacy

One-sided 2.5% significance levels and 95% confidence intervals will be used for all efficacy analyses with the exception of the primary and key secondary efficacy endpoints. A multiple testing procedure based on the graphical method ([Bretz et al., 2009](#)) will be applied to the primary and key secondary efficacy endpoints to control the overall Type I error rate at an overall one-sided 2.5% level.

Primary Efficacy Endpoint

The treatment effect on the primary endpoint will be evaluated using a mixed-effects repeated-measures model with fixed terms for treatment (ABC008 doses and placebo), baseline score, visit, and visit by treatment interaction.

Key Secondary Efficacy Endpoints

The same analysis models will be used for the key secondary endpoints.

Estimand Strategy

The main estimand will compare each ABC008 dose with placebo for the primary efficacy endpoint as well as potentially key secondary efficacy endpoints. The analysis of the primary efficacy endpoint will be based on a hybrid estimand using two different strategies for handling intercurrent events (ICEs): a “worst- case” hypothetical strategy for subjects who discontinued their randomized treatment regimen due to lack of efficacy and a “control-based” hypothetical strategy for subjects who discontinued their randomized treatment regimen due to an AE. Multiply imputed data for the primary efficacy endpoint will be analyzed using the primary analysis model. The final treatment effect estimates and p-values will be obtained using Rubin’s combination rules.

Safety

For Part A and Part B, safety and tolerability of ABC008 will be assessed through listings and summaries of the following measures by ABC008 dose vs. placebo: incidence of AEs including TEAEs and TESAEs, discontinuation from study medication or study participation due to TEAEs and drug-related TEAEs, observed and change from Baseline (Day 1) in vital signs and weight measurements, observed and change from Baseline (Day 1) in clinical laboratory test results, and observed and change from baseline in 12-lead ECG assessments. AEs will be coded using the most current version of MedDRA available at the start of the study.

Continuous safety data will be summarized with descriptive statistics (n, arithmetic mean, standard deviation [SD], median, minimum, and maximum). Categorical safety data will be summarized with incidence counts and percentages.

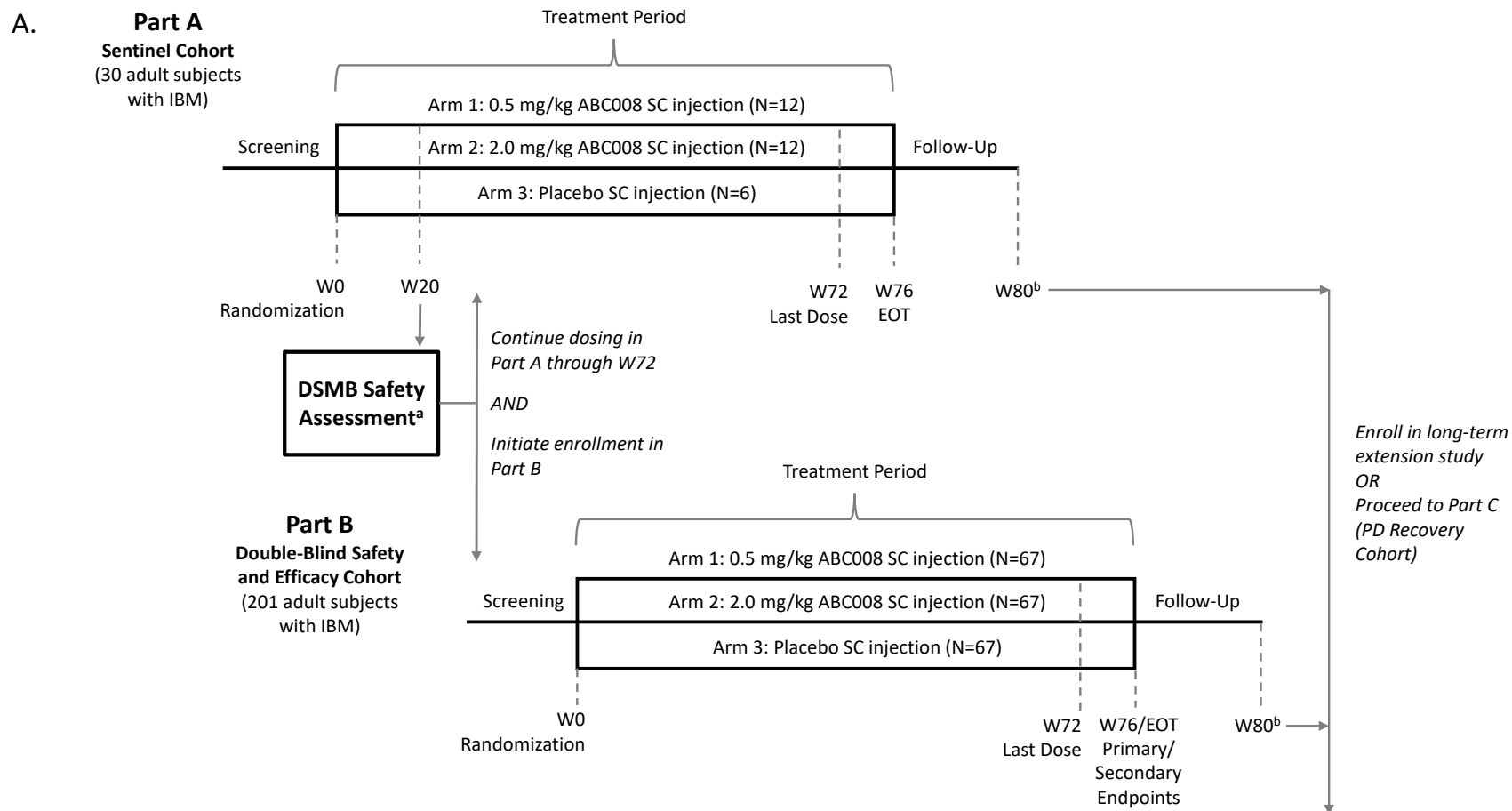
Pharmacokinetics

Descriptive statistics (n, geometric mean, arithmetic mean, SD, arithmetic coefficient of variation [CV], geometric CV, median, minimum, and maximum) will be used to summarize ABC008 concentration data at each planned sampling time point. All serum concentration data will be listed by subject using the SS and will be summarized by analyte, dose, and sampling time. Individual and mean serum concentration-time profiles will be presented by dose using nominal time points. Noncompartmental analysis may be completed, if feasible, to determine PK parameters.

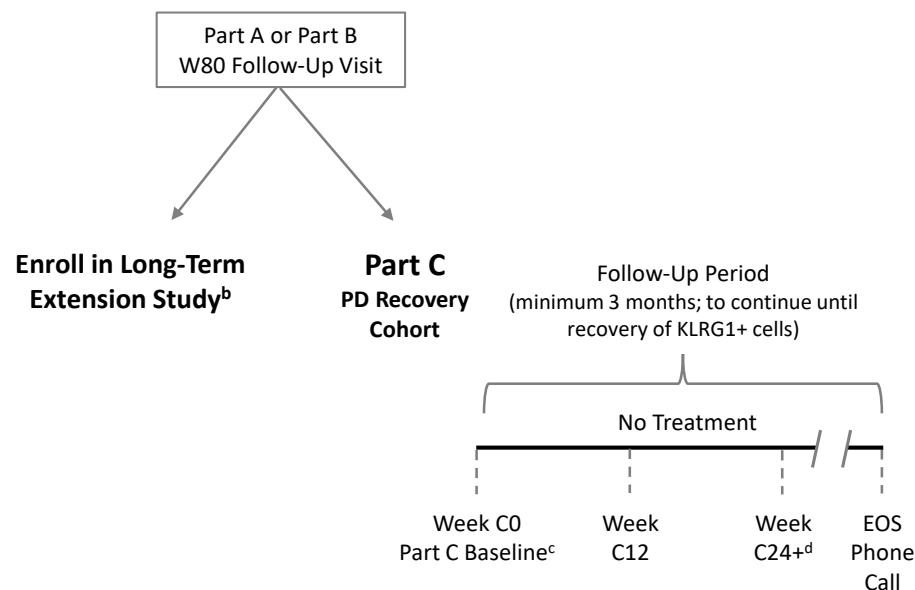
Protocol Version and Date: Amendment 6; 01 December 2025

STUDY SCHEMATIC

Figure 1: Study Schematic for Protocol ABC008-IBM-201



B.



DSMB, Data and Safety Monitoring Board; EOS, End-of-Study; EOT, End-of-Treatment visit; ETV, Early Termination visit; IBM, inclusion body myositis; KLRG1, killer cell lectin-like receptor G1, N, number of subjects; PD, pharmacodynamics; SC, subcutaneous; W, Week

- DSMB review based on safety data for all Part A subjects through at least the W20 visit. Part A subjects may continue in their assigned groups in a double-blind manner while the DSMB sentinel cohort review is pending. Continued dosing of Part A subjects through W72 will be predicated on a favorable DSMB assessment of safety, as will initiation of enrollment in Part B.
- For subjects enrolling in the long-term extension study, the W80 visit, if conducted in person, may serve as both the follow-up visit for Part A or B of the current study and as the Baseline Visit for the long-term extension study.
- All assessments completed at an in-person Part A or Part B Follow-up (for subjects who completed Part A or Part B, respectively) or the ETV (for subjects who prematurely discontinued study drug during Part A or B) will be used as the Part C Baseline assessments.
- Subjects will continue to have AE follow-up monthly and PD assessments (including flow cytometry) and pregnancy testing every three months until subject's KLRG1+ cells have recovered.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description
ADA	antidrug antibody (ies)
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-cN-1A	anti-cytosolic 5'-nucleotidase 1A
AST	aspartate aminotransferase
AUC	area under the drug concentration-time curve
C1q, C2, C4	Components of the Complement System, innate immunity
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CH50	hemolytic complement filtration
CHOK1	Chinese Hamster Ovary K1 cells
CL	clearance
C _{max}	maximum serum concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DSMB	Data and Safety Monitoring Board

Abbreviation	Description
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ENMC	European Neuromuscular Centre
EOS	End-of-Study
EOT	End-of-Treatment
EQ-5D-5L	EuroQol 5 Dimension, 5 Level, Quality-of-Life Questionnaire
ES	Enrolled Analysis Set
ETV	Early Termination visit
FAS	Full Analysis Set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpes virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRU	healthcare resource utilization
HSV	herpes simplex virus
IB	Investigator's Brochure
IBM	inclusion body myositis
IBMFRS	Inclusion Body Myositis Functional Rating Scale
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IMIG	intramuscular immunoglobulin
IRB	institutional review board
IRT	interactive response technology
IV	intravenous

Abbreviation	Description
IVIG	intravenous immunoglobulin
KLRG1	killer-like leptin receptor G1
mAb	monoclonal antibody
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MMT [REDACTED] 12	manual muscle testing of [REDACTED] or 12 muscle groups
mTUG	Modified Timed Up and Go
[REDACTED]	[REDACTED]
NK	natural killer
NOAEL	no observed adverse event level
OTC	over the counter
PCR	polymerase chain reaction
PCS	physical component summary
PD	pharmacodynamic(s)
PDCS	Pharmacodynamic Part C Analysis Set
PDS	Pharmacodynamic Analysis Set
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PPS	Per Protocol Analysis Set
PRO	patient-reported outcome
Q2W	once every two weeks
Q8W	once every eight weeks
QTL	quality tolerance limit
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCIG	subcutaneous immunoglobulin

Abbreviation	Description
SD	standard deviation
SF-36v2	Study Short Form 36-item Health Survey Version 2
SS	Safety Analysis Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T-LGLL	T-cell large granular lymphocyte leukemia
T _{max}	time of maximum serum concentration
ULN	upper limit of normal
US	United States
USV	unscheduled visit
VZV	varicella zoster virus
W	Week
WOCBP	women of childbearing potential

1. INTRODUCTION AND RATIONAL

1.1. Description of the Disease

Inclusion body myositis (IBM) is an inflammatory autoimmune disorder of skeletal muscle resulting in progressive limb weakness and loss of function (Needham & Mastaglia, 2007; Amato & Baron, 2009). The typical clinical presentation of IBM is in people aged 50 to 70 years (average age of symptom onset is 61 to 66 years) with slowly progressive difficulty in walking or using the hands as well as dysphagia (Dimachkie et al., 2014; Greenberg, 2019a). Physical examination typically demonstrates preferential involvement of muscles controlling finger flexion, knee extension, and ankle dorsiflexion with less involvement of the muscles that are typically affected in other acquired myopathies, such as those controlling proximal shoulder abduction, hip flexion, and hip abduction. IBM interferes with all activities of daily living (ADL), with particular disability due to loss of hand function and ambulation. Currently, there are no effective therapeutic agents for IBM, and standard of care involves no pharmacological treatment, resulting in high unmet medical need (Dimachkie et al., 2014; Mastaglia et al., 2015; Needham & Mastaglia, 2016; Greenberg, 2019a).

IBM is a rare disease with the highest estimated prevalence at 97 per million in those individuals ≥ 30 years of age (Shelly et al., 2021). A systematic review and meta-analysis of studies showed the prevalence of sporadic IBM as 46 per million (Callan et al., 2017). In the European Union, the estimated prevalence of IBM is approximately five per million (Orphanet 2022).

Since the seminal studies, IBM has been understood to be a T-cell mediated disease (Arahata et al., 1984, 1988) with documentation of invasion of muscle fibers by cytotoxic T cells and the increased likelihood of clonality of these T cells. Killer cell lectin-like receptor G1 (KLRG1)+ cluster of differentiation (CD) 8⁺ T cells are thought to be the key pathogenic drivers in several immune-mediated diseases including IBM, an inflammatory autoimmune disorder of skeletal muscle in which abundant KLRG1+ T cells invade the affected muscle fibers (Greenberg et al., 2019b). As the highly differentiated T-cell population is known to be relatively resistant to apoptosis and other mechanisms of immunosuppression, and corticosteroids are largely ineffective (Schirmer et al., 1998; Posnett et al., 1999; Spaulding et al., 1999; Vallejo et al., 2000), the treatment-refractory nature of IBM appears to be related to the abundance of this population of T cells. Therefore, targeting the depletion of KLRG1+ cells is expected to address a major element of IBM pathogenesis.

The microscopic pathology of IBM involves intense T-cell inflammation in skeletal muscle tissue, with cytotoxic T cells invading myofibers (Arahata et al., 1984, 1986, 1988; Dalakas et al., 2003), as well as sarcoplasmic accumulation of proteins (Mendell et al., 1991; Vattemi et al., 2004; Hohlfeld et al., 1997; Salajegheh et al., 2009; Nakano et al., 2017). The increased likelihood of clonality of these T cells is also well documented (Arahata et al., 1984, 1988). There have been decades of speculative debate about the relationship between autoimmunity and degeneration in IBM, the latter reflected by endoplasmic reticulum stress, autophagy, and accumulation of misfolded protein aggregates in muscle. However, the recent identification of genetic (Needham et al., 2008; Mastaglia et al., 2015; Rothwell et al., 2017) and acquired biomarkers of autoimmunity have characterized IBM as an autoimmune disease (Salajegheh et al., 2011; Larman et al., 2013; Pluk et al., 2013; Greenberg et al., 2016; Benveniste et al., 2019; Greenberg et al., 2019b).

The disease has also been called “sporadic IBM” and has sometimes been confused with an entirely distinct set of diseases called “hereditary inclusion body myopathies.”

1.2. Summary of Investigational Product and Mechanism of Action

Over the last decade, it has been recognized that the T cells which invade the muscle fibers in IBM are cytotoxic and express markers typical of terminal effectors (Pandya et al., 2010; Allenbach et al., 2014; Greenberg et al., 2016; Hohlfeld et al., 2016; Greenberg et al., 2019b). In particular, they express the differentiation marker, KLRG1 (Koch et al., 2008), and studies show upregulation of KLRG1 gene expression in IBM muscle (Knauss et al., 2019; Greenberg et al., 2019b). These KLRG1+ T cells not only invade IBM muscle but also tend to accumulate in the blood of IBM patients (Greenberg et al., 2019b). As the highly differentiated T-cell population is known to be relatively resistant to apoptosis and other mechanisms of immune cell control such as corticosteroids (Schirmer et al., 1998; Posnett et al., 1999; Spaulding et al., 1999; Vallejo et al., 2000), the treatment-refractory nature of IBM appears to be related to the abundance of this population of cells. Treatments aimed at addressing the direct cause of muscle damage, the attack by T cells on myofibers, are expected to provide clinical benefit.

ABC008 is being investigated for the treatment of IBM. ABC008 is an afucosylated humanized immunoglobulin (Ig) G Subclass 1 monoclonal antibody (mAb) specific for KLRG1, developed to deplete KLRG1+ cells. KLRG1 is expressed primarily in late-stage, highly differentiated, cytotoxic CD8⁺ T cells and natural killer (NK) cells. KLRG1 is highly upregulated in the T cells present in IBM muscle. ABC008 exerts its cytotoxic activity against KLRG1+ cells by engaging components of the immune system. Targeting the depletion of KLRG1+ cells is expected to address a major element of IBM pathogenesis.

Mechanisms by which ABC008 mediate the killing of KLRG1+ lymphocytes include induction of antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). Afucosylation of ABC008 increases ADCC activity by enhancing the affinity of the antibody for fragment crystallizable gamma receptor IIIa. Nonclinical pharmacology studies demonstrate that ABC008 induces ADCC, ADCP, and CDC of KLRG1+ Chinese hamster ovary K1 (CHOK1) cells with [REDACTED]

1.3. Nonclinical Studies

ABC008 has been evaluated for its biological activity, pharmacokinetics (PK), and toxicity in several *in vivo* and *in vitro* studies, the results of which are described in detail in the IBM Investigator's Brochure (IB).

1.3.1. Nonclinical Pharmacology

Nonclinical pharmacology studies demonstrate that ABC008 induces ADCC, ADCP, and CDC of KLRG1+ CHOK1 cells with [REDACTED]. Similarly, Good Laboratory Practice (GLP) toxicology studies indicate that ABC008 is a potent selective depleter of KLRG1+ cells when dosed weekly (one-month study) or every other week (six-month study) via subcutaneous (SC) administration to cynomolgus monkeys.

Nonclinical safety pharmacology, cardiovascular (electrocardiogram [ECG], heart rate, and blood pressure), respiratory function (respiration rate), and neurological functions were examined in a one-month repeat-dose GLP toxicology main study and in recovery animals following once weekly SC administration of ABC008 0, 10, or 30 mg/kg (four doses) to cynomolgus monkeys. ECGs, respiratory rate, and pulse oximetry assessments were also conducted prestudy and after the last dose in the three-month repeat-dose GLP toxicology study where cynomolgus monkeys were administered 0 or 50 mg/kg ABC008 SC once every two weeks for 13 weeks (seven total doses). Additionally, ECG assessments were conducted in the six-month repeat-dose GLP toxicology study where cynomolgus monkeys were administered 5, 25, or 50 mg/kg ABC008 SC once every two weeks for 26 weeks (13 total doses).

The results showed no abnormal safety pharmacology findings attributable to ABC008 in neither the one-month nor the six-month toxicology studies.

1.3.2. Nonclinical Pharmacokinetics

The nonclinical PK profile of ABC008 was examined in cynomolgus monkeys. Overall, the results indicate that the nonclinical PK and toxicokinetic properties of ABC008 support the SC route of administration in the clinical development program.

The serum PK of ABC008 following single intravenous (IV) doses from 0.3 to 30 mg/kg were linear with no evidence of target-mediated drug disposition. The mean clearance (CL) and volume of distribution of central compartment V₁ were linear with no evidence of target-mediated drug disposition. The terminal elimination half-life ranged from 9.7 to 16.4 days across dose groups with no apparent relationship with dose (33.5 to 40.3 mL/kg).

In a one-month GLP study, doses of 0.1 to 30 mg/kg were evaluated. Over the dose range studied, ABC008 maximum serum concentration (C_{max}) and area under the drug concentration-time curve (AUC) from time zero to 24 hours postdose increased in a generally dose-proportional manner. The time to C_{max} (T_{max}) was observed between 48 and 168 hours postdose on Day 1, between two and 144 hours postdose on Day 8, and between four and 48 hours postdose on Day 22.

