STUDY PROTOCOL

ANK-700-01

A Phase 1 Study of the Safety and Tolerability of Single and Multiple Doses of ANK-700 in Patients with Relapsing-Remitting Multiple Sclerosis

Protocol Number: ANK-700-01

Phase: 1

Date of Protocol: 06 June 2022

Version: Version 4

IND: 22932

Sponsor: Anokion US, Inc.
50 Hampshire St., Suite 402
Cambridge, MA 02139

INVESTIGATOR APPROVAL

I have read both the latest version of the ANK-700 Investigator's Brochure and Protocol ANK-700-01 and agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice (GCP) and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (dd/mmm/yyyy): _____

SPONSOR APPROVAL

[redacted]

CONTACT INFORMATION

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PROTOCOL SYNOPSIS

Title of Study

A Phase 1 Study of the Safety and Tolerability of Single and Multiple Doses of ANK-700 in Patients with Relapsing-Remitting Multiple Sclerosis

Name of Investigational Product

ANK-700

Name of Active Ingredient

[redacted]

Study Center(s)

Approximately 15 sites in the United States (US)

Study Period (Years)	**Phase of Development**
Estimated date first patient enrolled: October 2020 Estimated date last patient completed: September 2023	1

Objectives

- **Primary**
  - Assess the safety and tolerability of escalating doses of ANK-700 in patients with relapsing-remitting multiple sclerosis (RRMS)
- **Secondary**
  - Evaluate the pharmacokinetics (PK) of escalating doses of ANK-700 in patients with RRMS
- [redacted]

Methodology

This is a 2-part, multicenter, Phase 1 study of ANK-700 in patients with RRMS. The 2 parts include:

- Part A – First-in-human, single ascending dose (SAD) cohorts
- Part B – Randomized, double-blind, PBO-controlled, multiple ascending dose (MAD) cohorts

Part A and Part B will be conducted in adult patients (18 to 60 years inclusive, at screening), diagnosed with RRMS, and an EDSS score ≤ 6.5. Patients receiving a stable dose of a fumarate drug (i.e., dimethyl fumarate, diroximel fumarate) for ≥ 6 months will be allowed to remain on the fumarate drug throughout the study.

A copy of the EDSS is available in Appendix 2.

Part A – SAD

The SAD part will include up to 3 cohorts of 3 patients each. Patients within each dose cohort will each receive 1 dose of ANK-700 intravenously (IV) and will be monitored for up to 6 months. Patients will be dosed ≥ 14 days apart to monitor for acute and subacute reactions. Patients will arrive at the clinic on the morning of dosing (Day 1 [D1]) and will be monitored in the clinic for 8 hours after completion of the ANK-700 infusion for assessment of acute safety and PK blood sample collection. Patients will return to the clinic on D4±1, D15, D29±1, and at 3 and 6 months for follow-up. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for safety assessments and data collection may be employed to ensure the safety of the patient where appropriate.

Doses evaluated in Part A will include 0.3 mg/kg (Cohort 1), 1.0 mg/kg (Cohort 2), and 3.0 mg/kg (Cohort 3). After all patients within a given dose cohort have been followed for ≥ 14 days post-dose, a safety review will be performed by the Safety Monitoring Committee (SMC) to review all adverse events (AEs) and available laboratory test and PK data. Initiation of the next higher dose level will commence upon recommendation by the SMC and approval by the Sponsor.

Please see Table 1 for the complete schedule of assessments for Part A.

Part B - MAD

The first MAD cohort (Cohort 4) will be initiated after the safety review of SAD Cohort 2, a recommendation to proceed by the SMC, and approval from the Sponsor.

Patients in the MAD cohorts will be randomized 2:1 to either ANK-700 or PBO. Patients will be stratified based upon their use of fumarate medications at study entry within the interactive response technology system. A total of 12 patients will be enrolled per dose cohort (ANK-700, n = 8; PBO, n = 4). Patients will arrive at the clinic on the morning of dosing and will be monitored in-clinic for 8 hours after completion of their first infusion for assessment of acute safety and PK blood sample collection. A total of 3 doses (1 dose every 3 days) will be

administered in Part B, a regimen that was effective in animal models of multiple sclerosis (MS). Patients will return to the clinic on D22, D43, and at 3, 6, and 12 months for follow-up. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for safety assessments and data collection may be employed to ensure the safety of the patient where appropriate.

Doses planned for evaluation in Part B include 0.3 mg/kg (Cohort 4) and 1.0 mg/kg (Cohort 5). Both Part B cohorts will employ sentinel dosing to monitor for the acute and subacute safety of multiple doses of ANK-700. In this design, the first 2 patients in a cohort (1 ANK-700 and 1 PBO) will complete all 3 doses and then complete an additional 14 days of safety monitoring (through D22) before dosing can be initiated in any further patients.

Cohort 5 will only commence after review of the safety, tolerability, and available PK data of all the SAD cohorts (Cohorts 1 to 3) and Cohort 4, recommendation by the SMC, and approval by the Sponsor.

Please see Table 2 for the complete schedule of assessments for Part B.

Number of Patients (Planned)

It is anticipated that the study will enroll approximately 33 to 42 patients across 5 dose cohorts.

Part A (SAD) will enroll approximately 9 to 18 patients across 3 dose cohorts using a 3+3 dose escalation design without intra-patient dose escalation. In Part A, patients may be replaced if they do not receive the full dose of study drug or do not complete the D15 visit, as long as they did not discontinue the study because of dose-limiting toxicity (DLT). No patient with a DLT will be replaced.