In a three-month GLP study in which cynomolgus monkeys were administered 50 mg/kg ABC008 SC every two weeks (Q2W) for 13 weeks, all ABC008-treated animals maintained exposure throughout the dosing period, except for one female which showed clear impact of antidrug antibody (ADA) on exposure. After the last dose, the mean C_{max} and AUC_{0-t} for males were 1520 µg/mL and 7610 day*µg/mL (182640 hr*µg/mL) and for females 655 µg/mL and 3530 day*µg/mL (84720 hr*µg/mL), respectively. T_{max} was observed between two and 14 days postdose on Day 1 and between 0.33 and seven days postdose on Day 85. There were no apparent sex differences in exposure and accumulation.

In a six-month GLP study at 25 or 50 mg/kg once every two weeks, mean exposure, (C_{max} and AUC) from time zero to 168 hours postdose to ABC008 increased with increasing dose. Within the observed variability, the exposure was roughly dose proportional across the dose levels. The AUC from time zero to 168 hours postdose on Day 169 tended to be higher compared to Day 1 with individual accumulation ratios ranging from 0.921 to 2.84 across dose levels.

1.3.3. Toxicology

The toxicology profile of ABC008 was evaluated in a non-GLP single-dose IV study using male cynomolgus monkeys and three SC GLP toxicology studies: one-month, three-month, and six-month repeat-dose studies using male and female cynomolgus monkeys. ABC008 administration to cynomolgus monkeys produced sustained depletion of KLRG1+ lymphocyte subsets, as expected, in the GLP one-month and six-month repeat-dose toxicology studies and did not show signs of immune activation based on generally unperturbed cytokine levels in the one-month study, expected depletion of KLRG1+ lymphocyte subsets, a lack of proliferation in other lymphocyte subsets, and lack of associated clinical observations.

In the non-GLP single-dose study, single IV doses of ABC008 were well tolerated up to 30 mg/kg dose with no treatment-related changes in clinical observations, body weight, and hematology.

In the GLP one-month repeat-dose GLP toxicology study, SC ABC008 was well tolerated at all dose levels (0.1 to 30 mg/kg). Target organ effects were limited to non-adverse, minimal to mild increases in bone marrow cellularity at ≥ 10 mg/kg, which did not reverse during the six-week postdose observation period at 30 mg/kg. Changes in clinical pathology parameters, including decreased neutrophils, increased monocytes, increased fibrinogen, increased globulin, and decreased albumin (with corresponding decrease in albumin to globulin ratio) were observed at ≥ 10 mg/kg. These changes were considered consistent with inflammation and/or acute phase response and non-adverse, but unlikely due to immune activation based on generally unperturbed cytokine levels, lack of proliferation of lymphocyte subsets, and lack of associated clinical observations. In addition, ABC008 administration produced transient decreases in select NK cells and cytotoxic T cells and Th lymphocyte subsets, and sustained depletion of most KLRG1+ lymphocyte populations. Based on the one-month results, the no observed adverse effect level (NOAEL) was determined to be 30 mg/kg (i.e., the highest dose tested).

In the three-month repeat-dose GLP toxicology study in which cynomolgus monkeys were administered 50 mg/kg ABC008 SC Q2W for 13 weeks, ABC008 administered SC Q2W was well tolerated at 50 mg/kg. All animals survived until the scheduled necropsy on Day 92, seven days after the final dosing on Day 85. No test article-related changes were noted. Based on three-month results, the NOAEL was determined to be 50 mg/kg (i.e., the highest dose tested).

In the GLP six-month repeat-dose GLP toxicology study, ABC008 was well tolerated at all dose levels (5 to 50 mg/kg). There were no ABC008-related effects in the safety endpoints examined. One animal in the 50 mg/kg group had transient clinical pathology changes (including decreased neutrophils and increased monocytes) on Day 29 like those that were observed in the one-month study. These findings were not considered ABC008-related due to the single animal with this observation and the transient nature of the findings. Results for the six-month study including through Day 183 (Day 176 for bioanalysis) and ADA results are pending. Based on these interim results from the six-month study, the NOAEL was determined to be 50 mg/kg (the highest dose level tested).

1.4. Clinical Studies

ABC008 is being evaluated in a Phase I study (Study ABC008-IBM-101), which is currently ongoing in Australia. Study ABC008-IBM-101 is an ongoing open-label Phase I first-in-human single ascending dose (SAD) and multiple ascending dose study in adult subjects with IBM, with the first subject enrolled in April 2021. The primary objective of the study is to characterize the safety and tolerability of escalating dose levels of ABC008 when administered SC to subjects with IBM. Secondary objectives include assessment of PK and pharmacodynamic (PD) profiles as well as immunogenicity. While [REDACTED]

As of the data cutoff date of 18 May 2022, a total of 11 subjects have been dosed in the SAD portion of study ABC008-IBM-101, three at 0.1 mg/kg SC, three at 0.5 mg/kg SC, and five at 2.0 mg/kg SC, including three in the original SAD cohort and two in an expansion cohort. By the 18 May 2022 cutoff date, all 11 subjects in the SAD portion of the study had completed at least 28 days of postdosing follow-up, and six subjects (all those dosed at 0.1 and 0.5 mg/kg) had completed the 24-week postdosing follow-up.

The multiple ascending dose part of the ABC008-IBM-101 study will evaluate the same doses as the single ascending dose part administered to the SAD subjects once every eight weeks (Q8W) for 48 weeks (last dose of study medication at Week [W] 40). The multiple ascending dose part of the study was scheduled to begin in July 2022.

1.4.1. Preliminary Safety

As of the cutoff date of 18 May 2022, there have been no reported treatment-emergent dose-limiting toxicities, discontinuations due to adverse events (AEs), or deaths. One subject in Cohort 1 experienced a severe serious adverse event (SAE) of a fall (resulting in a muscle tear) more than four months after dosing with ABC008 0.1 mg/kg SC; the fall was reported as not related, and the subject had a history of falls including one prior AE of a fall within the study. There was one treatment-emergent AE of special interest (AESI) of oral herpes occurring approximately four months after dosing at 0.1 mg/kg in a subject with a history of cold sores and with positive herpes simplex virus type 1 (HSV-1) serology at baseline. The AE was classified as mild, related, and recovered.

Although not captured as AESIs of systemic injection reaction, several subjects in the ABC-IBM-001 study reported study drug-related AEs in the first 24 hours after SC dosing that could be consistent with this type of response to SC antibody administration. Examples include metallic taste in mouth (dysgeusia), rigors, fever, headache, malaise, nausea, and vomiting. All of these AEs resolved, with one subject receiving a single dose of paracetamol for headache.

No injection site reactions have been reported.

1.4.2. Preliminary Pharmacokinetics

Preliminary PK data from the first three cohorts in the Phase I IBM study (ABC008-IBM-101) suggest that SC administered ABC008 displays a long absorption phase (median T_{max} of ~10 to 14 days). Exposure appears to be generally dose proportional across the range evaluated (mean C_{max} 721 ng/mL to 10,105 ng/mL). The mean area under the concentration-time curve from time 0 to infinity for the 0.1 mg/kg and 0.5 mg/kg cohorts are 443,019 ng*hr/mL and

1,971,078 ng*hr/mL, respectively. ABC008 has a low apparent CL (mean 22.7 to 28.7 mL/h), and long $t_{1/2}$ (mean 12.3 to 14.3 days) in the 0.1 mg/kg and 0.5 mg/kg cohorts. Terminal phase parameters for the 2.0 mg/kg are not yet available as collection and analysis for this cohort are ongoing.

Overall, these findings indicate that ABC008 displays PK properties typical of therapeutic mAbs (Kamath, 2016).

1.4.3. Preliminary Pharmacodynamics

The pharmacodynamic analysis evaluated the response of lymphocyte subsets to treatment with ABC008, using characteristic markers for activation status: CD4, CD8, CD57, CD8/CD57, NK and regulatory T-cell markers. Cells with each of these markers were further evaluated as subpopulations that were high or low in KLRG1. For each of these lymphocyte subsets, the proportion that were KLRG1+ at baseline varied.

While individual subject's responses varied somewhat, the group geometric mean values indicated that ABC008 significantly depleted KLRG1+ population subsets, by up to 90% within one day of dosing, compared with the matched lymphocyte subsets that were relatively low in KLRG1 expression. The depletion effects were generally maintained for three weeks while some repopulation of KLRG1+ subsets was seen by Day 84, especially at lower doses of ABC008. By comparison, in general, lymphocyte subsets low in KLRG1 were depleted to a lesser extent and showed greater recovery trends than the matched KLRG1+ subset.

T-helper CD4+ cells, both with and without KLRG1+, were only slightly depleted. In contrast, the highly differentiated T-cell subset defined by being KLRG1+CD8+CD57+ was depleted by 100% on Day 2 and this was maintained through Day 84. A clear dose-dependent trend in extent of depletion and lack of recovery of this subset was seen over the study period.

Observation of overall lymphocyte cell counts shows mild decreases in numbers, with a dose relationship from 0.1 mg/kg to 2.0 mg/kg, however these effects were not of an extent associated with clear immunosuppression of circulating lymphocytes.

While the PD data are preliminary and limited in the number of subjects sampled, it strongly supports the concept that ABC008 selectively depletes KLRG1+ subsets associated with activated, differentiated lymphocyte populations that have been observed to be enriched in tissues in IBM. The sustained effects indicate that long-term control of this subpopulation and hence the disease state is feasible.

1.5. Study and Dose Rationale

The main purpose of this study is to determine the efficacy, safety, and tolerability of KLRG1+ targeting mAb ABC008 in subjects with IBM. In the Phase I IBM study a marked reduction was observed in circulating CD8+ KLRG1+ T cells at dose levels ranging from 0.1 to 2.0 mg/kg ABC008. However, it remains unknown what level of cytotoxic T-cell reduction has been achieved in the muscle as critical target tissue, and whether that level of reduction will halt disease progression and potentially allow recovery of injured muscle cells. For this progressive and disabling disease where no immunomodulatory interventions have proven efficacious to date, this study proposes to dose subjects with ABC008 at 0.5 and 2.0 mg/kg, both shown to be safe and well tolerated in the Phase I study, and to provide a durable and near maximal KLRG1+

cell reduction in circulation. The 0.1 mg/kg dose level demonstrated a mean reduction of KLRG1+ cells of 70% and will thus not be evaluated in this study.

With a nearly half-log difference, this dynamic range should allow determination of a therapeutic dose that optimizes the benefit/risk profile for this patient population.

In the Phase I SAD study (Study ABC008-IBM-101), target cell reduction at the following single-dose administration at 0.5 and 2.0 mg/kg generally was maintained through the W8 time point with evidence of subsequent recovery. This matches the preliminary PK results with a half-life of approximately 12 to 14 days. Hence, the proposed study dosing interval of eight weeks aligns with both PD response and the four to five drug half-lives.

As well as evaluating the effects of ABC008 on measures of disease activity, using various scales of muscular performance and health-related quality of life (HRQoL) measures, study endpoints will include [REDACTED] including depletion of lymphocyte subsets. In addition, [REDACTED]

[REDACTED] If results are considered to be sufficiently robust, data from this study may be used to support a marketing application for ABC008.

1.6. Benefit/Risk Assessment

1.6.1. Potential Benefits

The rationale for performing research with ABC008 is based on our understanding of the central role of KLRG1+ T cells in the destruction of muscle in patients with IBM, which leads to progressive limb weakness and disability including loss of hand function and ambulation. Currently, there is no effective pharmacological agent for the treatment of IBM, and there is no pharmacological treatment considered standard of care. In Study ABC008-IBM-101, preliminary data from the 0.1, 0.5, and 2.0 mg/kg doses show significant depletion of the highly differentiated cytotoxic T-cell populations, comprising primarily KLRG1+CD8+ T cells, with no significant impact on overall blood cell populations, indicating potential benefit in the treatment of patients with IBM.

1.6.2. Potential Risks

No significant risks have been identified in nonclinical studies of ABC008 in cynomolgus monkeys to date. Preliminary data in human subjects show that ABC008 has been well tolerated overall. Potential risks of administering a cell-depleting antibody include injection site reactions, systemic injection reactions (e.g., hypersensitivity, systemic inflammatory response), and infections (including, but not limited to, the reactivation of latent herpes viruses).

In this study and the entire program, thorough monitoring and assessment of all AEs will be performed, and safety assessments according to the protocol to be conducted throughout the study will include physical examination, vital sign measurements, ECGs, and clinical laboratory tests.

No injection site reactions have been reported in the Phase I Study ABC-IBM-101, but this is a potential risk with injected medications. Investigators will monitor for injection site reactions, including, but not limited to, injection site erythema, pruritus, and pain.

While there has been no evidence supporting systemic injection reactions related in the toxicology studies, there is potential for these to be seen clinically based on the expected mechanisms of action of ABC008. Potential risks of administering a cell-depleting antibody include systemic injection reactions and injection reactions related to cytokine release (Roselló et al., 2017; Shimabukuro-Vornhagen et al., 2018). Mild, self-limiting systemic injection reactions have been noted in early clinical trials and have been managed with time or paracetamol (further details are in the ABC008 IBM IB). Investigators will monitor for systemic injection reactions. Study subjects will be instructed on the symptoms of a systemic injection reaction and to seek medical care for these or other emergent symptoms.

Potential risks also include infection (including, but not limited to, reactivation of latent herpes viruses such as Epstein-Barr virus [EBV], cytomegalovirus [CMV], HSV-1, HSV-2, and varicella zoster virus [VZV]). In this study, herpes virus infection status will be assessed by measuring IgG levels to common herpes viruses (i.e., EBV, CMV, HSV-1 and -2, and VZV) as well as CMV and EBV viral loads by polymerase chain reaction (PCR) analysis.

1.6.3. Benefit/Risk Conclusion

Given the high unmet need and the measures taken to minimize risk to subjects participating in this study, the potential benefits of establishing safety and efficacy of ABC008 for the treatment of IBM outweighs the risk of study participation.

2. STUDY OBJECTIVES

The primary objective of Part A (Sentinel Cohort) is safety and tolerability as described in Section 2.2. The efficacy and other objectives listed below are objectives for Part B (Double-Blind Safety and Efficacy Cohort) only; however, subjects from Part A will be included in the efficacy and safety analyses for the overall study. The primary objective of Part C (PD Recovery Cohort) is PD as described in Section 2.3.

2.1. Efficacy Objectives (Part B)

2.1.1. Primary Efficacy Objective

To determine the efficacy of SC ABC008 in IBM at two SC dose levels as measured by IBM Functional Rating Scale (IBMFRS) at W76.

2.1.2. Key Secondary Efficacy Objectives

To determine the efficacy of SC ABC008 in subjects with IBM at W76, as measured using:

1. Manual muscle testing (MMT) 12;
2. Grip strength for the dominant hand by dynamometry;
3. Strength of quadriceps for the dominant leg by dynamometry;
4. Modified Timed Up and Go test (mTUG).

2.2. Safety Objectives (Part A and Part B)

Part A (Sentinel Cohort; Primary Objective)

To determine the safety and tolerability of recurrent dosing of ABC008 in subjects with IBM at two SC dose levels.

Part B (Double-Blind Safety and Efficacy Cohort)

To determine the safety and tolerability of SC ABC008 in subjects with IBM.

2.3. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Objectives (Part B and Part C)

Part B (Double-Blind Safety and Efficacy Cohort)

In subjects with IBM:

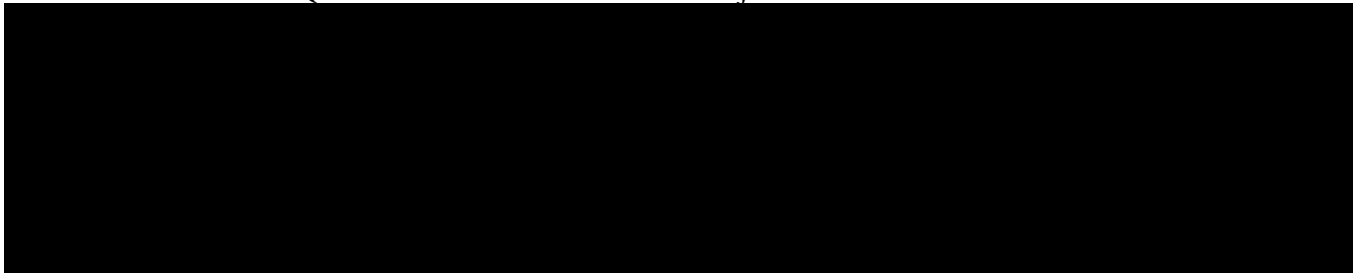


Part C (PD Recovery Cohort; Primary Objective)

To evaluate the PD recovery of the depletion of KLRG1+ cells after the end of treatment with SC ABC008 in subjects with IBM.

2.4. Health-related Quality-of-Life Objectives (Part B)

To determine the HRQoL related to SC ABC008 in subjects with IBM.



3. STUDY ENDPOINTS

The endpoints for Part A (Sentinel Cohort) are all related to safety as described in Section 3.2.1. The efficacy and other endpoints listed below are endpoints for Part B (Double-Blind Safety and Efficacy Cohort) only; however, subjects from Part A will be included in the efficacy and safety analyses for the overall study.

3.1. Efficacy Endpoints (Part B)

3.1.1. Primary Efficacy Endpoint

The primary endpoint of the study will be mean change from Baseline (Day 1) in IBMFRS at W76.

3.1.2. Key Secondary Efficacy Endpoints

The following key secondary endpoints will be analyzed in a sequential manner:

1. Mean change from Baseline (Day 1) in MMT 12 at W76;
2. Mean change from Baseline (Day 1) in hand grip strength for the dominant hand by dynamometry at W76;
3. Mean change from Baseline (Day 1) in quadriceps strength for the dominant leg by dynamometry at W76;
4. Mean change from Baseline (Day 1) in mTUG at W76.

3.2. Safety Endpoints (Part A and Part B)

3.2.1. Part A (Sentinel Cohort)

3.2.1.1. Primary Endpoint

The primary endpoint for Part A of the study will be safety, as assessed by the incidence, type, and severity of treatment-emergent adverse events (TEAEs).

3.2.1.2. Secondary Endpoints

1. Incidence, type, and severity of treatment-emergent serious adverse events (TESAEs);
2. Incidence, type, and severity of TEAEs with onset within 24 hours from the start of any study medication administration;
3. Incidence of TEAEs leading to study medication or study discontinuation;

4. Clinically significant changes in standard laboratory parameters, vital signs, and ECGs;
5. AESIs:
 - a. Injection site reactions;
 - b. Systemic injection reactions (e.g., hypersensitivity, systemic inflammatory response);
 - c. Infection, including but not limited to, reactivation of latent herpes viruses such as EBV, CMV, human herpes virus (HHV), HSV-1 or -2, or VZV.

3.2.2. Part B (Double-Blind Safety and Efficacy Cohort)

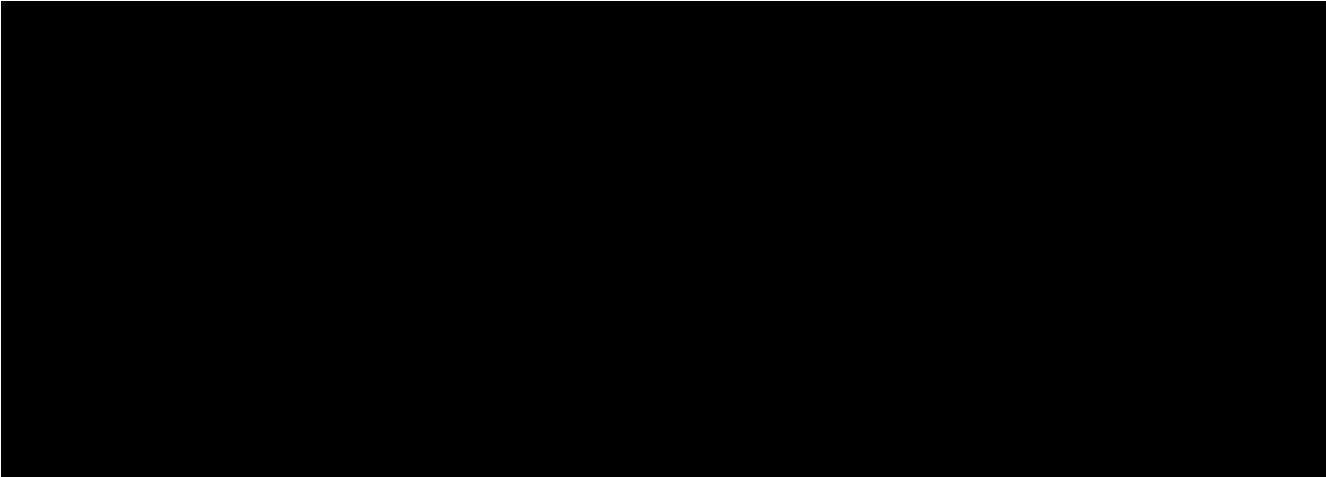
1. Incidence, nature, and severity of TEAEs;
2. Incidence, nature, and severity of TESAEs;
3. Incidence, nature, and severity of TEAEs with onset within 24 hours from the start of any study medication administration;
4. Incidence of TEAEs leading to study medication or study discontinuation;
5. Changes in standard laboratory parameters, vital signs, and ECGs;
6. AESIs:
 - a. Injection site reactions;
 - b. Systemic injection reactions (e.g., hypersensitivity, systemic inflammatory response);
 - c. Infection, including but not limited to, reactivation of latent herpes viruses such as EBV, CMV, HHV, HSV-1 or -2, or VZV.

3.3. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Endpoints (Part B and Part C)

3.3.1. Part B (Double-Blind Safety and Efficacy Cohort)

3.3.1.1. Pharmacokinetic Endpoints

Serum concentration and PK parameters, when feasible, of ABC008.



3.3.2. Part C (PD Recovery Cohort)

The endpoint for Part C of the study will be PD recovery as assessed by the time from End-of-Treatment (EOT)/Early Termination visit (ETV) to recovery of KLRG1+ cells.

3.4. Health-Related Quality-of-Life Endpoints (Part B)

- Mean change from Baseline (Day 1) in Study Short Form 36-item Health Survey Version 2 (SF-36v2) physical component summary (PCS) score, mental component summary (MCS) score, and individual domain score at W76;
- Mean change from Baseline (Day 1) in the EuroQol 5 Dimension, 5 Level, Quality-of-Life Questionnaire (EQ-5D-5L) at W76.

4. STUDY PLAN

4.1. Overall Study Design and Plan

This is a Phase II/III randomized, double-blind, placebo-controlled, parallel, multicenter study with three parts. Part A is a sentinel safety cohort in which subjects will receive three doses of study drug and the resultant safety and tolerability data will be evaluated by a Data and Safety Monitoring Board (DSMB). With a favorable DSMB review, the study will progress to Part B, with the main purpose of evaluating the efficacy, safety, and tolerability of two dose levels of ABC008 compared with placebo in subjects with IBM. Part C is a PD and safety follow-up to follow recovery of the depletion of KLRG1+ cells.

Adult males and females 40 years of age or older at the time of the first dose of study medication will be enrolled in the study. Subjects with a documented diagnosis of either clinico-pathologically defined IBM, clinically defined IBM, or probable IBM according to the European Neuromuscular Centre (ENMC) IBM 2011 research diagnostic criteria ([Rose et al., 2013](#)), modified to allow inclusion of subjects age ≥ 40 years with documented IBM, will be included.

It is anticipated that approximately 290 subjects will be screened to achieve approximately 231 subjects enrolled (in total for Part A and Part B). For Part A (Sentinel Cohort), approximately 30 enrolled subjects will be randomly assigned to three treatment arms in a 2:2:1 ratio (approximately 12 subjects each in the active arms and six subjects in the matching placebo arm). In Part B (Double-Blind Safety and Efficacy Cohort), approximately 201 additional enrolled subjects will be randomly assigned to three treatment arms in a 1:1:1 ratio (approximately 67 subjects per arm). Approximately 50 sites will be included from seven countries, including Australia, Belgium, Canada, France, Germany, the United Kingdom, and the United States (US).

The study design is outlined in [Figure 1](#) and the visit schedule and planned assessments at each visit are detailed in the Schedules of Events in [Appendix 1](#).

Part A (Sentinel Cohort) of the study comprises an up to five-week Screening Period, a 76-week Treatment Period (including 20 weeks of sentinel dosing followed by a DSMB review to determine continued dosing through the end of the Treatment Period), and safety follow-up four weeks after the W76 visit (eight weeks after the last dose at W72 in the Treatment Period). Part A will be double-blind and placebo-controlled. The study drug will be dosed via SC injection Q8W. After subjects have received three doses of study drug, a DSMB will review the interim safety data for all Part A subjects through at least the W20 visit. Subjects may continue in their assigned groups in a double-blind manner while the DSMB sentinel cohort review is pending. Continued dosing of Part A subjects through W72 will be predicated on a favorable DSMB assessment of safety, as will initiation of enrollment in Part B.

Part B (Double-Blind Safety and Efficacy Cohort) of the study comprises an up to five-week Screening Period, a 76-week Treatment Period, and safety follow-up four weeks after the W76 visit (eight weeks after the last dose of study medication at W72). The W80 safety follow-up visit may be conducted via phone. Part B will be double-blind and placebo-controlled.

In both Parts A and B, at the W80 follow-up visit, subjects will be eligible to enroll in an open-label long-term extension study. If conducted in person, the W80 visit may serve as both

the safety follow-up visit for Part A or B of the current study and as the Baseline Visit for the long-term extension study.

Subjects who choose not to enroll in the open-label long-term extension study and subjects who prematurely discontinue study drug during Part A or B will progress to Part C (PD Recovery Cohort) for follow-up. If conducted in person, the Part A or B W80 visit may serve as the Baseline Visit for Part C. Part C of the study will consist of AE follow-up monthly, PD assessments and pregnancy testing every three months. The Follow-up Period in Part C will be a minimum of three months and will continue for each subject until their KLRG1+ cells have recovered. This will be performed by flow cytometry. All subjects entering Part A and B will have baseline flow cytometry performed and subjects entering Part C will have flow cytometry performed every three months until recovery. Once KLRG1+ cell recovery has been documented, an End-of-Study phone call will be conducted to notify the subject and collect any AEs not previously reported.

The Investigator will obtain signed informed consent from the subject before any study procedures are performed. Further details regarding the informed consent process are in Section 10.2. Subjects will attend a Screening Visit within 35 days of Day 1; screening procedures may be completed over more than one visit, as long as the results of all screening tests are available at the time that subject eligibility is reconfirmed prior to dosing.

In both Parts A and B, subjects will be administered ABC008 at one of two dose levels, or matching placebo during the Treatment Period. ABC008 or placebo will be administered by SC injection Q8W. In Part A, approximately 30 subjects will be randomly assigned in a 2:2:1 ratio to ABC008 0.5 mg/kg, ABC008 2.0 mg/kg, or placebo. In Part B, approximately 200 subjects will be randomly assigned in a 1:1:1 ratio to ABC008 0.5 mg/kg, ABC008 2.0 mg/kg, or placebo. Further details on the method of assigning subjects to the treatment groups are in Section 7.3.

The scheduled dosing interval is every eight weeks $\pm$ seven days. Dose modification during the study will only be permitted in the event of a weight change, as detailed in Section 7.4. Subjects who discontinue dosing with study medication during Part A (Sentinel Cohort) or Part B (Double-Blind Safety and Efficacy Cohort) will progress to Part C (PD Recovery Cohort) for PD and safety follow-up (to continue until their KLRG1+ cells have recovered). Subjects may be prematurely discontinued from the study as described in Section 5.4.

The study is randomized and double-blinded regarding ABC008 and placebo to prevent bias in treatment allocation and in the assessment of treatment effect. The Investigator, site personnel, the Sponsor and their representatives involved in monitoring and conducting the study, and the subjects will be blinded to the study medication administered. Details on access to the treatment codes in the event of emergency unblinding are in Section 7.2.1.

Assessments are described in Section 6. The sequence for performing the assessments is in the Schedules of Events (Appendix 1). Assessments in Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort) will include:

- Patient-reported outcome measures (PROs) including:

- [REDACTED]
- [REDACTED] (Part B only);

- EQ-5D-5L;
- SF-36v2.
- Objective measures and physician-reported assessments including:
 - [REDACTED]
 - IBMFRS;
 - MMT [REDACTED] 12;
 - Grip strength and quadriceps strength by dynamometry;
 - mTUG;
 - [REDACTED]
 - [REDACTED]

Safety will be assessed throughout the study by monitoring of vital signs (blood pressure, pulse, temperature, and respiration rate), laboratory tests (hematology, chemistry, urinalysis, complement levels, and C-reactive protein [CRP]), physical examination results, ECGs, and all AEs.

[REDACTED]

Part C (PD Recovery Cohort) of the study will consist of PD and safety assessments.

4.2. Discussion of Study Design

ABC008 is an investigational-stage, novel biologic, directed against a novel target, and has not been approved in any country/region.

Adult males and females 40 years of age or older at the time of the first dose of study medication will be enrolled in the study. Subjects with a documented diagnosis of either clinicopathologically defined IBM, clinically defined IBM, or probable IBM according to the ENMC IBM 2011 research diagnostic criteria ([Rose et al., 2013](#)), modified to allow inclusion of subjects age ≥ 40 years with documented IBM, will be included. Subjects who are at least 40 years old will be considered eligible, since Brady, et al. ([Brady et al., 2013](#)) showed that approximately 7.5% of patients with IBM are under 45 years old. These subjects demonstrate the same features of the disease and are considered to help provide important data for this study. The inclusion criteria incorporate minimal functional capabilities such as ability to arise from a standard armchair without support from another person or device (required for mTUG assessment), walk three meters, turn around, walk back to the chair, and sit down, to avoid enrolling subjects whose disease has likely progressed beyond a point of potential benefit (i.e., still sufficient muscle function to preserve and measure improvement).

The doses of 0.5 mg/kg and 2.0 mg/kg at a frequency of Q8W are proposed based on an overall assessment of the safety and tolerability, and emerging PK/PD data from Study ABC008-IBM-101. Single ascending doses of 0.1 mg/kg to 2.0 mg/kg have been evaluated in the

ongoing Phase I study. Single-dose administration has been well tolerated and no serious or severe AEs related to ABC008 have been observed.

A sentinel safety cohort (Part A) was included to provide multiple-dose safety data for a cohort of subjects before proceeding with chronic treatment of a large number of subjects. An interim safety analysis will be conducted after completion of three doses in Part A and will be reviewed by a DSMB. Completion of dosing through W72 in Part A and enrollment of Part B (Double-Blind Safety and Efficacy Cohort) will be predicated on a favorable DSMB assessment of the interim safety data.

Preliminary immunophenotyping data support more consistent levels of depletion across subjects for the KLRG1+ subsets of CD8+, CD8+CD57+, and CD4+ T lymphocytes with increasing dose. For both the 0.5 mg/kg and 2.0 mg/kg cohorts, relatively maximal depletion of the KLRG1+ subsets of CD8+ and CD8+CD57+ T lymphocytes occurred, while there was evidence of further depletion for the KLRG1+CD4+ T cells with 2.0 mg vs. 0.5 mg.

Part C (PD Recovery Cohort) of the study has been included without a specified duration to follow subjects for PD and safety for a minimum of three months until their KLRG1+ cells (specifically CD8+ and CD4+) have recovered.

4.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be the mean change in IBMFRS at W76. This primary endpoint has been developed to capture the broad array of functional disabilities specific to patients with IBM.

The IBMFRS is an administered questionnaire that was developed by academic Investigators ([Jackson et al., 2008](#)), adapted from the amyotrophic lateral sclerosis functional rating scale. IBMFRS has been utilized as a primary endpoint in other randomized studies in IBM.

The timing for the primary analysis (76 weeks) is based on an analysis of the expected treatment difference from placebo for the proposed primary endpoint from prior randomized studies.

4.3. End of Study

A subject is considered to have completed the study if he/she has completed all study visits.

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

4.4. Stopping Criteria

Criteria for premature discontinuation of dosing for individual subjects are detailed in Section [5.4.1](#).

Any of the following will prompt a safety assessment by the Medical Monitor (MM) in discussion with the Investigator to determine whether dosing may proceed in additional subjects:

- Any TESAE;
- Any severe TEAE.

The following will prompt a consultation between the MM and the DSMB to determine whether dosing may proceed in additional subjects:

- $\geq$ two subjects with an SAE from the same Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, unless clearly attributed to underlying disease.
- $\geq$ two subjects with discontinuations due to AEs as detailed in Section 5.4.1, unless clearly attributed to clinical deterioration due to IBM.

Safety will be continuously assessed throughout the study and the Sponsor may stop the study for safety reasons without consulting the DSMB.

4.5. Long-term Open-label Extension Study

In Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort), all eligible subjects completing the W80 visit will be encouraged to enroll in a long-term open-label extension study to follow the safety and efficacy of chronic ABC008 dosing.

If conducted in person, the W80 visit may serve both as a safety follow-up visit for Part A or B of the current study and as the Baseline Visit for the long-term extension study. Subjects enrolling in the long-term extension will have their first dose given at the Baseline Visit, which will be eight weeks after their last dose in the current study and continue dosing once every eight weeks with safety and efficacy assessments at those times.

While both the current study and the long-term extension are active, the DSMB will review data from both studies on a regular schedule. Details of the design of the long-term extension study will be provided in a separate protocol.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

For both Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort), the following inclusion criteria must be met for a subject to be eligible for inclusion in the study. Eligibility criteria for this study should be assessed only after signing of informed consent for this study. All data from Screening and all data except for central laboratory results from Baseline (Day 1) Visit should be used to confirm subject eligibility.

1. Adult males and females age ≥ 40 years at the time of the first dose of study medication;
2. Able to read, understand, and provide signed informed consent prior to the performance of any study-related procedures;
3. Willing and able to comply with the requirements of the protocol, including traveling to the site for study-related assessments and SC injections, and using electronically administered diaries and questionnaires;
4. Weight ≥ 40 and ≤ 150 kg;
5. Diagnosis of either clinico-pathologically defined IBM, clinically defined IBM, or probable IBM according to the ENMC IBM 2011 research diagnostic criteria ([Rose et al., 2013](#)), modified to allow inclusion of subjects age ≥ 40 years with documented IBM. Documented histopathology results must be available prior to Baseline (Day 1) to confirm eligibility;
6. As required to complete the mTUG test, able to arise from a standard armchair (described in Section [6.2.6](#)), with use of their arms but without support from another person or device (e.g., cane, walking stick), at Screening and Baseline (Day 1);
7. As required to complete the mTUG test, able to walk three meters, turn around, walk back to the chair, and sit down, with or without an assistive device. Once arisen from the chair, subject may use any walking device but cannot be supported by another person, furniture, or a wall;
8. Agree to adhere to relevant local guidelines regarding minimizing exposure to severe acute respiratory syndrome coronavirus 2 from the first Screening Visit until EOT/ETV;
9. Negative coronavirus disease 2019 (COVID-19) test results within 48 hours of Baseline (Day 1) (PCR or rapid antigen testing as per local guidance);
10. Agree (to the best of their knowledge), to avoid contact with any person suspected or known to have an infectious disease of which they are at risk of contracting from the first Screening Visit until the EOT/ETV;

11. Women of childbearing potential (WOCBP) and male subjects with female partners who are WOCBP (based on gender assignment at birth) must agree to use highly effective (<1% failure rate) contraception (as detailed in Section 7.6.4) for at least 30 days prior to the first dose of study medication, during the study, and for 180 days following EOT/ETV;
12. Male subjects (based on gender assignment at birth) must refrain from sperm donation for the duration of the study and for 180 days after EOT/ETV;
13. WOCBP (based on gender assignment at birth) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).

5.2. Exclusion Criteria

For both Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort), a subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study. Eligibility criteria for this study should be assessed only after signing of informed consent for this study. All data from Screening and all data except for central laboratory results from Baseline (Day 1) Visit should be used to confirm subject eligibility.

1. Any other form of myositis or myopathy other than IBM, e.g., metabolic or drug-induced myopathy, drug-induced myositis, anti-synthetase syndrome, polymyositis or dermatomyositis, cancer-associated myositis (myositis diagnosed within three years, either before or after), myositis in overlap with another autoimmune disease (e.g., systemic lupus, systemic sclerosis, rheumatoid arthritis), or muscular dystrophy;
2. Any condition, e.g., severe degenerative arthritis with limited range of motion, which precludes the ability to quantitate muscle strength or perform functional assessments (e.g., mTUG), in the Investigator's opinion;
3. Presence of another autoimmune or autoinflammatory disease which, in the view of the Principal Investigator or MM, may impact the subject's ability to perform study procedures such that it would confound clinical assessment. Examples include rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, inflammatory bowel disease, systemic lupus erythematosus. Subjects with Sjogren's syndrome, T-cell large granular lymphocyte leukemia (T-LGLL), or well-controlled thyroid disease are permitted;
4. Receipt of any of the following treatments within the following time frames before Screening (or as otherwise specified):
 - a. Intravenous or intramuscular corticosteroids: four weeks;
 - b. Oral prednisone (or prednisone equivalent) >7.5 mg/day at Screening;
 - c. Use of nonbiologic immunosuppressants (e.g., cyclosporine, mycophenolate mofetil or sodium, azathioprine, methotrexate, sirolimus, Janus kinase inhibitors): 12 weeks;
 - d. Intra-articular therapies, such as corticosteroids or hyaluronic acid preparations: four weeks;

- e. Intravenous, intramuscular, or SC immunoglobulin (IVIG, IMIG, or SCIG): 12 weeks;
 - f. Cytokine, integrin, or activin antagonists or selective co-stimulation modulators, including but not limited to, interleukin (IL)-1, IL-6, IL-17, IL-12/23, IL-23, interferon, integrin, and tumor necrosis factor α antagonists, abatacept, bimagrumab: 12 weeks;
 - g. Cell-depleting or modulating therapies (e.g., alemtuzumab, antithymocyte globulin, atacicept, belimumab, obinutuzumab, ocrelizumab, ofatumumab, rituximab, siplizumab): 12 months;
 - h. Use of chemotherapeutic regimens or other cytotoxic therapies, e.g., cyclophosphamide, doxorubicin or hydroxyrubicin, vincristine, and prednisone; purine analogs, alkylating agents: 24 weeks;
 - i. Other immunomodulatory biologics: 12 weeks or five half-lives, whichever is longer;
 - j. Transfusion with blood, packed red blood cells, or platelets or treatment with plasmapheresis or plasma exchange: six weeks;
 - k. Anabolic steroids: four weeks;
 - l. Growth hormone: four weeks;
 - m. Physiologic supplementation with testosterone permitted provided dose stable for four weeks before Screening and expected to stay stable during the study;
 - n. Therapies associated with neuromuscular side effects including antimalarial drugs (e.g., chloroquine, hydroxychloroquine), colchicine, cholesterol-lowering drugs (e.g., statins) except if on stable dose for at least 12 weeks, and without impact on assessment of IBM progression;
5. Initiation of an exercise or a physical therapy regimen within four weeks of Screening. Any exercise or physical therapy regimen initiated prior to the Screening Visit must have been stable for at least four weeks prior to Screening;
6. Subject has had recent serious or ongoing infection, or risk for serious infection, including but not limited to:
- a. Acute or chronic infection defined as any infection requiring oral antibiotic, antifungal, or antiviral (antimicrobial) therapy within two weeks of Baseline (Day 1);
 - b. Hospitalization or receipt of a course of systemic (IV or intramuscular) antimicrobial therapy for infection within 24 weeks prior to Screening;
 - c. Symptomatic COVID-19 infection at Screening. In the setting of a positive COVID-19 test within two days of Baseline (Day 1), subject may be retested one additional time as long as they are within the study screening window;
 - d. Symptomatic herpes zoster or herpes simplex infection (oral herpes simplex virus lesions permitted) within 12 weeks prior to Screening or during the Screening Period. Chronic antiviral therapy with e.g., valacyclovir permitted;