Part B (MAD) will enroll approximately 24 patients across 2 dose cohorts. Sixteen patients will receive ANK-700 and 8 patients will receive PBO. In Part B, patients may be replaced if they do not receive all 3 doses and complete the D22 visit, as long as they did not discontinue the study because of a DLT. No patient with a DLT will be replaced.

Starting Dose and Dose Escalation

The starting dose of ANK-700 will be 0.3 mg/kg based on findings from Good Laboratory Practice (GLP) toxicology studies and animal models in MS, which identified the pharmacologically active doses.

Part A will employ a 3+3 design to evaluate single ascending doses of ANK-700. At any dose level, if none of the first 3 patients dosed experience a DLT within 14 days of treatment, then escalation to the next dose level may proceed if recommended by the SMC and approved by the Sponsor. If 1 of the first 3 patients in the cohort experiences a DLT within 14 days of treatment (D1 to D15), the dose level may expand to a maximum of 6 patients. If no DLT occurs among the additional patients enrolled at that dose level, then escalation to the next dose level may proceed if recommended by the SMC and approved by the Sponsor. The first

MAD cohort (Cohort 4) will be initiated after the safety review of SAD Cohort 2 (Part A), a recommendation to proceed by the SMC, and approval by the Sponsor. Cohort 5 will only commence after review of the safety, tolerability, and available PK data of all the SAD cohorts (Cohorts 1 to 3) and Cohort 4, recommendation by the SMC, and approval by the Sponsor.

DLTs include any Grade 2 AE not resolving within 14 days or any ≥ Grade 3 AE occurring during the dose-escalation safety monitoring period (D1 to D15 in Part A; D1 to D22 in Part B).

Any ≥ Grade 4 AE will result in notification to the Food and Drug Administration (FDA) in parallel with the SMC; all study dosing and enrollment will be paused pending review by the FDA.

The non-tolerated dose (NTD) is the dose level at which > 1 patient experiences a DLT during the dose-escalation safety monitoring period (D1 to D15 in Part A; D1 to D22 in Part B). The maximum tolerated dose (MTD) will be defined as the proximal dose level below the NTD administered during the study. Of note, dose escalation may not identify an NTD or MTD.

Safety Monitoring Committee

This study will utilize an independent SMC that will meet regularly during dose escalation to review all available data, including safety and PK. The SMC will make recommendations concerning dose escalation and/or any changes to the dosing paradigm based on review of the received data. The SMC will also make recommendations about the dose(s) selected for Part B. The final decisions related to dose escalation or the dosing paradigm will be made by the Sponsor.

Inclusion Criteria

Key Inclusion Criteria

1. Male or female adults aged 18 to 60 years inclusive at screening
2. Diagnosed with RRMS per revised McDonald criteria (2017) with an EDSS score ≤ 6.5 at screening
3. Neurologically stable with no evidence of relapse within the 28 days before signing the informed consent form (ICF)

   Note: Patients who experienced relapse during the screening period (i.e., after signing the ICF but before dosing) may be rescreened after 28 days
4. Either not currently receiving disease modifying MS therapy, **or** currently using fumarate drugs (i.e. dimethyl fumarate, diroximel fumarate)

   Note: Patients on fumarate drugs are only eligible if they have been on a stable dose ≥ 6 months before administration of study drug
5. Patients must use a highly effective method of birth control or are sterile or postmenopausal as confirmed by study Investigator for the first 3 months (through D90) of the study

6. Patient has signed and understands the ICF

Key Exclusion Criteria

1. Diagnosis of primary progressive MS or secondary progressive MS
2. Uncontrolled or significant medical conditions (including active infection, chronic hepatitis, or Neuromyelitis Optica Spectrum Disorder) which, in the opinion of the Investigator, preclude participation
3. Has any of the following laboratory parameters at screening:
    a. Hemoglobin < 10 g/dL
    b. Platelet count < 100×10^9/L
    c. White blood cell count outside the normal range and assessed as clinically significant by the Investigator
    d. Alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase > 1.5 × the upper limit of normal
    e. Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 based on the Cockcroft-Gault equation during screening
4. Positive for HIV, hepatitis B virus, or hepatitis C virus
5. Patients treated with glatiramer acetate, parenteral steroids or adrenocorticotropic hormone, β-interferon, or plasma exchange within the 3 months prior to first dose
6. Patients treated with sphingosine-1-phospate receptor modulators such as fingolimod, ozanimod, or siponimod within 6 months prior to first dose
7. Patients treated with cytotoxic agents (including, but not limited to, cladribine, mitoxantrone, cyclophosphamide, azathioprine, and methotrexate), laquinimod, teriflunomide, or IV gamma globulin within 12 months prior to first dose
8. Patients treated with monoclonal antibody therapy (including natalizumab, daclizumab, rituximab, ofatumumab, and ocrelizumab) within 24 months prior to first dose except anti-severe acute respiratory syndrome coronavirus 2 monoclonal antibodies
9. Patients previously treated with alemtuzumab, total lymphoid irradiation, mesenchymal stem cell or hematopoietic stem cell transplantation, or tolerance-inducing therapies for MS
10. Patients receiving any vaccination within 28 days prior to first dose
11. Patients with clinical signs and symptoms consistent with suspected COVID-19 or confirmed COVID-19 infection by appropriate laboratory test within the last 4 weeks prior to screening or on admission

    Note: Patients who experienced symptoms consistent with COVID-19 or confirmed infection during the screening period (i.e., after signing the ICF but before dosing) may be rescreened after 4 weeks
12. Patients with a prior severe course of COVID-19 requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation

13. Patient does not agree to limit alcohol intake to 2 drink equivalents or less per day during the study
14. Contraindication to or inability to undergo gadolinium-enhanced magnetic resonance imaging (MRI) scan
15. Use of any investigational drug or experimental procedure within previous 6 months that would interfere with the assessment of ANK-700
16. Patients who are pregnant or breastfeeding

Investigational Product, Dosage, and Mode of Administration

[redacted] Administration of ANK-700 [redacted] will be by IV infusion over approximately 30 minutes. For Part A, patients will receive a single IV infusion of ANK-700. For Part B, patients will receive a total of 3 IV infusions, administered 3 days apart, of either ANK-700 or PBO.