- e. History of severe and/or disseminated viral infections, and/or opportunistic infections within 12 months of Screening;
 - f. Seropositivity for or active infection by human immunodeficiency virus (HIV);
 - g. Active, chronic, or history of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (hepatitis B core antibody or surface antigen positive, or HCV antibody positive with reflex HCV RNA positive at Screening; subjects who have received curative therapy for HCV are permitted if therapy was completed at least 24 weeks prior to Screening and subject is HCV RNA negative);
 - h. Known active or untreated latent tuberculosis (TB) within 12 weeks prior to or at Screening and/or positive QuantiFERON®-TB Gold Plus and/or positive T-SPOT®.TB tests at Screening. Subjects with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines are allowed if no history of re-exposure to TB since treated. Intermediate or borderline test results require a repeat test to confirm negative status or medical evaluation to rule out a concern for TB disease. T-SPOT.TB may be performed locally, or QuantiFERON-TB Gold Plus test may be performed locally or centrally at site's discretion;
 - i. Receipt of a live attenuated vaccine within 30 days or a non-live vaccine within 14 days of first dose;
 - j. Primary immunodeficiency (unless otherwise considered, in the opinion of the Investigator and MM, to confer a clinically insignificant infection risk, such as deficiency in IgA, Components of the Complement System, innate immunity (C1q, C2, or C4) without a history of recurrent infections [three or more infections in one year requiring antimicrobial therapy]);
 - k. History of recurrent infections (three or more infections requiring antimicrobial therapy in the 12 months prior to Screening);
7. Any of the following laboratory values at Screening:
- a. Estimated glomerular filtration rate (eGFR) <30 mL/min by the Chronic Kidney Disease Epidemiology Collaboration equation;
 - b. Hemoglobin <10 g/dL;
 - c. White blood cell count <3.0× 10⁹/L;
 - d. Absolute neutrophil count <1.5× 10⁹/L (1500/mm³);
 - e. Platelet count <100× 10⁹/L;
 - f. Serum AST or serum ALT >3× the upper limit of normal [ULN]) unless considered consistent with muscle origin;
 - g. Total bilirubin >2× ULN (3× ULN for subjects with documented Gilbert's syndrome);

8. Presence of New York Heart Association Class III or IV heart failure, or uncontrolled blood pressure (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg at rest);
9. Mean (based on triplicate measurements) QT interval corrected using Fridericia's formula >450 msec for males or >470 msec for females on screening ECGs, and/or clinically significant ECG findings at Screening as per Investigator assessment (subjects with non-clinically significant bundle branch block are permitted);
10. Major surgery within 12 weeks before Screening, major surgery planned during the study period, or any surgery planned during the study period that would require corticosteroid therapy and/or could confound the results of the study, put the subject at undue risk, or interfere with protocol adherence;
11. Clinical evidence of significant unstable or uncontrolled diseases (e.g., cardiac [including congestive heart failure, angina, or recent (<6 months prior to Screening) myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring systemic corticosteroid therapy, pulmonary hypertension, or interstitial lung disease], hematologic, gastrointestinal, endocrinologic [e.g., hypothyroidism, diabetes], hepatic, renal, neurological, infectious, psychiatric [e.g., severe depression]) that, in the opinion of the Investigator or Sponsor, could confound the results of the study, put the subject at undue risk, or interfere with protocol adherence;
12. Evidence of current or previous clinically significant disease, medical condition (including abnormal laboratory values), or finding in the medical examination that in the Investigator's or Sponsor's opinion would compromise the safety of the subject or the ability to interpret the data;
13. Any active or suspected malignancy including myeloproliferative or lymphoproliferative disorder or history of documented malignancy within the last five years before Screening. Subjects with T-LGLL or appropriately excised and cured cervical carcinoma *in situ*, basal or squamous cell carcinoma of the skin are permitted;
14. Clinically significant abnormality in kappa/lambda ratio or evidence of monoclonal protein (M protein) indicating possible monoclonal gammopathy of undetermined significance or smoldering myeloma;
15. Alcohol abuse or drug abuse in the last one year prior to Screening in the opinion of the Investigator;
16. Columbia Suicide Severity Rating Scale (C-SSRS) score of 4 or 5 on the suicidal ideation items, intent in the last six months prior to randomization, or any "yes" on the Suicidal Behavior item that is related to suicidal behaviors or attempts occurring during the past two years;
17. Women who are pregnant, lactating, or discontinued lactation less than 12 weeks prior to Screening, or who plan to become pregnant or initiate lactation during the study;
18. Participation in another investigational drug study within 30 days prior to Screening (or five times the half-life of the drug, whichever is longer);

19. Has known hypersensitivity to ABC008, any component of the formulation of ABC008, or history of anaphylaxis to any prior mAb therapy;
20. Unable to comply with the protocol in the Investigator's or Sponsor's opinion;
21. For subjects in France only: Persons under court protection, persons not affiliated to a social security system, or protected adults (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1).

5.3. Screen Failures

Screen failures are defined as subjects who do not meet all study inclusion criteria (Section 5.1) and/or meet any exclusion criteria (Section 5.2). Information on screen failures will minimally include demography, screen failure details, eligibility criteria, and any SAE. Subjects who withdraw from the study for any reason, without completing all necessary screening assessments, will be considered screen failures.

If the subject is deemed a screen failure, rescreening may be allowed one time within the recruitment period, but rescreening must be approved by the MM.

5.4. Premature Discontinuation

5.4.1. Premature Discontinuation of Investigational Product for Individual Subjects

A subject will be discontinued from study drug dosing in the event of a confirmed pregnancy (as detailed in Section 8.6.1).

If an individual subject experiences any of the following, it will prompt a safety assessment by the MM in discussion with the Investigator to determine if the subject may continue treatment; no dosing may proceed for that subject without Sponsor approval:

- Any TESAE;
- Any other AE that, in the opinion of the Investigator or Sponsor, may represent a clinically significant safety risk to the subject;
- Two consecutive clinically significant increases in CMV or EBV viral load (Section 6.3.5.2.5).

Stopping criteria for the study are detailed in Section 4.4; discontinuation of multiple subjects due to AEs may prompt a consultation between the MM and DSMB to determine whether dosing may proceed in additional subjects.

Additional reasons for discontinuation from study drug may include, but are not limited to, the following:

- Investigator discretion (note reason);
- Subject request (note reason).

A subject may choose to discontinue the study drug at any time for any reason. If a subject discontinues study drug early, the reason for discontinuation and the date of discontinuation must be recorded on the appropriate electronic case report form (eCRF). If the reason for

discontinuation of study drug is an AE, the AE must also be recorded on the AE page of the eCRF.

If study medication is prematurely discontinued during Part A (Sentinel Cohort) or Part B (Double-Blind Safety and Efficacy Cohort), the subject will progress to Part C (PD Recovery Cohort) for PD and safety follow-up (to continue until their KLRG1+ cells have recovered).

5.4.2. Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason, without any reprisal.

The Investigator has the right to terminate participation of a subject for any of the following reasons:

- Violation of the protocol;
- Severe AEs or SAEs;
- Difficulties in obtaining blood samples;
- Two consecutive doses of study medication are missed;
- Any other reason relating to the subject's safety or integrity of the study data.
- If a subject is withdrawn from the study, the MM/Sponsor will be informed immediately.

If the subject withdraws consent for disclosure of further information, the Sponsor may retain and continue to use any collected data before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

In the event of premature termination from the study, the Investigator should make every effort to ensure the subject completes the assessments indicated at the EOT/ETV study visit.

Subjects who prematurely discontinue from the study cannot subsequently rejoin the study.

Details on the discontinuation of study sites or for the study are in Section [10.9](#).

5.4.3. Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit

schedule, and ascertain whether or not the subject wishes to and/or should continue in the study;

- Before a subject is deemed lost to follow-up, the Investigator (or designee) must make every reasonable effort to regain contact with the subject (where possible, two telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's eCRF;
- Should the subject continue to be unreachable, he/she will be considered to be lost to follow-up.

6. DESCRIPTION OF STUDY ASSESSMENTS

Study procedures should be completed as delineated in the Schedules of Events ([Appendix 1](#)): Part A (Sentinel Cohort) in [Table 4](#), Part B (Double-Blind Safety and Efficacy Cohort) in [Table 5](#), and Part C (PD Recovery Cohort) in [Table 6](#). However, if a subject is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the MM or appropriate designee. For visits where efficacy assessments and other patient- or physician-reported outcomes are conducted, the assessments should be conducted in the following order: C-SSRS, [REDACTED] IBMFRS, [REDACTED] measures (EQ-5D-5L, SF-36v2), objective measures of efficacy (MMT [REDACTED] 12, grip and quadriceps dynamometry, mTUG), and [REDACTED] Efficacy assessments should be conducted prior to collection of blood and urine samples for PK, PD, and laboratory assessments.

Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures. If necessary, to facilitate subjects' continued participation, alternative methods for study visits and safety assessments may be implemented, which may include remote study visits and assessments.

Blood samples will be collected for screening, for safety laboratory tests, including hematology and clinical chemistry as well as for PK/PD endpoints, at timepoints specified in [Appendix 1](#). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Unless indicated otherwise, all laboratory samples will be processed and shipped to the central laboratory, as described in the Laboratory Manual. The central laboratory will analyze the samples or send them to reference laboratory(ies) for analysis, as indicated in the Laboratory Manual.

6.1. Demographics and Other Screening Assessments

Safety assessments that are also part of the screening assessments are described in [Section 6.3](#).

6.1.1. Demographics

The year of birth, age (calculated), sex, ethnicity, and race will be recorded in the eCRF at Screening ([Appendix 1](#)).

6.1.2. Medical History

Medical history, including alcohol and smoking status, vaccinations, and any prior medications, as well as ongoing illnesses, any prestudy procedures and social history, will be recorded in the eCRF at Screening, with the start date and stop date (if applicable) of the illness/condition.

Documented IBM history, including ENMC criterion met, symptom onset, and assistance use, will also be collected.

Medical history terms will be coded using MedDRA Version 24.0 or higher. Medical history will be analyzed using descriptive statistics by MedDRA System Organ Class and Preferred Term.

6.1.3. Body Weight and Height

Body weight (kg) and height (cm) will be measured and recorded at the time points delineated in the Schedules of Events ([Appendix 1](#)) and other unscheduled time points if deemed necessary. The subject should be dressed in light clothing, without shoes. Body weight on Day 1 will be

used to calculate the dose for those subjects assigned to receive study medication; dose adjustment based on subsequent body weight measurements may occur as detailed in Section 7.4.

6.1.4. Screening Tests for Infectious Agent Exposure

Subjects will be tested at Screening for TB, COVID-19, viral infection, and pathologic antibodies as described in Section 6.3.5.2.

6.1.5. Coagulation

Whole blood samples will be collected at the time points defined in the Schedules of Events (Appendix 1) for activated partial thromboplastin time and international normalized ratio.

The [REDACTED] will be administered electronically at Screening and will provide a baseline status to facilitate interpretation of the subject's [REDACTED] scores at subsequent visits.

The [REDACTED] will be administered on paper at Screening and will provide a baseline status to facilitate interpretation of the Investigator's [REDACTED] scores at subsequent visits.

6.2. Efficacy Assessments

6.2.2. IBM Functional Rating Scale

The IBMFRS is an ordinal rating scale used to determine subjects' assessments of their capabilities. It includes 10 measures (swallowing, handwriting, cutting food and handling utensils, fine motor tasks, dressing, hygiene, turning in bed and adjusting covers, changing position from sitting to standing, walking, and climbing stairs) graded on a Likert scale from 0 (being unable to perform) to 4 (normal). The sum of the 10 items gives a value between 0 and 40, with a higher score representing less functional limitation ([Jackson et al., 2008](#); [Dooley, 2018](#)). Every effort should be made for the same site staff member to administer the IBMFRS to each subject at each time point.

6.2.4. Manual Muscle Testing

Muscle testing (MMT **■**12) will be performed as routinely done by neurologists in a clinical setting. This method is routinely performed in a clinical setting and has been shown to be reliable ([Rider et al., 2011](#)).

Arm and leg muscle groups are sequentially, bilaterally evaluated. Muscle groups to be tested (totaling 23) are neck flexion and both right and left shoulder abduction, elbow flexion, elbow extension, wrist extension, wrist flexion, flexor pollicis longus, hip flexors, hip abduction, hip extension, knee extension, and ankle dorsiflexion.

Scores are calculated by summing the outcomes, with the Investigator providing the score, on a scale of 0-5, which is then converted by a standard procedure to a Kendall score equivalent on a scale of 0-10. A higher score reflects better muscle strength.

6.2.5. Dynamometry

Dynamometry provides a precise measurement of the force that a muscle can exert and allow differences in strength to be tracked over time. In hand dynamometry, the subject squeezes a dynamometer that, in turn, records the force being applied. In quadriceps dynamometry, a dynamometer is used to measure the applied force of leg extension. Dynamometry will be performed on both sides at the time points specified in [Appendix 1](#). Details on the conduct of the dynamometry assessments are in the Study Manual.

6.2.6. Modified Timed Up and Go

The Investigator will assess the subject's ability to get up from a standard armchair [seat height approximately 17 to 19 inches (~43 to 48 cm)], allowing the subject to use their arms (since most with IBM cannot perform the task without pushing off), walk three meters, turn around, walk back to the chair, and sit down. The use of nearby walls or assistance from a caregiver is not allowed, but use of usual assistive device (e.g., cane, walker) is permitted ([Soto-Varela 2020](#)). Refer to the Study Assessments Manual and mTUG training slides for additional detail.

6.3. Safety Assessments

Refer to the Laboratory Manual for details regarding the collection, processing, and shipping of the blood and urine samples for safety laboratory assessments.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during the subject's participation in the study or within 30 days after the last dose of study medication should be repeated until the values return to normal, or baseline, or are no longer considered clinically significant by the Investigator or MM.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, then the etiology should be identified, and the Sponsor notified.

6.3.1. Vital Signs

Vital signs will be collected at time points defined in the Schedules of Events ([Appendix 1](#)). Vital signs include blood pressure, temperature, pulse, and respiration rate.

Temperature may be measured orally, axillary, forehead, or otic.

Blood pressure and pulse are strongly recommended to be collected after the subject has had at least five minutes of rest in the seated position. If blood pressure is elevated on the first measurement, it should be repeated after an additional five minutes of rest. Blood pressure is strongly recommended to be obtained from the same arm at each assessment.

Vital signs are strongly recommended to be performed after ECGs and prior to blood draws.

6.3.2. Physical Examinations

Physical examinations will be performed by a qualified health care provider at the time points specified in the Schedules of Events ([Appendix 1](#)).

Complete physical examinations will be performed at Screening, W48, and EOT/ETV. Complete physical examinations will include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (including heart and lungs), abdomen (including liver and spleen), skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.

The remaining examinations may be limited and symptom directed. Abbreviated physical examinations may be performed at the time points specified in the study schedule. An abbreviated examination will include general appearance, chest (heart, lungs), abdomen, extremities, and lymph nodes as well as additional body systems which are symptom directed.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as AEs, as appropriate, as described in [Section 8](#).

6.3.3. 12-Lead Electrocardiogram

Triplicate 12-lead ECG will be obtained as outlined in [Appendix 1](#) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals and QT interval corrected using Fridericia's formula. It is strongly recommended that the ECG be performed after at least five minutes of rest in a supine position and before vital sign collection and blood draws.

Three individual ECG tracings should be obtained as closely as possible in succession.

For safety monitoring, all ECG tracings will be reviewed by the Investigator or designee for local management of the subject. All ECGs, including the one collected at the Screening Visit, will be sent to a central ECG laboratory for analysis and measurement of the ECG intervals. Evaluation

of ECG based parameters for determination of exclusion criteria will be based on the central ECG results at Screening. Clinically significant changes from Baseline (as determined by the MM) will be recorded in the AE section of the eCRF. Presentation of ECG parameters will be outlined in the Statistical Analysis Plan (SAP).

6.3.4. Columbia Suicide Severity Rating Scale

The C-SSRS will be assessed by the Investigator or a qualified designee at Screening and at the visits indicated in [Appendix 1](#). The C-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Posner, et al., 2011). Study subjects respond to standardized clinical questions that are presented in a uniform fashion. The C-SSRS defines five subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The Investigator or trained study site personnel will interview the subjects and complete the C-SSRS.

Subjects with scores of 4 or 5 on the suicidal ideation items, intent in the last six months prior to randomization, or any “yes” on the Suicidal Behavior item, that is related to suicidal behaviors or attempts occurring during the past two years will be excluded from the study. Subjects with these results during the study will be discontinued from study medication. Any C-SSRS finding that, in the opinion of the Investigator, is new or considered to be worsening and clinically significant should be reported as an AE.

6.3.5. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory. All laboratory results will be blinded. Blood and urine samples will be collected at the times indicated in [Appendix 1](#). On dosing day(s) sampling for the analysis of clinical laboratory parameters will be performed before the administration of study medication.

6.3.5.1. Safety Laboratory Evaluations

The following parameters will be assessed:

6.3.5.1.1. Thyroid Hormones

Free T4 and thyroid stimulating hormone will be assessed in serum samples.

6.3.5.1.2. Hematology

Hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential (e.g., basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet count, percent and absolute CD4+ count, percent and absolute CD8+ count, and CD4:CD8 ratio. Percent and absolute CD3+, CD19+ (B cell), and CD16/56+ (NK cell) counts where available are also recommended.

6.3.5.1.3. Clinical Chemistry

Albumin, ALT, aldolase, alkaline phosphatase, AST, bicarbonate, blood urea nitrogen, CRP, calcium, [REDACTED] creatinine, gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, potassium, sodium chloride, total bilirubin, total protein, uric acid. eGFR will be calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.

6.3.5.1.4. Urinalysis

Color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocyte esterase with reflex microscopic analysis.

6.3.5.1.5. Serum Immunoglobulins

At Screening and later time points per [Appendix 1](#), serum samples will be tested for serum immunoglobulins, M protein, and light chain ratio. Results of these markers will be used in safety assessments.

6.3.5.1.6. Complement

C3, C4, and hemolytic complement filtration (CH50) will be screened at timepoints per [Appendix 1](#).

6.3.5.2. Tests for Infectious Agent Exposure

6.3.5.2.1. Tuberculosis Test

A tuberculosis test for active/latent TB will be performed at Screening and unscheduled visits if medically indicated ([Appendix 1](#)). Tuberculosis assessment includes central or local QuantiFERON-TB Gold Plus test or local T-SPOT.TB test. Indeterminate or borderline test results require a repeat test to confirm negative status or medical evaluation to rule out a concern for TB disease.

6.3.5.2.2. COVID-19 Test

COVID-19 testing should be performed as described in [Appendix 1](#) at Screening, Baseline (Day 1) and any unscheduled visit (USV) via PCR or rapid antigen test (as per local guidance). Testing is required at any time there is clinical suspicion of COVID-19 infection.

6.3.5.2.3. Viral Serology

At Screening and USV, serum samples will be tested for HIV-1 and -2, HBV core antibody and surface antigen, and HCV antibody with reflex HCV RNA, and herpes viruses such as EBV, CMV, HSV-1 and -2, and VZV.

6.3.5.2.4. Pathologic Antibody Tests

At Screening, serum samples will be collected for anti-cytosolic 5'-nucleotidase 1A (anti-cN-1A; NT5c1A), antinuclear antibodies (ANAs), anti-SSA/SSB assessments.

6.3.5.2.5. Cytomegalovirus and Epstein-Barr Virus Loads

Blood samples will be collected to determine plasma CMV and EBV viral loads by PCR analysis at Screening and later time points per [Appendix 1](#). If in the opinion of the MM, a subject has clinically significant increases from Screening in CMV or EBV viral loads at two consecutive postscreening visits, that subject should be discontinued from study medication and, as appropriate, should be referred for follow-up with an infectious disease specialist at the discretion of the Investigator. Such subjects will progress to Part C (PD Recovery Cohort) for PD and safety follow-up (to continue until their KLRG1+ cells have recovered).