Study Duration per Patient

The maximum duration of study participation for patients in Part A is approximately 210 days, which includes a screening period of up to 28 days, followed by a single dose of ANK-700 on D1, and clinic visits on D4, D15, D29, and at 3 and 6 months.

The maximum duration of study participation for patients in Part B is approximately 393 days, which includes a screening period of up to 28 days, followed by 3 doses of ANK-700 or PBO on D1, D4, and D7, and clinic visits on D22, D43, and at 3, 6, and 12 months.

Assessment of Safety

Safety will be assessed through the monitoring of AEs, clinical laboratory, vital signs, and physical examination findings, and disease relapse through EDSS and MRI evaluations.

Patients will be monitored continuously for AEs from the signing of the ICF until the final follow-up visit. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 5.0 or higher.

In relation to patient safety during the COVID-19 pandemic, current national laws and local recommendations should be strictly adhered to during the study.

Patient safety will be evaluated during Part A (SAD) and Part B (MAD) to determine dose escalation. The dose-escalation safety monitoring period in Part A is from the single IV administration of ANK-700 through the D15 clinic visit. The dose-escalation safety monitoring period in Part B is from the first IV administration of ANK-700 through the D22 clinic visit. In both parts, patients will be monitored in the clinic for AEs for 24 hours after completion of the first IV infusion. In Part B, patients will be monitored in the clinic for AEs for 4 hours after completion of the second and third IV infusion. Any DLT experienced during

the dose-escalation safety monitoring period will result in a pause in the study and review of all the available safety data by the SMC before treating additional patients and/or continuing dose escalation.

Primary Endpoint

- Incidence and severity of treatment-emergent AEs as assessed by the NCI-CTCAE v5.0 or higher

Secondary Endpoint

- Plasma concentrations and PK parameters of ANK-700

[redacted]

Pharmacokinetics

PK samples will be collected during both Part A and Part B to understand the PK profile of escalating doses of ANK-700 in humans. PK parameters and concentration data will be summarized for Part A and Part B and will be combined for doses with more than 2 patients in each dose group.

In Part A and Part B, samples for PK assessment will be collected according to the schedules outlined in Table 1 and Table 2.

Statistical Methods

Statistical methods will be descriptive. No hypothesis will be formally tested. For Part A and Part B, summary statistics will be provided by cohort. For Part B only, placebo-treated patient data will be pooled. Categorical variables will be summarized using numbers and percentages. Continuous variables will be summarized by total number (n), mean, standard deviation, median, and range (minimum and maximum).

For the first dose, Part A and Part B will be pooled and summarized for demographic and PK analysis. A formal statistical analysis plan will be developed and finalized before study database lock.

Table 1: Schedule of Assessments Part A (SAD)

Assessment[a]	Screening	Study Period						Early Term.[b]
Study Day	**-28 to 0**	**1[c]**	**4±1**	**15**	**29±1**	**90±7**	**182±7**	
Screening Assessments								
Informed consent	X							
Medical history/demographics	X							
Disease history	X							
Inclusion/exclusion	X							
ECG	X							
HIV, HBV, HCV testing	X							
Clinical Procedures								
Physical examination[d]	X[e]							X
Pregnancy test	X[f]	X[f,g]						
Vital signs[h]	X	X[g]		X				X
Concomitant medications and procedures	X	X	X	X	X	X	X	X
EDSS[i]	X	X[g]		X		X	X	
Safety Assessments								
Adverse events	X	X	X	X	X	X	X	X
Laboratory tests (safety)	X	X[g]	X	X				X
MRI[i]	X[j]			X[k]				
Study Drug Administration								
ANK-700 administration		X[m]						
Additional Blood Samples								
PK blood sample		X[l]	X					
ADA samples		X[g]			X			X
[redacted]		[redacted]						
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	

[a] All patients should be contacted by site staff 1 day prior to each study visit for assessment of COVID-19 signs and symptoms.

[b] Early termination visit only if patient discontinues within 28 days of dosing.

[c] On D1 patients will be observed in the clinic/hospital unit for 8h after completion of IV infusion and followed up with by phone following discharge 24 hours after dosing.

[d] Additional PEs will also be conducted as clinically indicated.

[e] Includes weight at screening only.

[f] Pregnancy test at screening must be serum; serum or urine tests are acceptable on Day 1 (D1) prior to dosing. Screening and D1 pregnancy test must be negative before ANK-700 is administered. Additional pregnancy monitoring per local guidelines may be implemented.

[g] Samples/measurements to be taken pre-dose.

[h] Vital signs include pulse rate, temperature, and diastolic and systolic blood pressure.

[i] In the event of a suspected disease relapse, an unscheduled MRI and EDSS assessment may be performed if deemed clinically necessary.

[j] The screening MRI must be performed ≥ 10 days prior to dosing on D1. For re-screening, the MRI only needs to be repeated if the previous assessment has been completed >3 months of scheduled dosing or if a relapse has occurred since last assessment.

[k] The MRI at D15 may be performed up to 3 days before the D15 Visit.