6.3.6. Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in Section 8.

6.4. Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Samples for PK, PD, and immunogenicity assessment may be stored for a maximum of two years after the end of the study (or according to local regulations) to enable further analysis of markers of drug response and changes in subject disease characteristics as well as immune responses to ABC008.

6.4.1. Pharmacokinetics

Blood samples will be collected for measurement of concentrations of ABC008 at the study visits specified in the Schedules of Events ([Appendix 1](#)). When PK sampling coincides on a study medication administration day, blood samples for PK should be drawn within two hours prior to ABC008 administration.

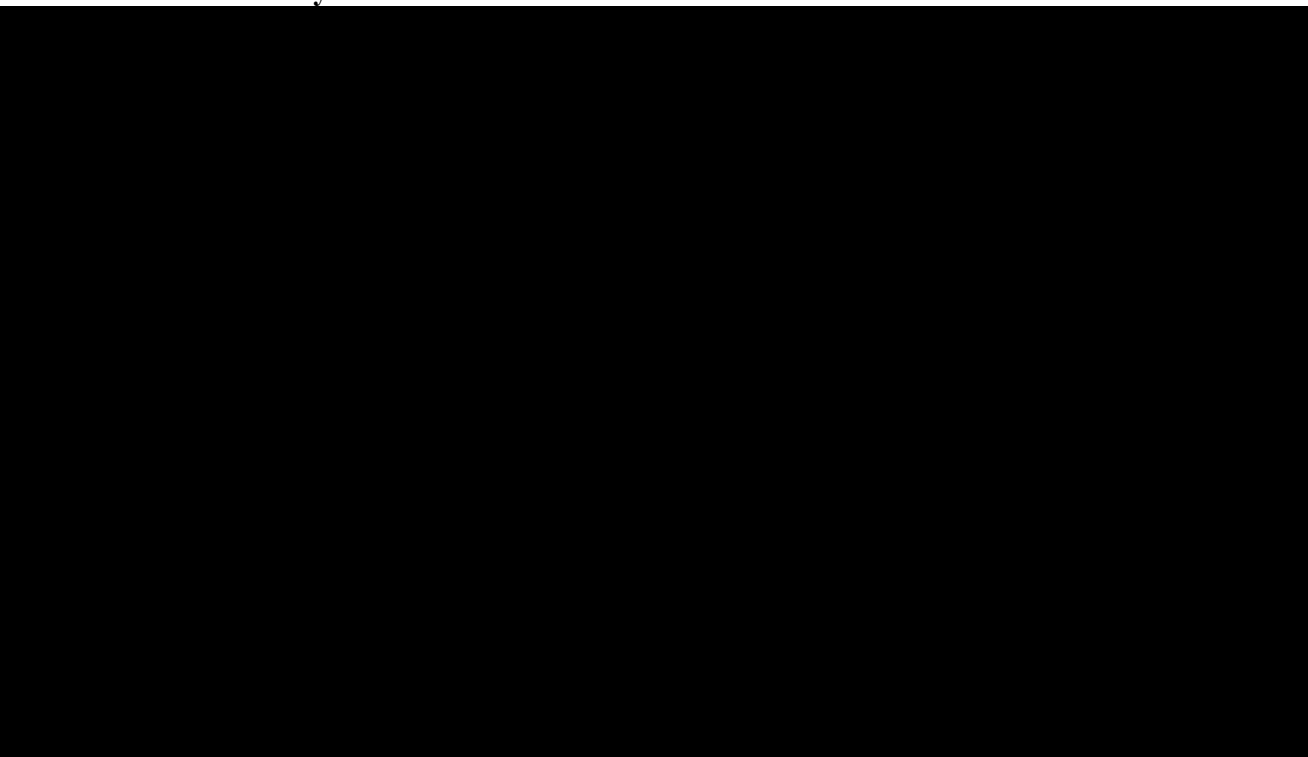
Where possible, PK samples will be collected after PRO assessments are performed.

ABC008 concentrations will be measured by a validated bioanalytical method.

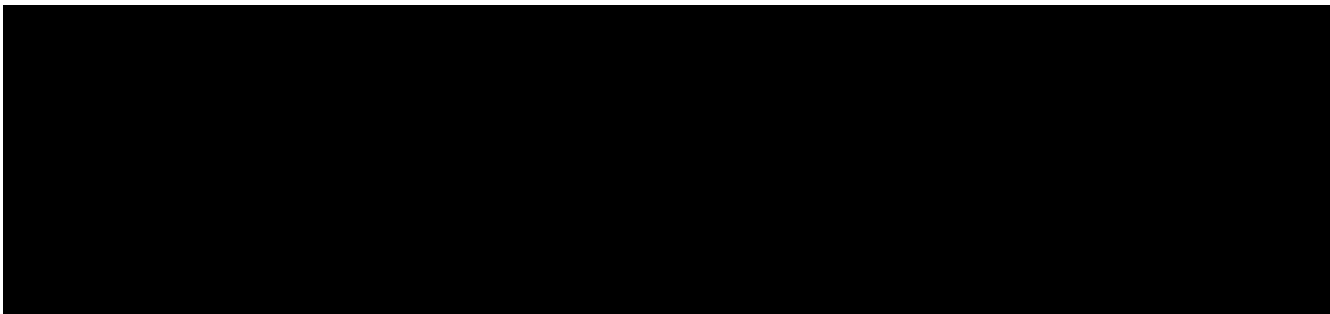
The exact date, time, and volume of the sample collection must be recorded in the source document and transcribed into the subject's eCRF.

Instructions on processes for collection, processing, storage, shipment, documentation, and destruction of these samples can be found in the Laboratory Manual.

6.4.2. Pharmacodynamics



6.4.3. Immunogenicity



6.5. Quality-of-Life Assessments

6.5.1. EuroQol 5-dimension, 5-level Quality-of-Life Questionnaire

EQ-5D-5L is a standardized measure of HRQoL that assesses health status in terms of five dimensions of health: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Subjects will be asked to rate the severity of problems in each dimension on a 1- to 5-point scale:

1 = not /no problems;

2 = slight problems;

3 = moderate problems;

4 = severe problems;

5 = ‘unable to’ (mobility, self-care, usual activities), ‘extreme’ (pain/depression), or ‘extremely’ (anxiety/depression).

The EQ-5D-5L will be administered electronically at the visits outlined in [Appendix 1](#).

6.5.2. Study 36-item Short Form Health Survey 2

The SF-36v2 is a 36-item generic subject-reported outcome measure that quantifies health status and measures HRQoL. The SF-36v2 captures subject perceptions of their own health and well-being. The SF-36v2 has 36 items grouped in eight dimensions, including: physical functioning, physical and emotional limitations, social functioning, bodily pain, general and mental health. A higher score reflects better health ([Ware et al., 1998](#)).

The SF-36v2 will be administered electronically at the visits outlined in [Appendix 1](#).

6.5.3. Patient Exit Survey

Subjects at participating US sites may complete an optional Patient Exit Survey at the EOT/ETV visit. The Patient Exit Survey is designed to help identify subjects’ perspectives on the effect of ABC008 on daily life.

Subjects should complete the optional Patient Exit Survey after completing the blinded portion of the study and before enrolling in the open-label long-term extension study.

6.7. Home Healthcare Visits

At the discretion of the Investigator, the following study visits in Part B (Double-Blind Safety and Efficacy Cohort) may be conducted at home or another qualified facility by a home health agency:

- Visit 3 (W1/Day 8 ± 1 day);
- Visit 4 (W2/Day 15 ± 7 days);
- Visit 7 (W12/Day 85 ± 7 days).

After approval from the Investigator, the investigative site staff will schedule a visit to the subject's home or other preferred site. The home health provider will collect all study-related samples and perform procedures as per this study protocol and will forward the original source documentation collected to the investigative site after the visit is completed.

6.8. Decentralized Trial Data Collection

Throughout the study, the Sponsor will contract with a vendor to collect various information such as PRO measures and Clinical Outcome Assessments in an electronic format. To support the subject's education, engagement, and activity completion in the study, the subjects will have an option to participate by using their own mobile phone or other smart device or be provided with a study-specific device. The subject will decide if they would prefer to use their mobile device versus a provisioned one. The subject will be required to use the provisioned device if the subject's own device and/or operating system does not meet the minimum technology requirements as confirmed by the vendor. The Investigator and authorized site representatives will have access to a website portal via unique access credentials to access the study data from the completed activities.

Each subject will be assigned a unique identifier by the Sponsor. Any subject records or datasets transferred to the Sponsor will contain only the identifier. Subject names or any information which would make the subject identifiable will not be transferred.

7. TREATMENTS

7.1. Investigational Products

7.1.1. Description of Investigational Products

ABC008 (anti-KLRG1 afucosylated humanized IgG₁) drug product is supplied as a sterile liquid with no preservatives for SC administration, at a concentration of [REDACTED] mg/mL. The test product is provided as a single use vial comprised of [REDACTED] mg/mL (1 mL) of ABC008 formulated with [REDACTED] and [REDACTED].

Matching placebo is supplied as a solution without ABC008. Additional details are provided in the ABC008 IBM IB.

ABC008 drug product and placebo vials will be shipped at 2 to 8 °C. Upon receipt, study medication must be stored in accordance with the Pharmacy Manual.

7.1.2. Packaging, Labelling, and Shipment

Study medication is packaged in [REDACTED]

ABC008 is packaged in [REDACTED]

Study medication vials and outer carton will be labelled in accordance with local regulatory requirements and will be shipped to an unblinded pharmacist who will prepare the study medication for blinded administration to the subject.

The label will identify the investigational product for clinical use only, include the protocol number and an investigational use Caution Statement, and will comply with all regulatory requirements.

Procedures relating to ABC008 and placebo preparation and dispensing are outlined in the Pharmacy Manual.

7.2. Blinding

The study is double-blinded; therefore, the Sponsor study team, Investigators, study personnel, and the study subjects will remain blinded to treatment allocation and results of all study assessments except in an emergency.

Randomization of subjects to study treatment will be via the interactive response technology (IRT) system. Randomization data will be kept strictly confidential, accessible only to authorized staff (not at study sites) and the DSMB until the time of unblinding after database lock as described per Abcuro standard operating procedures. Authorized staff will include an unblinded statistician and unblinded programmers, who will provide the DSMB with unblinded data for review, as required, in accordance with the procedures described in the DSMB Charter. All authorized unblinded staff must be documented.

ABC008 and placebo will be coded and labelled in a manner that protects blinding. The IRT will permit rapid identification of the product (in case of medical emergencies), in a way that does not permit undetectable breaking of the blind.

7.2.1. Unblinding

Treatment unblinding in the context of an SAE is discouraged since knowledge of the affected subject's treatment assignment should not materially change the planned management of the SAE. The Investigator will receive training from the Sponsor regarding unblinding treatment assignments.

If, in the opinion of the Investigator, a subject is having a medical emergency, then the Investigator is permitted to unblind that subject's treatment assignment so that the Investigator may institute appropriate follow-up care. The Investigator will notify the MM of the unblinding as soon as possible/practical. The Investigator will break the treatment code for that subject via the IRT. The reason for breaking the code must be recorded in the subject's source documents.

If a subject's treatment assignment is unblinded for any reason prior to completing Part A or Part B, the subject will return to the study site for an ETV.

7.3. Method of Assigning Treatment

Randomization will be performed via an IRT. Each subject will have a unique subject screening number obtained from the IRT. This will be assigned at the Screening Visit. The Investigator will keep a record (the subject screening log) of subjects who entered screening.

Once the subject has been successfully screened and the Investigator has determined that the subject is eligible, the subject will be confirmed as enrolled within the IRT.

On Day 1, eligible subjects will receive a unique, blinded, IRT-generated randomization code that will assign the subject to treatment with one of the dosages of ABC008 or placebo in a 2:2:1 ratio in Part A and in a 1:1:1 ratio in Part B. Enrollment in Part B will not begin unless the DSMB assessment of the interim safety data is favorable.

7.4. Dose and Administration

On Day 1, the dose to be administered will be calculated based on the body weight of the subject as described in the ABC008 Pharmacy Manual. The dose calculated on Day 1 will be continued for the duration of the study, unless the subject has a weight change (increase or decrease) from Day 1 of $\geq 10\%$ on two consecutive visits or $\geq 20\%$ on any single visit, which will trigger a review by the Investigator and Sponsor MM as to the etiology and potential need for dose adjustment.

The blinded study medication will be administered as a SC injection in the left or right anterior thigh or in the right or left upper or lower quadrant of the abdomen at least two inches away from the navel and other injection sites for the blinded study medication administered at the same visit by assigned clinical staff. Areas that are scarred or are inflamed (e.g., erythematous, oedematous, indurated) should not be used for injection sites. Details of the correct procedure, including injection volume, are included in the study's Pharmacy Manual.

The Investigator or designee is responsible for the education of study staff as to the correct SC administration of blinded study medication.

Subjects need to be monitored for two hours after dosing at Baseline (Day 1) and W8.

7.4.1. Dose Modification

Dose reductions or increases are not permitted other than those related to significant weight change described in Section 7.4.

If a subject misses a dose within a regularly scheduled dosing window (every eight weeks $\pm$ seven days), the dose may be made up at a USV, as long as it is within four weeks of the scheduled dose. If greater than four weeks from the scheduled dose have elapsed, then the missed dose should not be given, the next dose should be administered on schedule, and a protocol deviation recorded. If two consecutive doses are missed, then the subject is to be withdrawn from the study as discussed in Section 5.4.2.

Criteria for premature discontinuation of dosing for individual subjects are detailed in Section 5.4.1.

If a subject experiences a TESAE or any other AE that, in the opinion of the Investigator or Sponsor, may represent a clinically significant safety risk to the subject that would be a treatment-limiting toxicity, the Investigator may temporarily or permanently discontinue study medication treatment in consultation with the MM as discussed in Section 5.4.1.

7.4.2. Intervention After the End of the Study

Following participation in Part A or Part B of this study, subjects will be eligible to enroll in a long-term extension study. No other intervention will be available.

7.5. Precautions and/or Lifestyle Considerations

As is described for vaccinations prior to the first dose of study drug (Exclusion Criterion 6[i]), subjects should avoid vaccination prior to each subsequent dose, 30 days prior for live attenuated viral vaccines and 14 days prior for non-live vaccines.

7.6. Concomitant Therapies

Concomitant medications are defined as all medications, including over the counter (OTC) medications, vitamins, and herbal supplements, taken after the first study medication administration. Initiation of any therapy after study drug administration should be discussed in advance with the MM except in the case of necessary treatment of AEs or where appropriate medical care necessitates that therapy should begin before the Investigator can consult with the MM. Paracetamol/acetaminophen (up to 2 g/day) may be used during the study, at the discretion of the Investigator, without prior consultation with the MM.

As is described for vaccinations prior to the first dose of study drug (Exclusion Criterion 6[i]), subjects should avoid vaccination prior to each subsequent dose, 30 days prior for live attenuated viral vaccines and 14 days prior for non-live vaccines.

All concomitant medications and vaccinations taken from the start of study medication dosing through the study follow-up will be recorded in the appropriate section of the eCRF. The following details must be recorded in the CRF:

- Medication name, ideally the generic name;

- Reason for use;
- Start and end date of administration;
- The dose, route, and frequency of administration.

7.6.1. Prohibited Medications

Medications prohibited before and during screening are discussed in Section 5. The following medications are prohibited during the study:

1. Intravenous or intramuscular corticosteroids;
2. Oral prednisone (or prednisone equivalent) >7.5 mg/day;
3. Use of nonbiologic immunosuppressants (e.g., cyclosporine, mycophenolate mofetil or sodium, azathioprine, methotrexate, sirolimus, Janus kinase inhibitors);
4. Intra-articular therapies, such as corticosteroids or hyaluronic acid preparations;
5. Intravenous, intramuscular, or SC immunoglobulin (IVIG, IMIG, or SCIG);
6. Cytokine, integrin, or activin antagonists or selective co-stimulation modulators, including but not limited to, IL-1, IL-6, IL-17, IL-12/23, IL-23, interferon, integrin, and tumor necrosis factor α antagonists, abatacept, bimagrumab;
7. Cell-depleting or modulating therapies (e.g., alemtuzumab, antithymocyte globulin, atacicept, belimumab, obinutuzumab, ocrelizumab, ofatumumab, rituximab, siplizumab);
8. Chemotherapeutic regimens or other cytotoxic therapies, e.g., cyclophosphamide, doxorubicin or hydroxyrubicin, vincristine, and prednisone; purine analogs, alkylating agents;
9. Other immunomodulatory biologics;
10. Anabolic steroids;
11. Growth hormone;
12. Initiation of testosterone supplementation or change in dose other than for weight-based adjustment;

7.6.2. Permitted Therapies or Prior Medications

Prior medications are defined as any prescription or non-prescription drugs, including OTC medications, vitamins, and herbal supplements, taken during the 12 weeks prior to the first study medication administration, but discontinued before dosing.

All prior medications will be recorded in the eCRF and reviewed by the Investigator to determine whether the subject is suitable for inclusion in the study. Any biologic agents, e.g., mAb, ever used should also be recorded in the eCRF. Vaccination history should also be reviewed and recorded in the eCRF by the Investigator with respect to adult vaccinations such as pneumococcal, influenza, shingles, pertussis, and COVID-19 vaccines. It is strongly recommended that prior medications be discussed with the MM before study medication administration.

During the study period, initiation of therapies deemed as medically necessary that are associated with neuromuscular side effects should be discussed with the MM prior to implementation. Examples include new initiation of antimalarial drugs (e.g., chloroquine, hydroxychloroquine), colchicine, cholesterol-lowering drugs (e.g., statins), or change in stable doses of these agents other than for weight-based adjustment.

7.6.3. Drug Interactions

There are no known interactions of ABC008 with other medications. No studies to explore drug-drug interactions have been performed.

7.6.4. Contraception

Female subjects considered to be of childbearing potential (WOCBP, defined as women who have experienced menarche and who are not permanently sterile or postmenopausal [defined as 12 consecutive months of amenorrhea not due to an alternative medical cause]) must use one of the following highly effective methods of birth control throughout the study from the time of signing informed consent and for 180 days after the EOT/ETV:

- Intrauterine device;
- Intrauterine hormone-releasing system;
- Combined (estrogen- and progesterone-containing; oral, intravaginal, or transdermal) hormonal contraception associated with inhibition of ovulation, plus a barrier method;
- Progesterone-only (oral, injectable, or implantable) hormonal contraception associated with inhibition of ovulation, plus a barrier method;
- Vasectomized partner (provided that partner is the subject's sole sexual partner and has received medical assessment of the surgical success, then the subject is not required to use an additional form of contraception);
- Bilateral tubal occlusion.

Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. In this event, abstinence is a highly effective method of birth control only if the subject refrains from heterosexual intercourse from the time of signing informed consent, during the study, and for 180 days after the EOT/ETV.

Regarding the double-barrier method, sites should follow applicable country-specific recommendations and guidelines, as the double-barrier method may not be considered as highly effective. (Note: in countries following the Clinical Trial Facilitation and Coordination Group recommendations related to contraception, the double-barrier method is not considered highly effective and thus, in these regions, would not be acceptable for use in this study).

Periodic abstinence (e.g., calendar, symptothermal, or postovulation methods), declaration of abstinence for the duration of the clinical study, withdrawal method (i.e., coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable as methods of contraception.

Within these limits, the specific forms of contraception employed are left to the discretion of the subject, the Investigator, and/or the subject's physician.

Male subjects with female partners of nonchildbearing potential or who are pregnant are not required to change their usual contraception practice. Male subjects with non-pregnant female partners of childbearing potential should use a condom and adhere to the contraception requirements listed above.

Male subjects must refrain from sperm donation for the duration of the study and for 180 days after EOT/ETV.