[l] One PK sample will be taken pre-dose (≥at least 5 min prior to infusion), with all subsequent PK samples taken after the end-of-infusion (EOI) at the following time points: EOI 0 (+2) min, EOI 7 (±2) min, EOI 15 (±2) min, EOI 30 (±5) min, EOI 1 h (±5 min), EOI 2 h (±5 min), EOI 3 h (±5 min), EOI 4 h (±5 min), EOI 6 h (±5 min), and EOI 8 h (±5 min). PK samples to be taken from the arm that did not receive the infusion. The exact date and time of each sample collection must be recorded for all collected samples.

[m] The prepared saline bag and infusion line should be weighed before and after administration. These weights should be recorded using any available scale with a precision to at least one tenth of a gram (0.1 grams). Both weight measurements should be conducted using the same scale to reduce variability.

Abbreviations: ADA = anti-drug antibodies; D=day; Early Term = early termination; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; [redacted]t; h= hours; EOI = end of infusion; HBV = hepatitis B virus; HCV = hepatitis C virus; [redacted]; min = minute; MRI = magnetic resonance imaging; [redacted]; PE = physical examination; PK = pharmacokinetics; SAD = single ascending dose.

Table 2: Schedule of Assessments Part B (MAD) COHORT 4 ONLY

Assessments[a]	Screening	Treatment Period			Study Period					Early Term.[b]
Study Day	**-28 to 0**	**1[c]**	**4**	**7**	**22**	**43±2**	**90±7**	**182±7**	**365±14**	
Screening Assessments										
Informed consent	X									
Medical history/demographics	X									
Disease history	X									
Inclusion/exclusion	X									
ECG	X									
HIV, HBV, HCV testing	X									
Clinical Procedures										
Physical examination[d]	X[e]									X
Pregnancy test	X[f]	X[f,g]	X[f,g]	X[f,g]						
Vital signs[h]	X	X[g]			X					
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X
EDSS[i]	X	X[g]			X		X	X	X	
Safety Assessments										
Adverse events		X	X	X	X	X	X	X	X	X
Laboratory tests (safety)	X	X[g]	X[g]	X[g]	X					X
MRI[i]	X[j]				X[k]		X[l]			
Study Drug Administration										
Randomization		X								
ANK-700 or PBO administration		X[m,q]	X[n,q]	X[o,q]						
Additional Blood Samples										
PK blood sample		X[o]	X[g]	X[p]	X					
ADA samples		X[g]			X		X	X	X	X
[redacted]		[redacted]								
[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

[a] All patients should be contacted by site staff 1 day before each study visit for assessment of COVID-19 signs and symptoms.

[b] Early termination visit only if patient discontinues within 28 days of dosing.

[c] On D1 patients will be observed in the clinic/hospital unit for 8h after completion of IV infusion and followed up with by phone following discharge 24 hours after dosing.

[d] Pes will also be conducted on study as clinically indicated.

[e] Includes weight at screening only.

[f] Pregnancy test at screening must be serum; serum or urine tests are acceptable on D1, D4, and D7 prior to dosing. Screening and dosing day pregnancy tests must be negative before study drug is administered. Additional pregnancy monitoring per local guidelines may be implemented.

[g] Samples/measurements taken pre-dose.

[h] Vital signs include pulse rate, temperature, and diastolic and systolic blood pressure.

[i] In the event of a suspected disease relapse, an unscheduled MRI and EDSS assessment may be performed if deemed clinically necessary.

[j] The screening MRI must be performed ≥ 10 days prior to dosing on D1. For re-screening, the MRI only needs to be repeated if the previous assessment has been completed >3 months of scheduled dosing or if a relapse has occurred since last assessment

[k] The MRI at D22 may be performed up to 3 days before the D22 visit.

[l] The MRI at D90 may be performed within 2 weeks of the scheduled D90 visit.

[m] On D1, patients will be observed in the clinic for 8 h after completion of IV infusion.

[n] On D4 and D7, patients will be observed for 4 h after completion of IV infusion.

[o] On D1, 1 PK sample will be taken pre-dose (≥ 5 min prior to infusion), with all subsequent PK samples taken after the end of infusion (EOI) at the following time points: EOI 0 (+2) min, EOI 7 (±2) min, EOI 15 (±2) min, EOI 30 (±5) min, EOI 1 h (±5 min), EOI 2 h (±5 min), EOI 3 h (±5 min), EOI 4 h (±5 min), EOI 6 h (±5 min) and EOI 8 h (±5 min). PK samples to be taken from the arm that did not receive the infusion. The exact date and time of each sample collection must be recorded for all collected samples.

[p] On D7, PK samples to be taken at pre-dose (≥ 5 min prior to infusion), and the following time points after the end of infusion (EOI): EOI 0 (+ 2) min, EOI 7 (± 2) min, EOI 15 (± 2) min, EOI 30 (± 5) min, EOI 1 h (± 5 min), EOI 2 h (± 5 min), EOI 3 h (± 5 min), and EOI 4 h (± 5 min). PK samples to be taken from the arm that did not receive the infusion. The exact date and time of each sample collection must be recorded for all collected samples.

[q] The prepared saline bag and infusion line should be weighed before and after administration. These weights should be recorded using any available scale with a precision to at least one tenth of a gram (0.1 grams). Both weight measurements should be conducted using the same scale to reduce variability.

Abbreviations: ADA = anti-drug antibodies; D = day; Early Term = early termination; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; [redacted]; EOI = end of infusion; h = hours; HBV = hepatitis B virus; HCV = hepatitis C virus; [redacted] IV = intravenous; MAD = multiple ascending dose; min = minutes; MRI = magnetic resonance imaging; PBO = placebo; PD = pharmacodynamics; PK = pharmacokinetics; [redacted]

Table 3: Schedule of Assessments Part B (MAD) COHORT 5 ONLY

Assessments[a]	Screening	Treatment Period			Study Period					Early Term.[b]
Study Day	**-28 to 0**	**1[c]**	**4**	**7**	**22**	**43±2**	**90±7**	**182±7**	**365±14**	
Screening Assessments										
Informed consent	X									
Medical history/demographics	X									
Disease history	X									
Inclusion/exclusion	X									
ECG	X									
HIV, HBV, HCV testing	X									
Clinical Procedures										
Physical examination[d]	X[e]									X
Pregnancy test	X[f]	X[f,g]	X[f,g]	X[f,g]						
Vital signs[h]	X	X[g]			X					
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X
EDSS[i]	X	X[g]			X		X	X	X	
Safety Assessments										
Adverse events		X	X	X	X	X	X	X	X	X
Laboratory tests (safety)	X	X[g]	X[g]	X[g]	X					X
MRI[i]	X[j]				X[k]		X[l]			
Study Drug Administration										
Randomization		X								
ANK-700 or PBO administration		X[m,r]	X[n,r]	X[o,r]						
Additional Blood Samples										
PK blood sample		X[o]	X[g]	X[p]	X					
ADA samples		X[g]			X		X	X	X	X
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										
[redacted]										

[a] All patients should be contacted by site staff 1 day before each study visit for assessment of COVID-19 signs and symptoms.

[b] Early termination visit only if patient discontinues within 28 days of dosing.

[c] On D1 patients will be observed in the clinic/hospital unit for 8h after completion of IV infusion and followed up with by phone following discharge 24 hours after dosing.

[d] PEs will also be conducted on study as clinically indicated.

[e] Includes weight at screening only.

[f] Pregnancy test at screening must be serum; serum or urine tests are acceptable on D1, D4, and D7 prior to dosing. Screening and dosing day pregnancy tests must be negative before study drug is administered. Additional pregnancy monitoring per local guidelines may be implemented.

[g] Samples/measurements taken pre-dose.

[h] Vital signs include pulse rate, temperature, and diastolic and systolic blood pressure.

[i] In the event of a suspected disease relapse, an unscheduled MRI and EDSS assessment may be performed if deemed clinically necessary.

[j] The screening MRI must be performed ≥ 10 days prior to dosing on D1. For re-screening, the MRI only needs to be repeated if the previous assessment has been completed >3 months of scheduled dosing or if a relapse has occurred since last assessment

[k] The MRI at D22 may be performed up to 3 days before the D22 visit.

[l] The MRI at D90 may be performed within 2 weeks of the scheduled D90 visit.

[m] On D1, patients will be observed in the clinic for 8 h after completion of IV infusion.

[n] On D4 and D7, patients will be observed for 4 h after completion of IV infusion.

[o] On D1, 1 PK sample will be taken pre-dose (≥ 5 min prior to infusion), with all subsequent PK samples taken after the end of infusion (EOI) at the following time points: EOI 0 (+2) min, EOI 7 (±2) min, EOI 15 (±2) min, EOI 30 (±5) min, EOI 1 h (±5 min), EOI 2 h (±5 min), EOI 3 h (±5 min), EOI 4 h (±5 min), EOI 6 h (±5 min) and EOI 8 h (±5 min). PK samples to be taken from the arm that did not receive the infusion. The exact date and time of each sample collection must be recorded for all collected samples.

[p] On D7, PK samples to be taken at pre-dose (≥ 5 min prior to infusion), and the following time points after the end of infusion (EOI): EOI 0 (+ 2) min, EOI 7 (± 2) min, EOI 15 (± 2) min, EOI 30 (± 5) min, EOI 1 h (± 5 min), EOI 2 h (± 5 min), EOI 3 h (± 5 min), and EOI 4 h (± 5 min). PK samples to be taken from the arm that did not receive the infusion. The exact date and time of each sample collection must be recorded for all collected samples.

[redacted]

[r] The prepared saline bag and infusion line should be weighed before and after administration. These weights should be recorded using any available scale with a precision to at least one tenth of a gram (0.1 grams). Both weight measurements should be conducted using the same scale to reduce variability.

Abbreviations: ADA = anti-drug antibodies; D = day; Early Term = early termination; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; [redacted]; EOI = end of infusion; h = hours; HBV = hepatitis B virus; HCV = hepatitis C virus; [redacted] IV = intravenous; MAD = multiple ascending dose; min = minutes; MRI = magnetic resonance imaging; PBO = placebo; PD = pharmacodynamics; PK = pharmacokinetics; [redacted].

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 4: List of Abbreviations and Definitions of Terms

Acronym / Abbreviation	Definition
ADA	Anti-drug antibodies
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CIS	Clinically isolated syndrome
CNS	Central nervous system
COVID-19	Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CS	Clinically significant
D	Study day
DLT	Dose-limiting toxicity
DMT	Disease modifying therapy
ECG	Electrocardiogram
eCRF	Electronic case report form
EDSS	Expanded disability status scale
[redacted]	[redacted]
FDA	Food and Drug Administration
FIH	First in human
GCP	Good clinical practice
GLP	Good laboratory practice
HBV	Hepatitis B
HCV	Hepatitis C
[redacted]	[redacted]
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
[redacted]	[redacted]
IRB	Institutional review board