7.7. Compliance

Subjects will be administered study medication by the Investigator or site personnel, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and in the eCRF. Treatment compliance will be assured by site reconciliation of all study medication supplies.

7.8. Accountability

The study medication must not be used for any purpose other than that defined in this protocol. All supplies of study medication will be accounted for in accordance with Good Clinical Practice (GCP) guidelines.

The unblinded pharmacist or (designee) should maintain accurate records of all study medication supplies received during the study and monitored by an unblinded Sponsor Clinical Research Associate. These records should include the dates and amounts of study medication that were received at the site, dispensed, and destroyed or returned to the Sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study medication and study subjects. If errors or damage in the study medication shipments occur, the Investigator should contact the Sponsor (or its designee) immediately. Copies of the study medication accountability records will be provided by each Investigator for inclusion in the trial master file. The study monitor will periodically check the supplies of study medication held by the Investigator or pharmacist to verify accountability of the study medication used.

The Investigator (or designee) will administer the study medication only to the identified subjects in this study, according to the procedures described in this study protocol. Details of study medication administered to subjects will be recorded in the eCRF. Specified unblinded site staff should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all study medication received from the Sponsor (or designee).

After the end of the study, all unused study medication and all medication containers should be returned to the Sponsor (or designee). In either instance, complete documentation will be returned to the Sponsor. The study medication resupply will be managed by the IRT.

8. SAFETY MONITORING AND ADVERSE EVENT MONITORING

8.1. Overview of Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of all subjects at his/her study site and to report all AEs including SAEs that are observed or reported during the study, regardless of the relationship to study drug (as assessed by the Investigator) or clinical significance of these events.

The MM has medical authority to evaluate the safety aspects of this clinical study. AEs will be characterized by expectedness, intensity (severity), causality, and seriousness, based on the regulatory definitions.

Regardless of severity and causality, the Investigator will consult with the MM regarding any AE that, in their opinion, may represent a clinically significant safety risk to the subject, in order to assess the safety of continued dosing in that subject (Section 5.4.1).

8.2. Adverse Event Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in any person partaking in a clinical investigation, regardless of the suspected cause. An AE can therefore be any unfavorable and unintended sign, symptom, disease, concurrent illness, or clinically significant abnormal laboratory finding that emerges or worsens (i.e., aggravated in severity or frequency from the Baseline condition) during the study.

An AE also includes abnormal results of diagnostic procedures if they lead to:

- Discontinuation of the study drug or from the study;
- Treatment or any other therapeutic intervention, or ;
- Clinical signs or symptoms judged by the Investigator to have a clinically significant impact.

8.2.2. Treatment-emergent Adverse Events

A TEAE is defined as an AE that first appears or worsens after initiation of study drug.

8.2.3. Serious Adverse Events

A serious adverse event (SAE) is any AE that results in any of the following outcomes:

- Death;
- Life-threatening event (i.e., an event in which the subject was at *immediate* risk of death at the time of the event; does not include an event that hypothetically might have caused death if it were more severe);
- Hospitalization or prolonging an existing hospitalization, except for the following:
 - Elective hospitalization or prolonged hospitalization for diagnostic or elective procedures for a pre-existing condition that did not worsen from Baseline;

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study;
- Hospital admissions due to social circumstances and/or convenience;

Note: “Inpatient” hospitalization means the subject has been formally admitted to a hospital for medical reasons, i.e., ≥ 24 hours.

- Persistent or significant disability or incapacity (i.e., a substantial disruption of a person’s ability to conduct normal life functions);
- A congenital anomaly or birth defect (i.e., an adverse outcome in a child or fetus of a female subject exposed to study drug);
- An important medical event.

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes noted above.

Adverse events that do not meet any of the outcome criteria for seriousness should be regarded as nonserious AEs.

8.2.4. General Definitions and Reporting

8.2.4.1. Adverse Event Reporting Period

All AEs are to be followed and reported from the time that a subject signs the informed consent form (ICF) (i.e., enters Screening) until the last study visit. Follow-up requirements for SAEs are provided in Section [8.2.3](#).

8.2.5. Abnormal Laboratory Assessments

Specific information on handling of clinical laboratory abnormalities is in Section [6.3.5.1](#).

A clinical laboratory abnormality should be documented as an AE only if it is not an expected result of study drug and is clinically significant or leads to:

- Discontinuation of the study drug or from the study;
- Treatment or any other therapeutic intervention, or;
- Clinical signs or symptoms judged by the Investigator to have a clinically significant impact.

If an abnormal laboratory value or assessment is clearly related to a medically defined diagnosis or syndrome or requires treatment or a change in current treatment regimen, the diagnosis or syndrome will be recorded on the AE eCRF page, not the individual laboratory value.

8.2.5.1. Pre-Existing Conditions

A pre-existing condition is one that is present at the time the subject signs the ICF. A pre-existing condition should be captured in the Medical History eCRF. A pre-existing condition

should be recorded as an AE only if the condition worsens from what was captured as medical history during the study period, and this should be noted on the AE eCRF page.

8.2.5.2. General Physical Examination Findings

Any clinically significant abnormality identified at the screening physical examination should be recorded as a pre-existing condition. At subsequent physical examinations, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

8.2.5.3. Planned Procedures or Hospitalizations

Any planned procedures or hospitalizations should not be considered or reported as AEs or SAEs, unless the outcome meets any of the serious criteria defined in Section 8.2.3.

8.2.6. Adverse Events of Special Interest

The AESIs for this study are:

1. Injection site reactions;
2. Systemic injection reactions, e.g., hypersensitivity, systemic inflammatory response, with signs and symptoms that may include, but are not limited to, fever, chills, abdominal pain, back pain, headache, nausea, rash, dyspnea, low or high blood pressure, low or high heart rate. Usually these are considered infusion/injection-related if occurring within the first 24 hours postdosing;
3. Infection, including but not limited to, reactivation of latent herpes viruses such as EBV, CMV, human herpesvirus, HSV-1 or -2, or VZV.

8.3. Adverse Event Evaluation and Classification

8.3.1. Severity

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is related to a subject outcome and is classified by regulatory reporting criteria. An AE of severe intensity need not necessarily be classified as SAE.

Investigators will grade all AEs by severity using the Common Terminology Criteria for Adverse Events (CTCAE) criteria (Version 5, November 2017).

If an AE is not listed in the CTCAE criteria, a corresponding grading is to be performed by the Investigator based on his/her best medical judgement as follows:

- Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Moderate (Grade 2): minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental ADL;
- Severe (Grade 3): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care ADL;

- Life-threatening (Grade 4): life-threatening consequences; urgent intervention indicated;
- Death (Grade 5): death related to an AE.

8.3.2. Causality

The Investigator must make a causality assessment (related or not related) for all AEs/SAEs and must decide whether there is a reasonable possibility that the AE may have been caused by the study drug. Guidelines for assessment of AE/SAE causality are provided in [Table 1](#).

Table 1: Adverse Event Causality Assessment

Causality	Definition
Not Related	Applies to AEs that, after careful medical consideration, are due to either extraneous causes (e.g., underlying disease, environment, etc.) or judged unrelated to the study drug under one of the following circumstances: • AE does not follow a reasonable temporal sequence after administration of study drug • AE could readily have been produced by the subject's clinical state or other modes of therapy administered to the subject
Related	Applies to AEs that, after careful medical consideration, are felt to have a high degree of certainty of being related to the study drug. • An AE may be considered related when at least two of the following apply: • AE follows a reasonable temporal sequence after administration of study drug • AE could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapies administered to the subject • AE disappears or decreases on cessation of study drug. Sometimes an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists • It follows a known pattern of response to the study drug

8.3.3. Expectedness

An AE is judged to be “expected” if its description agrees in nature, severity, or frequency with the description of AEs previously noted with ABC008 as detailed in the Reference Safety Information within the current ABC008 IBM IB. An “unexpected” AE is one whose specificity, severity, or frequency is not consistent with the description in the Reference Safety Information within the current ABC008 IBM IB. The Sponsor is responsible for assessing the expectedness of all AEs.

8.4. Documenting and Reporting Adverse Events

Reporting of AEs will begin when the subject has provided informed consent and will continue up to the subject's last follow-up visit.

Occurrence of AEs may be volunteered spontaneously by the subject; discovered as a result of general, nonleading verbal questioning by the study staff; or determined by physical examination or other safety assessments. All AEs will be monitored and recorded in the eCRF throughout the entire study.

For all AEs, the Investigator must pursue and obtain adequate information (a description of the event, severity, time of occurrence [including whether the AE onset was before, during, or after the study medication administration if the AE started on a dosing day], duration, and any action, e.g., treatment/follow-up tests). The outcome of the event should be provided along with the Investigator's assessment of the relationship to the study medication. The Investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the Investigator's responsibility to review all documentation (e.g., hospital notes, laboratory reports, and diagnostic reports) related to an AE. Wherever possible, the Investigator's diagnosis, not the individual signs and symptoms, will be documented as the AE.

Investigators are not obligated to actively seek AEs or SAEs after the subject's conclusion of study participation. However, if the Investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the Investigator must promptly notify the Sponsor.

8.5. Reporting of Serious Adverse Events

If, in the opinion of the Investigator, the AE occurring from informed consent through end of the follow-up period meets the criteria of an SAE, it is to be reported by the Investigator to Syneos Clinical Safety within 24 hours of the point in time when the Investigator becomes aware of the SAE. The same 24-hour timeline applies for any follow-up information received by the Investigator. All SAEs regardless of expectedness and causality must be reported.

Syneos Health

Drug Safety and Pharmacovigilance

Email: safetyreporting@syneoshealth.com

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It is the responsibility of the Sponsor to report all SAEs to regulatory authorities and sites as applicable within the required time.

8.5.1. Institutional Review Board/Independent Ethics Committee Notification by Investigator

Reports of all SAEs (including follow-up information) must be submitted by the Investigator to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in accordance with IRB/IEC requirements. This information includes, but is not limited to, any safety alert letter received from the Sponsor and any SAEs occurring at their investigative site. Copies of each report and documentation of IRB/IEC notification and receipt will be kept in the Investigator Site File.

8.6. Adverse Event and Serious Adverse Event Follow-up

During the study, all AEs and SAEs should be followed proactively by the Investigator until the event resolves or the condition stabilizes to a level acceptable to the Investigator, until the event is otherwise explained, or until the subject is lost to follow-up. At the time the subject's study participation ends, all ongoing AEs and SAEs should be evaluated for resolution. New or

updated information will be recorded in the eCRF. For SAEs, the Investigator will submit any updated SAE information to the Sponsor within 24 hours of receipt of the information.

8.6.1. Pregnancy

All subjects are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (Section 5.1 and Section 5.2 respectively).

Serum (beta human chorionic gonadotrophin) or urine pregnancy tests will be performed for WOCBP at the time points indicated in Appendix 1. Serum pregnancy tests will be analyzed by the central laboratory; urine pregnancy tests will be analyzed locally. Serum and urine sample handling and local testing is described in the ABC008 Laboratory Manual.

All WOCBP will have a serum pregnancy test at Screening and at EOT/ETV. Urine pregnancy tests will be performed for WOCBP at all other specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

A pregnancy test must be performed prior to each dose; the result must be negative for the subject to be eligible for dosing. If the test result is positive, the subject must be excluded from the study.

Postmenopausal status may be confirmed through testing for follicle stimulating hormone at Screening.

Male subjects will be required to inform the Investigator if their partner becomes pregnant during the study or until 180 days after EOT/ETV. The Investigator should enter information into the eCRF within 24 hours of learning of the pregnancy or partner pregnancy.

If a subject becomes pregnant, she will be withdrawn from the study and will not receive any further study medication. The subject should perform the assessments planned for the EOT/ETV. Any pregnant subject and the fetus will be closely followed up throughout the duration of the pregnancy to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality). The Investigator will ask the subject to provide informed consent to record information on the health of the baby. Generally, follow-up will be required for no longer than six to eight weeks beyond the estimated delivery date.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

For any male study subject whose partner becomes pregnant, the Investigator will collect pregnancy information on the male subject's partner while the male subject is in this study and for 180 days following their last dose of study medication.

The Investigator will record pregnancy information on the eCRF within 24 hours of learning of the partner's pregnancy. The Investigator will obtain informed consent from the female partner to collect information about the pregnancy and its outcome. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than six to eight weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the

procedure. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

8.7. Special Situations Reporting

Special situation reports include reports of overdose, misuse, abuse, and medication error.

All special situation reports must be reported on the special situations report form and forwarded to Syneos Clinical Safety within 24 hours.

All AEs associated with these special situation reports should be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome will be reported, when available.

8.7.1. Overdose

Overdose refers to the administration of an excess quantity of medicinal product (per administration or cumulatively [accidentally or intentionally]), which is potentially harmful to the subject; clinical judgement should always be applied in the determination of potential harm. In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken excess dose(s) or the Investigator has reason to suspect that the subject has taken additional dose(s).

8.7.2. Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions and may or may not be accompanied by harmful physical and/or psychological effects.

8.7.3. Abuse

Abuse is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

8.7.4. Medication Error

Medication error is a significant error in the dispensing or administration of a medicinal product. For additional information, please refer to the Pharmacy Manual. The administration or consumption of the unassigned treatment and administration of an expired study drug are always reportable as medication errors. However, cases of missed doses of the study drug are not considered reportable as medication error.

8.8. Medical Safety Monitoring

8.8.1. Principal Investigator

It is the responsibility of the Investigator to oversee the safety of all subjects at his/her site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above.

8.8.2. Medical Monitor

The MM has medical authority to evaluate the safety aspects of the clinical study and may be a Sponsor representative or a representative of a contract research organization (CRO) if this

obligation is transferred. Investigators may contact the MM with specific medical questions on the study protocol, subject eligibility, or for discussion of AEs (including assessment of clinically significant safety risk that may impact continued dosing as detailed in Section [5.4.1](#)). Contact information will be provided as a supplement to this protocol.

9. STATISTICS

9.1. General Procedures

This section briefly describes the statistical and analytical methods to be used in the study. A detailed summary of the statistical methodology for summarizing and analyzing the data collected in this study will be documented in the SAP, which will be finalized prior to the database lock. The statistical methodology and considerations outlined in the protocol may be modified in the SAP; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.2. Analysis Populations

The following analysis sets will be defined for Parts A and B:

- The Enrolled Analysis Set (ES) will include all subjects screened and enrolled into the study. This set will be used to summarize subject disposition.
- The Safety Analysis Set (SS) will include all subjects who randomized and received at least one dose of study medication. The analyses using this set will be based upon the actual treatment assignment. All safety endpoints (e.g., AEs, laboratory results, vital signs, and ECG measurements) will be performed for the Safety Analysis Set. In addition, demographics and baseline characteristics, protocol deviations, study drug exposure will be summarized using the Safety Analysis Set
- The Full Analysis Set (FAS) will include all subjects in the ES randomized to receive the study drug. The analyses using this set will be based upon the randomized treatment assignment. The FAS will be used to evaluate efficacy measures.
- The Per Protocol Analysis Set (PPS) will include all subjects in the FAS who completed the Treatment Period without an important protocol deviation that may impact efficacy assessment. Protocol deviations will be reviewed in a blinded fashion prior to the database lock to assess which subjects meet criteria for an important protocol deviation for exclusion from the PPS analyses. The analyses using this set will be based upon the actual treatment assignment. Select efficacy assessments may be evaluated using the PPS.
- The Pharmacokinetic Analysis Set (PKS) will include all subjects in the SS with at least one postbaseline time point with valid ABC008 concentration data.
- The Pharmacodynamic Analysis Set (PDS) will include all subjects in the SS with at least one postbaseline time point with valid PD assessments.

In addition, the following analysis set will be used in Part C:

- PD Part C Analysis Set (PDCS) will include all subjects in the PDS with valid PD assessments in Part C. The treatment assignments in this analysis set will be based on the original assignments in the PDS.

9.3. Sample Size

In total, approximately 231 subjects (79 subjects in each of the ABC008 arms and 73 subjects in the placebo arm) will be administered study medication in Parts A and B. This sample size provides overall power of at least 90% for the primary efficacy analysis at an overall one-sided 2.5% level if the true effect size at each ABC008 dose is 0.5448 for IBMFRS at 76 weeks. This effect size of 0.5448 is computed under the assumption of halting disease progression at 76 weeks. In addition, 15% of the subjects are expected to be lost to follow-up by the end of the 76-week Treatment Period.

9.4. Statistical Methods

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, standard deviation (SD), median, first and the third quartiles, and minimum/maximum values. Categorical variables will be summarized using frequency counts and percentages. Baseline will be defined as the last non-missing measurement before or on the date of first administration of study medication. One-sided 2.5% significance levels and 95% confidence intervals will be used for all efficacy analyses with the exception of the primary and key secondary efficacy endpoints.

The final analysis will rely on the totality of the data from Part A (Sentinel Cohort) and Part B (Double-Blind Safety and Efficacy Cohort). Details will be provided in the SAP.

The primary and key secondary efficacy analyses will be performed within subgroups of interest such as subgroups based on key demographic and clinical factors. Additional subject subgroups may be specified in the SAP before the database lock.

9.4.1. Endpoints

Study endpoints are provided in Section 3.

9.4.2. Efficacy Analyses

9.4.2.1. Analysis Methods

The efficacy analyses will be performed using the FAS. Supportive analyses will be performed using the PPS.

The treatment effect on the primary efficacy endpoint will be evaluated using a mixed-effects repeated-measures model with fixed terms for treatment (ABC008 doses and placebo), baseline score, visit, and visit by treatment interaction. Within-subject correlations will be modeled directly by specifying a covariance structure. By default, an unstructured covariance matrix for within-subject errors (common across the trial arms) will be fitted. If the model fails to converge, simpler covariance structures will be attempted within a pre-defined sequence (Toeplitz, heterogeneous autoregressive with lag (1), autoregressive (1), compound symmetry) until convergence is achieved. The Kenwood-Rogers correction will be used to estimate denominator degrees of freedom if an unstructured covariance structure is specified and the robust sandwich estimator of variance will be used if a simpler covariance structure is chosen to avoid possible underestimation of the standard error due to covariance model misspecification.

The same model will be used for the key secondary and [REDACTED] endpoints.

9.4.2.2. Multiplicity Adjustment

A multiple testing procedure based on the graphical method (Bretz et al., 2009) will be applied to the primary and key secondary efficacy endpoints to control the overall Type I error rate at an overall one-sided 2.5% level.

The procedure will be applied to the null hypotheses of no treatment effect corresponding to the primary and key secondary efficacy endpoints at 76 weeks:

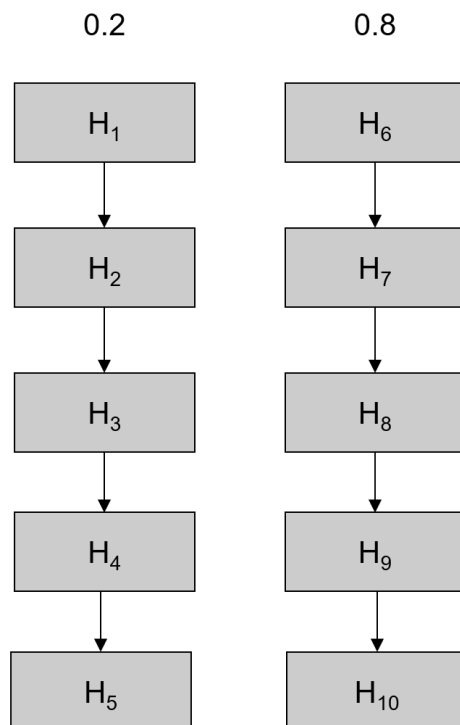
- Endpoint 1: IBMFRS;
- Endpoint 2: MMT 12;
- Endpoint 3: Grip strength for the dominant hand by dynamometry;
- Endpoint 4: Quadricep strength for the dominant leg dynamometry;
- Endpoint 5: mTUG.