Acronym / Abbreviation	Definition
IRR	Infusion-related reaction
IRT	Interactive response technology
IV	Intravenous
LEC	Local ethics committee
mAb	Monoclonal antibody
MAD	Multiple ascending dose
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute common terminology criteria for adverse events
NOAEL	No observed adverse effect level
NTD	Non-tolerated dose
[redacted]	[redacted]
PBO	Placebo
PD	Pharmacodynamic(s)
PE	Physical examination
PK	Pharmacokinetics
PI	Principal investigator
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMC	Study Monitoring Committee
SPMS	Secondary progressive multiple sclerosis
StD	Standard deviation
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WCBP	Women of childbearing potential

1. BACKGROUND

1.1. MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic and often disabling autoimmune disease of the central nervous system (CNS) characterized by loss of motor, sensory, cognitive, and autonomic function. The prevalence has increased noticeably, with a recent study determining the prevalence in the United States to be 309 per 100,000, and more commonly occurring (2.8 times higher) in women than men (Wallin 2019). The prevalence of MS varies with geography and ethnicity, with northern Europeans having the highest prevalence (Leray 2016). MS is associated with the human leukocyte antigen (HLA) DRB1*15:01 allele, and patients with a homozygous genotype have an increased risk, both for susceptibility of inheriting the disease and in the severity of their disease (Barcellos 2003).

The course and disease progression vary depending on the type of MS. Relapsing forms of MS, including relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS), typically evolve over time, displaying early signs of inflammation and neurodegeneration, but progress to non-relapsing disability. Primary progressive MS (PPMS) lacks the initial relapsing-remitting course and typically results in earlier disability compared to relapsing MS. Clinically isolated syndrome (CIS) is classified as the first episode exhibiting 1 or more neurological symptoms for ≥ 24 hours. If the diagnosis of MS is subsequently confirmed, CIS represents the first relapse. Diagnosis of MS is typically made after a symptomatic attack using magnetic resonance imaging (MRI) and the McDonald criteria (Thompson 2018).

The characteristic pathology of MS includes perivenular inflammatory lesions, which produce demyelination and axonal damage (Frohman 2006). The inflammation is autoimmune, involving T cells reactive to myelin self-antigens (Allegretta 1990, Bronge 2019, Zhang 1994). During the RRMS phase of the disease, the peripheral immune response against myelin is thought to drive the disease process (Hemmer 2015).

1.2. ANK-700

ANK-700 is a synthetic [redacted] composed of a CNS-derived synthetic peptide, ANK-07, [redacted] to enable liver-specific distribution and immune tolerance induction. The mechanism of action of ANK-700 harnesses natural tolerogenic pathways in the liver to re-educate pathogenic immune cells to become tolerant towards MS antigens. ANK-700 specifically targets the immune cells that drive MS and leaves the otherwise healthy components of the immune system intact to perform their natural, protective functions. Surrogates of ANK-700 have demonstrated efficacy in mouse models of MS. The mechanism by which ANK-700 induces immunologic tolerance is mediated by 3 mechanisms:

- Deletion of antigen-specific T cells
- Induction of anergy/clonal exhaustion of antigen-specific T cells
- Induction of regulatory T cells which control the antigen-specific T-cell response

Previous clinical research exploring the use of altered peptide ligands, derived from myelin peptides, to induce immunological tolerance in MS patients have observed an exacerbation of disease and/or an increase in inflammatory lesions (Bielekova 2000). However, subsequent studies using different peptide sequences and technologies to induce antigen-specific T-cell tolerance to myelin antigens have not shown these effects (Chataway 2018, Zubizarreta 2019).

Treatment for RRMS depends upon patient characteristics and comorbidities, the severity and activity of disease, and the safety profile of available therapies (Montalban 2018). Many current therapies suppress or modulate the immune system, but without the ability to target specific antigens. Many of the approved therapies for RRMS require vigilant monitoring against toxicities, including serious infections. There remains an unmet medical need for effective, targeted, well-tolerated therapies to treat RRMS.

For more information on the nonclinical findings, please see the ANK-700 Investigator's Brochure.

This first-in-human (FIH) study will be conducted in patients with RRMS with the aim of evaluating the tolerability of single and multiple intravenous (IV) administrations of ANK-700.

1.3. SELECTION OF PATIENT POPULATIONS

An RRMS patient population has been selected for the FIH study of ANK-700. T cells that react to myelin antigens have been observed in healthy subjects (Hellings 2001). Considering the potential risk that treatment with antigen-specific tolerizing agents in healthy subjects may provoke symptoms consistent with MS, an RRMS patient population is considered appropriate for this FIH study.

The study population includes adults with RRMS based on revised McDonald criteria (2017) with an Expanded Disability Status Scale (EDSS) score ≤ 6.5. Patients must be neurologically stable with no evidence of relapse within the 28 days before signing the informed consent form. These criteria have been implemented to evaluate the safety and tolerability of ANK-700 in a diverse RRMS population which has an appropriate risk/benefit profile based upon the severity of their disease. Efficacy is not being assessed in this study and enrolled patients are not expected to receive direct clinical benefit from treatment with ANK-700. The population selected for this study (i.e., those with relatively well controlled and neurologically stable RRMS) is appropriate for the FIH study, as highly active disease may obscure the assessment of safety and tolerability of ANK-700 and may require active management during the study period.

Patients who experience a relapse during screening may be rescreened after 28 days. Patients who have renal or hepatic impairment will be excluded. The age range will be limited to patients 18 to 60 years to avoid confounding by the possible neurological conditions prevalent in older individuals.

Patients will be allowed to remain on stable doses of fumarates (dimethyl fumarate or diroximel fumarate) during the study because fumarate drugs do not interfere with the mechanism of action of ANK-700. Because both dimethyl fumarate and diroximel fumarate are metabolized to the

same active metabolite, either drug will be allowed during the study. Patients using any other disease modifying therapies (DMT) to treat MS will be excluded.

1.4. DETERMINATION OF DOSES AND REGIMEN

The planned doses of ANK-700 in this FIH study allow for a robust characterization of the safety and pharmacokinetics (PK) profile of ANK-700 encompassing pharmacologically active doses identified in nonclinical models of MS. The cumulative toxicology, safety pharmacology, and PK data acquired from animal studies support dosing of ANK-700 in humans. A 4-week repeat-dose Good Laboratory Practice (GLP) toxicity study examining doses up to 87.5 mg/kg in naïve Sprague Dawley rats demonstrated no significant findings at any dose of ANK-700 examined. The no-observed-adverse-effect-level (NOAEL) was established as 87.5 mg/kg (the highest dose tested) from the GLP study, which supports a starting dose of 0.3 mg/kg in the FIH study, a dose that is more than 40-fold lower than the NOAEL.

In nonclinical mouse models of MS, administration of surrogate molecules of ANK-700 were effective at ameliorating disease. From these nonclinical models, it was concluded:

- Doses of surrogate molecules equivalent to 0.3 to 7.2 mg/kg of ANK-700 have demonstrated efficacy on disease severity in nonclinical models of MS.
- Three doses of surrogate molecules administered every 3 days was significantly more effective in inducing tolerance and improving disease outcome compared with 3 doses administered weekly.

The starting dose of 0.3 mg/kg was chosen based on the pharmacologically active doses observed in nonclinical models of disease and is supported by the NOAEL. For additional information on the dose selection and safety margins, please see the Investigator's Brochure.

In Part A (single ascending dose [SAD]), 3 escalating dose groups are planned: 0.3 mg/kg (Cohort 1), 1.0 mg/kg (Cohort 2), and 3.0 mg/kg (Cohort 3). The dosing schedule requires that successively higher doses will only be administered after the safety, tolerability, and available PK data of the preceding dose group have been evaluated by the Safety Monitoring Committee (SMC) and dose escalation is approved by the Sponsor. If necessary, doses may be adjusted based on the PK and safety findings of the preceding dose group(s) with a protocol amendment.

For Part B (multiple ascending dose [MAD]), Cohort 4 will be initiated only after SMC review of the SAD Cohort 2, recommendation by SMC, and approval by the Sponsor. Part B will examine multiple doses (3) of ANK-700 and includes 2 escalating dose cohorts: 0.3 mg/kg (Cohort 4) and 1.0 mg/kg (Cohort 5). During Part B, ANK-700 will be administered every 3 days for a total of 3 doses. Cohort 5 will only commence after review of the safety, tolerability, and available PK data of all the SAD cohorts (Cohorts 1 to 3) and Cohort 4, recommendation by the SMC, and approval by the Sponsor.

Based on data obtained during both the SAD and MAD parts of the study, the protocol may be amended to explore additional higher dose levels and alternative dosing schedules if supported by the data, recommended by the SMC, and approved by the Sponsor.

2. OBJECTIVES

2.1. PRIMARY

- Assess the safety and tolerability of escalating doses of ANK-700 in patients with RRMS

2.2. SECONDARY

- Evaluate the PK of escalating doses of ANK-700 in patients with RRMS

2.3. [redacted]

- [redacted]
- [redacted]

3. ENDPOINTS

3.1. PRIMARY ENDPOINT

- Incidence and severity of treatment-emergent adverse events (TEAEs) as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 or higher

3.2. SECONDARY ENDPOINT

- Plasma concentrations and PK parameters of ANK-700

3.3. [redacted]

- [redacted]
- [redacted]

4. STUDY DESIGN

Study ANK-700-01 is a Phase 1, FIH study designed to evaluate the initial safety, tolerability, and activity of ANK-700 in patients with RRMS. An overview of the 2 parts and proposed dose cohorts is presented in Figure 1.

4.1. PART A – SINGLE ASCENDING DOSE

The SAD phase will include up to 3 cohorts with 3 patients each. Patients within each dose cohort will receive 1 dose of ANK-700 IV and will be monitored for up to 6 months. All patients in Part A will be dosed ≥ 14 days apart to monitor for acute and subacute reactions; this length of time is supported by nonclinical exposure data that suggest ANK-700 will have cleared > 5 half-lives and nonclinical animal model data demonstrating that the tolerance induction mechanism can develop and immunologically active peptide is cleared within 1 week from dosing (see Section 4.7 for more information).

Patients will arrive at the clinic on the morning of dosing (Day 1 [D1]) and will be monitored in-clinic for 8 hours after completion of ANK-700 infusion for assessment of acute safety and PK blood sample collection. A follow up phone call 24 hours after dosing must be performed to ensure the patient did not experience any acute safety events after discharge.

- If patients are experiencing active AE(s) which require clinical monitoring at the end of the clinic/hospital unit monitoring period, they should not be discharged and followed up per PI assessment
- If feasible, patients should be advised to have someone stay with them after discharge until 24 hours have elapsed after study drug administration on D1.
- If patients do not live within 1-hour travel time of an emergency medical facility, they should remain in the clinic/hospital unit for the first 24 hours after study drug administration.
- Patients should be instructed not to drive themselves to seek emergency medical treatment at any time during the study.

Doses evaluated in Part A include 0.3 mg/kg (Cohort 1), 1.0 mg/kg (Cohort 2), and 3.0 mg/kg (Cohort 3). After all patients within a given dose cohort have been followed for ≥ 14 days post-dose, a safety review will be performed by the SMC to review all adverse events (AEs) and available clinical laboratory and PK data. Initiation of the next dose level will commence upon recommendation by the SMC and approval by the Sponsor.