The resulting null hypotheses are defined in Table 2. As shown in the table, the hypotheses will be grouped into two sequences corresponding to the two ABC008 doses. The one-sided 2.5% level will be split between the two dose-placebo comparisons as follows: a one-sided 0.5% level will be assigned to the comparison of 0.5 mg/kg vs placebo and a one-sided 2% level will be assigned to the comparison of 2.0 mg/kg vs placebo. The resulting significance levels for each sequence is shown in Table 2. Within each sequence, the hypotheses will be tested in a sequentially rejective manner at the sequence-specific significance level beginning with the hypothesis corresponding to Endpoint 1, as shown in Figure 2. For example, for Sequence 1, testing will begin with H_1 and proceed to the next hypothesis if all preceding hypotheses in the sequence have been rejected. Similarly, testing will begin with H_6 in Sequence 2 and proceed to the next hypothesis if all preceding hypotheses in the sequence have been rejected.

Table 2: Null Hypothesis Based on the Primary and Key Secondary Efficacy Endpoints

Endpoint	Sequence 1 (0.5 mg/kg vs Placebo) Sign Level = 0.5%	Sequence 2 (2.0 mg/kg vs Placebo) Sign Level = 2%
Endpoint 1	H_1	H_6
Endpoint 2	H_2	H_7
Endpoint 3	H_3	H_8
Endpoint 4	H_4	H_9
Endpoint 5	H_5	H_{10}

Figure 2: Testing Strategy for the Primary and Key Secondary Efficacy Endpoints



The diagram uses the conventions proposed by Bretz et al. (Bretz et al., 2009), i.e., the number shown at the top of each sequence represents the fraction of the overall one-sided $\alpha = 2.5\%$ assigned to this sequence, the arrows define the rules for alpha recycling.

9.4.2.3. Estimand Strategy

The primary estimand will be defined as a hybrid estimand, which combines several strategies for handling intercurrent events presented below.

- Treatment condition: Administration of an ABC008 dose or placebo;
- Population: Randomized subjects with IBM;
- Endpoints: Change from Baseline to 76 weeks in IBMFRS;
- Intercurrent events (ICEs): Two types of ICEs are defined below;
- Population-level summary: Between treatment group difference for each ABC008 dose expressed in terms of the mean change.

The following ICEs will be defined for the primary estimand and analysis:

- ICE-1: Discontinuation of treatment due to lack of efficacy or death. This ICE will be handled using the “worst-case” hypothetical strategy implying that such subjects would have received no benefit from randomization until the end of the 76-week Treatment Period.

- ICE-2: Discontinuation of treatment due to an AE. This ICE will be handled using the “control-based” hypothetical strategy implying that such subjects would have switched to the control treatment (i.e., placebo) starting from the occurrence of ICE-2 to the end of the 76-week Treatment Period.

The main estimand will compare each ABC008 dose to placebo for the primary efficacy endpoint at the end of the corresponding Treatment Period. A hybrid strategy for handling ICEs during the Treatment Period will be used.

For subjects who experienced any of the two ICEs, the outcome for the primary efficacy endpoint will be considered missing starting from the occurrence of each ICE (even if outcomes are collected following an ICE) and the missing outcomes will be imputed using appropriate imputation strategies:

- For ICE-1, the missing outcomes will be imputed using a Bayesian regression model fitted to the subset of subjects with 10% worst outcomes (based on the primary outcome at Week 76) within each treatment arm and an observed outcome at Week 76. Key demographic variables, endpoint-specific baseline scores, and intermediate outcomes collected prior to the ICE will be included as covariates.
- For ICE-2, the missing outcomes will be imputed from a similar regression model fitted to the placebo arm alone with key demographic variables, endpoint-specific baseline scores, and intermediate outcomes collected prior to the ICE included as covariates.

Missing data due to reasons unrelated to the two intercurrent events, e.g., intermittent missingness caused by skipped visits, will be imputed using a combination of Markov chain Monte-Carlo imputation to complete missingness to a monotone pattern followed by the same Bayesian regression model using monotone missingness as for ICE-1 and ICE-2 but fitted separately by treatment arm on all data based on the missingness at random assumption.

The final treatment effect estimates and p-values will be obtained using Rubin’s combination rules to produce a single inferential statement (mean treatment difference and p-value). A pre-defined seed value (123456) will be used for all calls to implement multiple imputations using PROC MI in SAS and the number of imputations will be set to 100.

Sensitivity analyses based on control-based imputation and delta-adjusted imputation (tipping point) will be conducted. The details of these analyses are presented in [Table 3](#). In all cases, a multiple imputation approach will be applied and imputation models will be based on the Bayesian regression model using monotone missingness. The estimated effects and associated standard errors from the individual completed data sets will be combined using Rubin’s rules. The details of the sensitivity analyses will be defined in the SAP.

Table 3: Sensitivity Analyses for Two Types of Intercurrent Events

Analysis	ICE-1	ICE-2
Control-based imputation	Impute missing outcomes caused by ICE-1 for both treatment arms based on an imputation model informed by placebo subjects who did not have any of the ICEs using only the subset of data with 10% worst outcomes (based on the primary outcome at Week 76) from the placebo arm. The baseline data (key demographic variables and endpoint-specific baseline scores) and intermediate outcomes prior to the ICE will be used in the imputation model.	Impute missing outcomes by ICE-2 for both treatment arms based on an imputation model informed by placebo subjects who did not have any of the ICEs using only the data from the placebo arm with no ICEs. The baseline data (key demographic variables and endpoint-specific baseline scores) and intermediate outcomes prior to the ICE will be used in the imputation model. Note this is the same as the analytic strategy for ICE-2 in the primary efficacy analysis except the imputation model will be trained only on subjects who were free of any ICEs.
Delta-adjusted imputation	Similar to the strategy for ICE-1 in the primary analysis, i.e., imputations will be informed by the 10% worst outcomes within each treatment arm, but the primary efficacy outcome at Week 76 will be adjusted post-imputation by adding a predefined delta. Separate values of the delta parameter may be used in the ABC008 and placebo arms.	Same as the strategy for ICE-2 in the primary analysis but the primary efficacy outcome at Week 76 will be adjusted post-imputation by adding a predefined delta. Separate values of the delta parameter may be used in the ABC008 and placebo arms (although the same model fitted only to the placebo arm will be used for imputing data in all trial arms).

ICE, intercurrent event.

The same strategies for handling ICEs will be applied to the key secondary endpoints.

9.4.3. Analysis of Safety

The SAS will be used for the analysis of safety data (AEs, exposure to study medication, clinical laboratory, vital signs, and ECG assessments).

AEs will be coded using the most current version of MedDRA available at the start of the study. Clinical laboratory test results will be converted to Système International units for reporting and processing purposes.

TEAEs will be defined as AEs with an onset date on or after the date of first administration of study medication and before the date of last administration of study medication plus 30 days.

For Part A and Part B, safety and tolerability of ABC008 will be assessed using the following measures for each ABC008 dose vs. placebo:

- Incidence, type, and severity of AEs including TEAEs and TESAEs, discontinuation due to TEAEs and drug-related TEAEs;

- Absolute values and changes from baseline in vital sign and weight measurements, clinical laboratory test results, and 12-lead ECG parameters;
- Incidence of abnormal vital sign and weight measurements, clinical laboratory test results, and 12-lead ECG parameters. The abnormal values will be defined with respect to the normal ranges and shift tables for changes from baseline to the end of the Treatment Period will be presented as appropriate;
- Incidence of AESIs, including injection site reactions, systemic injection reactions, and infection (as detailed in Section 3.2).

All safety data will be listed for each subject.

9.4.4. Pharmacokinetic Endpoints

The PK data will be analyzed using the PKS. Individual and mean serum ABC008 concentrations by treatment group at each sampling time point will be listed and summarized in a tabular form. Descriptive statistics (n, arithmetic mean, SD, arithmetic coefficient of variation [CV], median, minimum, and maximum) will be used to summarize ABC008 concentration data at each planned sampling time point. All serum concentration data will be listed by subject using the SS and will be summarized by analyte, dose, and sampling time.

PK parameters will be calculated using noncompartmental analysis when feasible. Summary statistics of PK parameters including geometric mean, arithmetic mean, SD, arithmetic CV, geometric CV, median, minimum, and maximum will be presented when feasible.

9.4.5. Pharmacodynamic Endpoints

All PD data in the PDS will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. Statistical analysis will be performed on PD parameters to evaluate the PD profiles of the treatment groups in Part A and B.

In addition, the time to recovery will be evaluated in Part C using the PDCS. The time to recovery will be summarized using Kaplan-Meier curves and inferences may be performed using the log-rank test.

9.5. Interim Safety Analysis

An interim safety analysis will be performed during Part A (Sentinel Cohort) of the study. The purpose of the interim safety analysis is to assess the safety and tolerability of recurrent dosing with ABC008 in this sentinel cohort of subjects. Safety and tolerability data for all Part A subjects through at least the W20 visit will be analyzed by an authorized unblinded data analysis group, who will provide the DSMB with unblinded data for review. The decision to continue dosing through W72 in Part A and begin enrollment in Part B will be based upon the DSMB review of the interim safety analysis as described in the DSMB charter.

The data provided to the DSMB will also include multiple-dose safety data from the Phase I study ABC008-IBM-101 in order to provide a more comprehensive view of the safety of recurrent dosing with ABC008.

10. STUDY ADMINISTRATION

10.1. Good Clinical Practice

This study will be conducted in accordance with applicable International Council for Harmonization (ICH) GCP guidance, US Food and Drug Administration CFR (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the European Union Regulation 536/2014.; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

10.2. Informed Consent

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the Investigator should have the IRB/IEC's written approval/favorable opinion of the written ICF and any other written information to be provided to subjects.

The Investigator or his/her representative will explain the study to the subject or his/her legally acceptable representative and answer all questions regarding the study.

The Investigator or his/her representative will enable the subject or his or her legally designated representative to understand:

- The nature, objectives, benefits, implications, risks, and inconveniences of the clinical study;
- The subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical study at any time without any resulting detriment and without having to provide any justification;
- The conditions under which the clinical study is to be conducted, including the expected duration of the subject's participation in the clinical study; and
- The possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical study is discontinued.

Subjects must be informed that their participation is voluntary, and consent can be withdrawn at any point.

Subjects or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of applicable local regulations, ICH guidelines, and the IRB/IEC or study site.

Prior to a subject's participation in the study, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained.

The original copy of the signed ICF will be retained at the study site.

A copy of the ICF and any other written information must be provided to the subject or the subject's legally acceptable representative.

If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favorable opinion in advance of its use. Subjects must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The subject will be informed that the summary of the results of the clinical study and a summary presented in terms understandable to a layperson will be made available in the ClinicalTrials.gov, European Union Drug Regulating Authorities Clinical Trials (EudraCT), EU Clinical Trials Registry (CTR), and australianclinicaltrials.gov.au databases, irrespective of the outcome of the clinical study, and, to the extent possible, when the summaries become available.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness should sign and personally date the ICF after:

- The written ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative;
- The subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study;
- The subject or the subject's legally acceptable representative has signed and personally dated the ICF if they are capable of doing so.

By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

10.3. Subject Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB/IEC personnel, the Sponsor and its authorized representatives are allowed full access to the records.

All study subjects must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the ICF. The subjects must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Identification of subjects and eCRFs shall be by unique subject identification numbers. All personal identifiers according to applicable regulations (e.g., name, phone number) must be

redacted permanently by the site personnel and replaced with the subject's unique identification number in all records and data before transfer to the Sponsor (or designee).

All personal details will be treated as confidential by the Investigator and staff.

10.4. Institutional Review Board/Independent Ethics Committee

Before initiating a study, the Investigator/institution must have written and dated approval/favorable opinion from the IRBs/IECs for the study protocol/amendment(s), written ICF, any ICF updates, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects and a statement from the IRBs/IECs that these comply with GCP requirements (if applicable). A current copy of the ABC008 IBM IB should be included as part of the written application to the IRB/IEC.

The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of SAEs or other significant safety findings, including adverse drug reactions that are both serious and unexpected, as required by IRB/IEC procedures;
- Providing oversight of the conduct of the study at the site and adherence to the requirements of all applicable regulations;
- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study subjects.

10.5. Recruitment Arrangements

The study sites will be responsible for the recruiting of study subjects. Advertising may be used in subject recruitment, but must be approved by the Sponsor and the IRB/IEC.

Rescreening will be allowed one time within the recruitment period for the study with MM approval. No waivers of inclusion or exclusion criteria will be issued.

10.6. Investigator Responsibility

10.6.1. General Responsibility

All Investigators are responsible for carrying out the study in accordance with the protocol and the above guidelines and regulations and for collecting, documenting, and reporting the study data accurately.

All Investigators must be familiar with the background and requirements of the study and with the properties of ABC008, as described in the current version of the ABC008 IBM IB.

The Principal Investigator is responsible for distributing study information and documentation to all appropriate study site personnel prior to and during the study as updated information becomes available.

The Principal Investigator is also responsible for ensuring the privacy, health, and welfare of all subjects during and after the clinical study and must ensure that fully functional resuscitation equipment and study site personnel trained in its use are immediately available in the event of an emergency.

The Principal Investigator has the overall responsibility for the conduct and administration of the study at the study sites and for contacts with the Sponsor, the IRB/IEC, and local authorities.

10.6.2. Protocol Compliance

Except for a change intended to eliminate an immediate hazard to a study subject, the protocol shall be conducted as described herein without any changes or deviations. Any change, intentional or otherwise, must be reported to the Sponsor and to the relevant IRB/IEC and/or regulatory authority as required by guidelines or regulation.

10.6.3. Protocol Amendments

Protocol Amendments will be prepared and approved by the Sponsor or designee and sent to the appropriate IRB/IEC for review and approval. For each protocol amendment, the Investigator Protocol Agreement page must be signed by the Principal Investigator. Documentation of IRB/IEC approval must be forwarded to the Sponsor or designee.

If a protocol amendment significantly alters the study design, increases potential risk to study subjects, or otherwise affects statements in the ICFs, the ICFs must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved ICFs must be used to obtain informed consent from new subjects prior to registration and must be used to reobtain informed consent from subjects already registered if they are affected by the protocol amendment.

10.7. Data and Safety Monitoring Board

The study will be subject to oversight by an independent DSMB, which will be governed by a Charter. The composition of the DSMB will be outlined in the DSMB Charter.

The DSMB will review interim safety and tolerability data for all Part A (Sentinel Cohort) subjects through at least the W20 visit, after subjects have received three doses of study drug, as described in the DSMB charter. Subjects may continue in their assigned groups in a double-blind manner while the DSMB sentinel cohort review is pending. Continued dosing of Part A subjects through W72 will be predicated on a favorable DSMB assessment of safety, as will initiation of enrollment in Part B (Double-Blind Safety and Efficacy Cohort) of the study.

Throughout the study and in accordance with the DSMB charter, the DSMB will review aggregate safety data on a regular basis and as necessary based on the occurrence of SAEs (if any) and will make necessary recommendations to the Sponsor for any decisions related to the conduct of the clinical study. The DSMB will be unblinded with regard to subject treatment allocation.

Based on the regular review of the safety data, the DSMB will make recommendations regarding whether the study should continue and institution of additional safety measures to reduce any identified safety risks to enrolled subjects (e.g., use of premedications).

All recommendations proposed by the DSMB require final approval from the Sponsor and will be communicated to all sites. Further details are provided in the DSMB Charter.

10.8. Quality Assurance

10.8.1. Clinical Quality Assurance

The procedures of this study may only be carried out by the PI or trained study site personnel under the direction of the Principal Investigator. Study-related procedures will be conducted in accordance with provided written materials.

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IRB/IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study site personnel to the auditors to discuss findings and issues.

10.8.2. Professional Licensure

All study physicians must provide evidence of current medical licensure as applicable to the study location(s) if they are practicing medicine, diagnosing, and/or treating subjects.

10.8.3. Laboratory Accreditation

Samples of blood for the evaluation of hematology and blood chemistry parameters will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency.

10.9. Study Start and Termination

The study start date is the date on which the first subject provides informed consent.

The end of the study is defined as the last subject's last assessment.

Both the Sponsor and the Investigator reserve the right to terminate the study or the participation in the study at an Investigator's site at any time. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

If the study is prematurely terminated or suspended for any reason, the Sponsor/Investigator/site personnel should promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. Where required by the applicable regulatory requirements, the IRB/IEC should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the Investigator terminates or suspends a study without prior agreement of the Sponsor, the Investigator should inform the site personnel. The Investigator/site personnel should promptly inform the Sponsor and the IRB/IEC. The Investigator/site personnel should also provide the Sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

10.10. Publications

Publication by any study site of any data from this study must be carried out in accordance with the Clinical Trial Agreement.

10.11. Financing and Insurance

10.11.1. Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

10.11.2. Insurance, Indemnity, and Compensation

Abcuro, Inc. will maintain an appropriate clinical study insurance policy.

10.11.3. Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

11. DATA HANDLING, RECORD KEEPING AND DIRECT ACCESS TO DATA

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

An eCRF will be used to store and transmit subject information. The eCRF must be reviewed and electronically signed and dated by the Investigator. The Investigator is responsible for verifying that the data entries are accurate and correct by signing the eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (e.g., Investigators and the study coordinator). The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the subject's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule;
- General condition and status remarks by the subject, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is related to study medication;
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures;
- A general reference to the procedures completed;
- The signature or initials of all physicians making an entry in the medical record (progress notes).

In addition, any contact with the subject via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initialed and dated on the day the change is made by the Investigator (or designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

The CRO will write a data management plan, which will be finalized prior to performing any data validation.

11.1. Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, screening logs, completed scales, HRQoL questionnaires, and recorded data from automated instruments.

The Investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

All source documents from this study are to be maintained by the Investigator and made available for inspection by authorized persons. The Investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The Sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

11.2. Electronic Case Report Form Completion and Data Management

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (e.g., Investigators and the study coordinator). The eCRF must be completed as soon as possible after any subject evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

11.3. Study Files and Record Retention

All data derived from the study will remain the property of the Sponsor. The Sponsor assumes accountability for actions delegated to other individuals, e.g., the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of subjects, source documents, eCRFs, and the study medication inventory, must be kept on file.

Essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least two years have elapsed since the formal discontinuation of clinical development of ABC008. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator is not to dispose of any records relevant to this study without written permission from the Sponsor and is to provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an Investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

11.4. Data Protection

The contract between Sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches, respective communication, and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

11.4.1. Medable Cloud Platform Security

The Medable application will be utilized on a mobile device for electronic administration of PRO assessments, including the [REDACTED] EQ-5D-5L, and SF-36v2.

[REDACTED] will be administered when available.

All Medable application data are authenticated and securely encrypted for data transmission and storage. Data are uploaded in real-time and once the upload has completed, the encrypted cache of data is deleted, so data do not persist on the device. Encryption keys are managed in the US by Google Cloud, and in the EU by a third-party key management service, according to an escrow model implemented to comply with EU data protection laws.

11.5. Auditing and Monitoring

Sponsor- and/or CRO-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRF, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the Investigator will assist with the Sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The Sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the Sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the Study Monitoring Plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRF with source documents. Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator (or designee) should contact the Sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The Investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

11.5.1. Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the start of the study. Details on the identification and documentation of QTLs is provided in the Quality Management Plan.

The Sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) is described in the Quality Management Plan.

11.5.2. Protocol Adherence and Deviations

The Investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the Investigator, site personnel, or the subject.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The Investigator should not implement any deviation from the protocol without agreement from the Sponsor and prior review and approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study subject, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number.

In the event of an important protocol deviation, the Investigator will discuss the deviation with the MM and will come to an agreement as to whether the subject should be withdrawn from the study due to the important protocol deviation.

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APPENDIX 1. SCHEDULES OF EVENTS

Table 4: Schedule of Events (Part A – Sentinel Cohort)

Study Period	Screen- ing	Treatment Period															EOT/ ETV ¹	Follow -up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9 ³	10	11	12	13	14	15	16	17	18	-
Week	-5	0	1	2	4	8	12	16	20	24	32	40	48	56	64	72	76	80	-
Day	-35 to -1	1	8	15	29	57	85	113	141	169	225	281	337	393	449	505	533	561	-
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-
Informed consent	X																		
Inclusion/exclusion criteria ⁴	X	X																	
Randomization		X																	
Demographic data	X																		
IBM history (includes ENMC criterion met, symptom onset, and assistance use)	X																		
Medical history (includes procedures, social history)	X																		
Prior medication and vaccinations	X																		
Concomitant medications and vaccinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and height ⁵	X	X				X		X		X	X	X	X	X	X	X	X		X

Table 4: Schedule of Events (Part A – Sentinel Cohort) (Continued)

Study Period	Screen- ing	Treatment Period															EOT/ ETV ¹	Follow- up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9 ³	10	11	12	13	14	15	16	17	18	-
Week	-5	0	1	2	4	8	12	16	20	24	32	40	48	56	64	72	76	80	-
Day	-35 to -1	1	8	15	29	57	85	113	141	169	225	281	337	393	449	505	533	561	-
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-
Vital signs ⁶	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical examination ⁷	X	X			X			X	X		X		X				X		X
ECG ⁸	X							X	X		X						X		X
Pregnancy test ⁹	X	X				X		X		X	X	X	X	X	X	X	X		X
FSH ¹⁰	X																		
Free T4, TSH	X							X									X		X
Tuberculosis testing ¹¹	X																		X
COVID-19 testing ¹²	X	X																	X
HBV, HCV, and HIV tests ¹³	X																		X
CMV, EBV, HSV-1, HSV-2, and VZV IgG titers	X																X		X
Anti-cN-1A (NT5c1A), ANA, anti-SSA/SSB	X																		
Coagulation ¹⁴	X																		
Hematology and chemistry ^{15,16}	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X

Table 4: Schedule of Events (Part A – Sentinel Cohort) (Continued)

Study Period	Screen- ing	Treatment Period															EOT/ ETV ¹	Follow- up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9 ³	10	11	12	13	14	15	16	17	18	-
Week	-5	0	1	2	4	8	12	16	20	24	32	40	48	56	64	72	76	80	-
Day	-35 to -1	1	8	15	29	57	85	113	141	169	225	281	337	393	449	505	533	561	-
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-
Serum immunoglobulins, M protein, and light chain ratio	X																X		
CMV and EBV viral loads PCR analysis	X	X				X		X			X				X		X		X
Complement ¹⁷	X	X				X		X									X		X
Urinalysis ¹⁸	X	X				X		X			X				X		X		X
C-SSRS	X	X				X		X		X			X				X		
	X																		
	X																		
						X		X			X				X		X		X
IBMFRS ¹⁹	X	X				X		X			X		X		X		X		X
EQ-5D-5L, SF-36v2 ¹⁹	X	X				X		X			X				X		X		X
MMT ████ MMT 12	X	X				X		X			X				X		X		X
Dynamometry (grip, quadriceps) ²⁰	X	X				X		X			X				X		X		X
mTUG	X	X				X		X			X				X		X		X

Table 4: Schedule of Events (Part A – Sentinel Cohort) (Continued)

Study Period	Screen- ing	Treatment Period															EOT/ ETV ¹	Follow- up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9 ³	10	11	12	13	14	15	16	17	18	-
Week	-5	0	1	2	4	8	12	16	20	24	32	40	48	56	64	72	76	80	-
Day	-35 to -1	1	8	15	29	57	85	113	141	169	225	281	337	393	449	505	533	561	-
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-
						X		X			X				X		X		X
PK ²¹	X	X	X	X	X	X		X			X				X		X		X
Blood sample for KLRG1 analysis	X	X									X						X		X
PD ^{21,22}	X	X									X						X		X
	X	X									X						X		X
	X	X				X		X			X				X		X		X
		X				X		X			X				X		X		
Study medicine administration ²⁴		X				X		X		X	X	X	X	X	X	X			
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

ANA, antinuclear antibody; anti-cN-1A, anti-cytosolic 5'-nucleotidase 1A; anti-SSA/SSB, anti-Sjogren's Syndrome type A/type B; CD, cluster of differentiation; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; C-SSRS, Columbia Suicide Severity Rating Scale; DSMB, Data and Safety Monitoring Board; EBV, Epstein-Barr virus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ENMC, European Neuromuscular Centre; EOT, End-of-Treatment visit; EQ-5D-5L, EuroQol EQ-5D 5-dimension, 5-level Quality-of-Life Questionnaire; ETV, Early Termination visit; FSH, follicle stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; IBM, inclusion body myositis; IBMFRS, IBM Functional Rating Scale; Ig, immunoglobulin; KLRG1, killer-like leptin receptor G1; MMT, manual muscle test; mTUG, modified Timed Up and Go test; PCR, polymerase chain reaction; PD, pharmacodynamic; PK, pharmacokinetic; RNA, ribonucleic acid; SC, subcutaneous; SF-36v2, Short Form 36-item Health Survey Version 2; TB, tuberculosis; TSH, thyroid stimulating hormone; USV, unscheduled visit; VZV, varicella zoster virus; W, week; WOCBP, women of childbearing potential.

- ETV should be performed for all subjects that withdraw from the study prior to W76. W76 serves as the end of the Treatment Period and includes all assessments as listed prior to dosing of study medication at that visit. Subjects who prematurely discontinue study drug during Part A will progress to Part C for PD and safety follow-up.

2. Subjects will have a follow-up visit four weeks after the W76 visit. At the W80 visit, subjects will be eligible to enroll in a long-term extension study or, if they do not choose to enroll in the long-term extension study, will continue into Part C of the study for PD and safety follow-up. The W80 visit is intended to serve as both the follow-up visit for the current study and as the Baseline Visit for either the long-term extension study or Part C of this study. Only those activities related to the follow-up visit for the current study are shown here.
3. DSMB review for the sentinel cohort will be based on safety data for all Part A subjects at least through the W20 visit. Subjects may continue in their assigned treatment groups in a double-blind manner while the DSMB sentinel cohort review is pending. Continued dosing of Part A subjects through W72 will be predicated on a favorable DSMB assessment.
4. Eligibility criteria for this study should be assessed only after signing of informed consent for this study. All data from Screening and all data except for central laboratory results from Baseline (Day 1) Visit should be used to confirm subject eligibility.
5. Weight will be collected at Screening, Baseline (Day 1), study medication administration visits (predose), and EOT/ETV; height will be collected at Screening only.
6. Vitals include blood pressure, temperature, pulse, and respiration rate. Temperature may be measured orally, axillary, forehead, or otic. Blood pressure and pulse are strongly recommended to be collected after the subject has had at least five minutes of rest in the seated position. If blood pressure is elevated on the first measurement, it should be repeated after an additional five minutes of rest. Blood pressure is strongly recommended to be obtained from the same arm at each assessment. Vital signs are strongly recommended to be performed after ECGs and prior to blood draws.
7. Physical examination should be complete physical examination at Screening, W48, and EOT/ETV. The remaining examinations may be limited and symptom directed.
8. Strongly recommended to be performed after at least five minutes of rest in a supine position and before vital sign collection and blood draws.
9. All WOCBP will have a serum pregnancy test at Screening and at EOT/ETV. Urine pregnancy tests will be performed for WOCBP prior to dosing at all other specified visits; the result must be negative for the subject to be eligible for dosing. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. On Day 1, the pregnancy test should be performed prior to randomization and a confirmed positive test is exclusionary.
10. Postmenopausal status may be confirmed through testing for FSH at Screening.
11. Tuberculosis assessment includes central or local QuantiFERON-TB Gold Plus test or local T-SPOT.TB test. Intermediate or borderline test results require a repeat test to confirm negative status or medical evaluation to rule out concern for TB disease.
12. Subjects must have negative COVID-19 test results within 48 hours of Baseline (PCR or rapid antigen testing as per local guidance).
13. HIV-1 and -2, HBV core antibody and surface antigen, and HCV antibody with reflex HCV RNA.
14. Activated partial thromboplastin time and international normalized ratio.
15. Hematology: hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential (e.g., basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet count, CD4, CD8, CD19, and CD4:CD8.
16. Clinical chemistry: albumin, alanine aminotransferase, aldolase, alkaline phosphatase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, C-reactive protein, calcium, [REDACTED] creatinine, gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, potassium, sodium chloride, total bilirubin, total protein, uric acid. eGFR will be calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.
17. C3, C4, and CH50.
18. Urinalysis: color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocyte esterase with reflex microscopic analysis.
19. These patient- and physician-reported outcome measures are recommended to be completed first at each visit where performed, i.e., prior to any other procedures or assessments other than signing of informed consent [REDACTED] and [REDACTED] will be completed at the Screening visit only.
20. Dynamometry to measure grip strength and quadriceps strength. Both sides will be evaluated throughout the study.

21. When PK and PD sampling coincides on a study medication administration day, blood samples for PK and PD analysis should be drawn within two hours prior to ABC008 administration.

24. Subjects need to be monitored for two hours after dosing at Baseline (Day 1) and W8.

Table 5: Schedule of Events (Part B – Double-Blind Safety and Efficacy Cohort)

Study Period	Screen- ing	Treatment Period														EOT/ ETV ¹	Follow- up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	-
Week	-5	0	1	2	4	8	12	16	24	32	40	48	56	64	72	76	80	-
Day	-35 to -1	1	8	15	29	57	85	113	169	225	281	337	393	449	505	533	561	-
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-
Informed consent	X																	
Inclusion/exclusion criteria ³	X	X																
Randomization		X																
Demographic data	X																	
IBM history (includes ENMC criterion met, symptom onset, and assistance use)	X																	
Medical history (includes procedures, social history)	X																	
Prior medication and vaccinations	X																	
Concomitant medications and vaccinations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and height ⁴	X	X				X		X	X	X	X	X	X	X	X	X		X
Vital signs ⁵	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical examination ⁶	X	X			X			X		X		X				X		X
ECG ⁷	X							X		X						X		X
Pregnancy test ⁸	X	X				X		X	X	X	X	X	X	X	X	X		X

Table 5: Schedule of Events (Part B – Double-Blind Safety and Efficacy Cohort) (Continued)

Study Period	Screen- ing	Treatment Period														EOT/ ETV ¹	Follow- up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	-
Week	-5	0	1	2	4	8	12	16	24	32	40	48	56	64	72	76	80	-
Day	-35 to -1	1	8	15	29	57	85	113	169	225	281	337	393	449	505	533	561	-
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-
FSH ⁹	X																	
Free T4, TSH	X							X								X		X
Tuberculosis testing ¹⁰	X																	X
COVID-19 testing ¹¹	X	X																X
HBV, HCV, and HIV tests ¹²	X																	X
CMV, EBV, HSV-1, HSV-2, and VZV IgG titers	X															X		X
Anti-cN-1A (NT5c1A), ANA, anti-SSA/SSB	X																	
Coagulation ¹³	X																	
Hematology and chemistry ^{14,15}	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X
Serum immunoglobulins, M protein, and light chain ratio	X															X		
CMV and EBV viral loads PCR analysis	X	X				X		X		X				X		X		X
Complement ¹⁶	X	X				X		X								X		X
Urinalysis ¹⁷	X	X				X		X		X				X		X		X

Table 5: Schedule of Events (Part B – Double-Blind Safety and Efficacy Cohort) (Continued)

Study Period	Screen- ing	Treatment Period															EOT/ ETV ¹	Follow- up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	-	
Week	-5	0	1	2	4	8	12	16	24	32	40	48	56	64	72	76	80	-	
Day	-35 to -1	1	8	15	29	57	85	113	169	225	281	337	393	449	505	533	561	-	
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-	
C-SSRS	X	X				X		X	X			X				X			
	X																		
	X																		
						X		X		X				X		X		X	
IBMFRS ¹⁸	X	X				X		X		X		X		X		X		X	
EAT-10 ¹⁸	X	X				X		X		X				X		X		X	
EQ-5D-5L, SF-36v2 ¹⁸	X	X				X		X		X				X		X		X	
MMT MMT 12	X	X				X		X		X				X		X		X	
Dynamometry (grip, quadriceps) ¹⁹	X	X				X		X		X				X		X		X	
mTUG	X	X				X		X		X				X		X		X	
						X		X		X				X		X		X	
PK ²⁰	X	X	X	X	X	X		X		X				X		X		X	
Blood sample for <i>KLRG1</i> analysis	X	X	X	X	X	X		X		X				X		X		X	
PD ^{20,21}	X	X	X	X	X	X		X		X				X		X		X	
	X	X								X						X		X	

Table 5: Schedule of Events (Part B – Double-Blind Safety and Efficacy Cohort) (Continued)

Study Period	Screen- ing	Treatment Period														EOT/ ETV ¹	Follow- up ²	USV
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	-
Week	-5	0	1	2	4	8	12	16	24	32	40	48	56	64	72	76	80	-
Day	-35 to -1	1	8	15	29	57	85	113	169	225	281	337	393	449	505	533	561	-
Visit Window	-	0	±1	±1	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	-
Site-specific intensive immunophenotyping ²³	X	X	X	X	X	X		X		X				X		X		X
	X	X				X		X		X				X		X		X
			X			X		X		X				X		X		
Study medicine administration ²⁴		X				X		X	X	X	X	X	X	X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Exit Survey																X ²⁵		

ANA, antinuclear antibody; anti-cN-1A, anti-cytosolic 5'-nucleotidase 1A; anti-SSA/SSB, anti-Sjogren's Syndrome type A/type B; CD, cluster of differentiation; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; C-SSRS, Columbia Suicide Severity Rating Scale; EBV, Epstein-Barr virus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ENMC, European Neuromuscular Centre; EOT, End-of-Treatment visit; EQ-5D-5L, EuroQol EQ-5D 5-dimension, 5-level Quality-of-Life Questionnaire; ETV, Early Termination visit; FSH, follicle stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; IBM, inclusion body myositis; IBMFRS, IBM Functional Rating Scale; Ig, immunoglobulin; KLRG1, killer-like leptin receptor G1; MMT, manual muscle test; mTUG, modified Timed Up and Go test; PCR, polymerase chain reaction; PD, pharmacodynamic; PK, pharmacokinetic; RNA, ribonucleic acid; SC, subcutaneous; SF-36v2, Short Form 36-item Health Survey Version 2; TB, tuberculosis; TSH, thyroid stimulating hormone; US, United States; USV, unscheduled visit; VZV, varicella zoster virus; W, week; WOCBP, women of childbearing potential.

1. ETV should be performed for all subjects that withdraw from the study prior to W76. W76 serves as the end of the Treatment Period and includes all assessments as listed prior to dosing of study medication at that visit. Subjects who prematurely discontinue study drug during Part B will progress to Part C for PD and safety follow-up.
2. Subjects will have a follow-up visit four weeks after the W76 visit. The W80 safety follow-up visit may be conducted via phone. At the W80 visit, subjects will be eligible to enroll in a long-term extension study or, if they do not choose to enroll in the long-term extension study, will continue into Part C of the study for PD and safety follow-up. If conducted in person, the W80 visit may serve as both the follow-up visit for the current study and as the Baseline Visit for either the long-term extension study or Part C of this study. Only those activities related to the follow-up visit for the current study are shown here.

3. Eligibility criteria for this study should be assessed only after signing of informed consent for this study. All data from Screening and all data except for central laboratory results from Baseline (Day 1) Visit should be used to confirm subject eligibility.
 4. Weight will be collected at Screening, Baseline (Day 1), study medication administration visits (predose), and EOT/ETV; height will be collected at Screening only.
 5. Vitals include blood pressure, temperature, pulse, and respiration rate. Temperature may be measured orally, axillary, forehead, or otic. Blood pressure and pulse are strongly recommended to be collected after the subject has had at least five minutes of rest in the seated position. If blood pressure is elevated on the first measurement, it should be repeated after an additional five minutes of rest. Blood pressure is strongly recommended to be obtained from the same arm at each assessment. Vital signs are strongly recommended to be performed after ECGs and prior to blood draws.
 6. Physical examination should be complete physical examination at Screening, W48, and EOT/ETV. The remaining examinations may be limited and symptom directed.
 7. Strongly recommended to be performed after at least five minutes of rest in a supine position and before vital sign collection and blood draws.
 8. All WOCBP will have a serum pregnancy test at Screening and at EOT/ETV. Urine pregnancy tests will be performed for WOCBP prior to dosing at all other specified visits; the result must be negative for the subject to be eligible for dosing. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. On Day 1, the pregnancy test should be performed prior to randomization and a confirmed positive test is exclusionary.
 9. Postmenopausal status may be confirmed through testing for FSH at Screening.
 10. Tuberculosis assessment includes central or local QuantiFERON-TB Gold Plus test or local T-SPOT.TB test. Indeterminate or borderline test results require a repeat test to confirm negative status or medical evaluation to rule out a concern for TB disease.
 11. Subjects must have negative COVID-19 test results within 48 hours of Baseline (PCR or rapid antigen testing as per local guidance).
 12. HIV-1 and -2, HBV core antibody and surface antigen, and HCV antibody with reflex HCV RNA.
 13. Activated partial thromboplastin time and international normalized ratio.
 14. Hematology: hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell count with differential (e.g., basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet count, CD4, CD8, CD19, and CD4:CD8.
 15. Clinical chemistry: albumin, alanine aminotransferase, aldolase, alkaline phosphatase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, C-reactive protein, calcium, [REDACTED] creatinine, gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, potassium, sodium chloride, total bilirubin, total protein, uric acid. eGFR will be calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.
 16. C3, C4, and CH50.
 17. Urinalysis: color, appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrite, leukocyte esterase with reflex microscopic analysis.
 18. These patient- and physician-reported outcome measures are recommended to be completed first at each visit where performed, i.e., prior to any other procedures or assessments other than signing of informed consent. [REDACTED] and [REDACTED] will be completed at the Screening visit only. Note: [REDACTED] will be administered when available.
 19. Dynamometry to measure grip strength and quadriceps strength. Both sides will be evaluated throughout the study.
 20. When PK and PD sampling coincides on a study medication administration day, blood samples for PK and PD analysis should be drawn within two hours prior to ABC008 administration.
- [REDACTED]
23. Approximately 40 subjects at selected sites in the US will have additional PD [REDACTED]
 24. Subjects need to be monitored for two hours after dosing at Baseline (Day 1) and W8.

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25. Subjects at participating US sites should complete the optional Patient Exit Survey after completing the blinded portion of the study and before enrolling in the open-label long-term extension study.

Table 6: Schedule of Events (Part C – PD Recovery Cohort)

Study Period	Part C Baseline/ Part A or B Follow-Up/ Part A or B ETV ¹	Follow-up Period						ETV ¹	EOS Phone Call ²	USV
Visit Number	C1	C2	C3	C4	C5	C6	C7+ ³	-	-	-
Week	C0	C4	C8	C12	C16	C20	C24+	-	-	-
Day	C1	C29	C57	C85	C113	C141	C169+	-	-	-
Visit Window	-	±7	±7	±7	±7	±7	±7	-	-	-
Telephone Contact?		Y	Y		Y	Y			Y	
Pregnancy test ⁴	X			X			X	X		X
	X			X			X	X		X
Adverse events	X	X	X	X	X	X	X	X	X	X

AE, adverse event; CD, cluster of differentiation; EOS, End-of-Study; ETV, Early Termination visit; KLRG1, killer-like leptin receptor G1; PD, pharmacodynamic; USV, unscheduled visit.; WOCBP, women of childbearing potential.

1. All assessments completed at the Part A or Part B Follow-up (for subjects who completed Part A or Part B, respectively) or the ETV (for subjects who prematurely discontinued study drug during Part A or B) will be used as the Part C Baseline assessments; procedures should not be repeated.
2. Once KLRG1+ cell recovery has been documented, an EOS phone call will be conducted to notify the subject and collect any AEs not previously reported.
3. Follow-up visits every three months (all assessments) and monthly telephone contacts (AEs only) will continue until subject's KLRG1+ cells have recovered.
4. All WOCBP will have a serum pregnancy test at Part A or B ETV; WOCBP for whom the Part C Baseline corresponds to Part A or B Follow-Up will have a urine pregnancy test at Part C Baseline. Urine pregnancy tests will be performed for WOCBP at all other specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.