Part A will employ a 3+3 design to evaluate single ascending doses of ANK-700. At any dose level, if none of the first 3 patients dosed experience a dose-limiting toxicity (DLT) within the dose-escalation safety monitoring period (D1 to D15), then escalation to the next dose level may proceed if recommended by the SMC and approved by the Sponsor. If 1 of the first 3 patients in the cohort experiences a DLT within the dose-escalation safety monitoring period (D1 to D15), the dose level may expand to a maximum of 6 patients. If no DLT occurs among the 3 additional

patients enrolled at that dose level, then escalation to the next dose level may proceed if recommended by the SMC and approved by the Sponsor.

For all patients in Part A, the study will consist of a 28-day screening period, a single dose of ANK-700 administered on D1, and an 8-hour monitoring period in the clinic/hospital unit and a phone call 24 hours after dosing. Patients will return to the clinic on D4±1, D15, and D29±1. Additionally, patients will return to the clinic after 3 and 6 months for follow-up. Blood and serum samples will be collected for PK and anti-drug antibody (ADA) assessments during Part A. Patients in Part A may be replaced if they do not receive the full dose of study drug or do not complete the D15 visit, as long as the discontinuation was not due to a DLT. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for safety assessments and data collection may be employed to ensure the safety of the patients where appropriate.

Please see Table 1 for the complete schedule of assessments for Part A.

4.2. PART B – MULTIPLE ASCENDING DOSE

The first MAD cohort (Cohort 4) will be initiated after the safety review of SAD Cohort 2 (Part A), a recommendation to proceed by the SMC, and approval by the Sponsor.

Patients in the MAD part will be randomized 2:1 to either ANK-700 or PBO. Patients will be stratified based upon their use of fumarate at study entry within the interactive response technology (IRT) system. A total of 12 patients will be enrolled per dose cohort (ANK-700, n = 8; PBO, n = 4). Patients will arrive at the clinic on the morning of dosing and will be monitored in-clinic for 8 hours after completion of their first infusion for assessment of acute safety and PK blood sample collection. A follow up phone call 24 hours after dosing will be performed to ensure the patient did not experience any acute safety events after discharge.

- If patients are experiencing active AE(s) which require clinical monitoring at the end of the clinic/hospital unit monitoring period they should not be discharged and followed up per PI assessment
- If feasible, patients should be advised to have someone stay with them after discharge until 24 hours have elapsed after study drug administration on D1.
- If patients do not live within 1-hour travel time of an emergency medical facility, they should remain in the clinic/hospital unit for the first 24 hours after study drug administration.
- Patients should be instructed not to drive themselves to seek emergency medical treatment at any time during the study.

A total of 3 doses (1 dose every 3 days on D1, D4, and D7) will be administered in Part B, a regimen that was effective in animal models of MS. Patients will return to the clinic on D22, D43±2, and at 3, 6, and 12 months for follow-up.

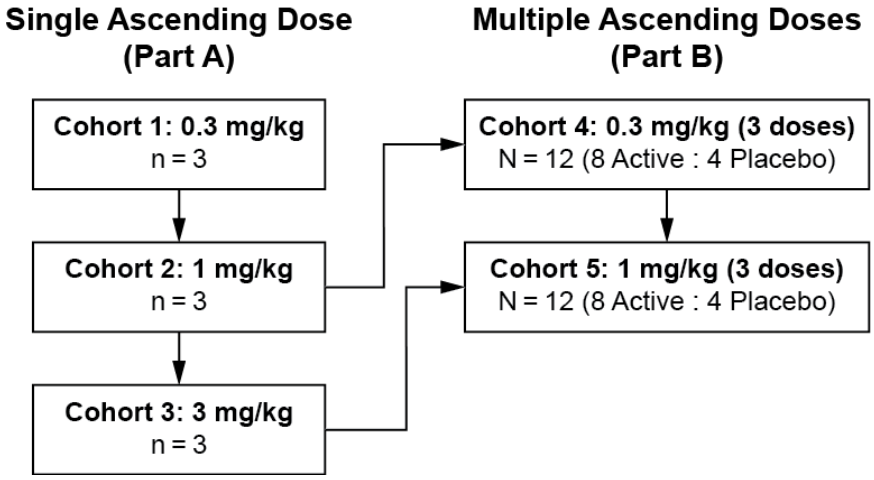
Doses planned for evaluation in Part B include 0.3 mg/kg (Cohort 4) and 1.0 mg/kg (Cohort 5). Both Part B cohorts will employ sentinel dosing to monitor for the acute and subacute safety of multiple doses of ANK-700. In this design, the first 2 patients in each cohort (1 ANK-700 and 1 PBO) will complete all 3 doses and complete an additional 14 days of safety monitoring (through D21) before initiating dosing for any subsequent patients. Based upon the expected short half-life (< 7 minutes) of ANK-700, no accumulation is anticipated with multiple doses administered 3 days apart.

After all patients within the first MAD cohort (Cohort 4) have been followed for 21 days, a safety review will be performed by the SMC to review all AEs and available laboratory test and PK data from Cohort 4 and all SAD cohorts. Initiation of Cohort 5 will only commence after review of the safety, tolerability, and available PK data of all the SAD cohorts (Cohorts 1 to 3) and Cohort 4 through D22, recommendation by the SMC, and approval by the Sponsor.

For all patients in Part B, the study will consist of a screening period of up to 28 days, followed by 3 doses of ANK-700, 1 dose administered on D1, D4, and D7. The first dose on D1 will be followed by a 8-hour monitoring period in the clinic/hospital unit; each additional dose will be followed by a 4-hour monitoring period in the clinic/hospital unit. Blood and serum samples will be collected for PK and ADA assessments during Part B of the study. Patients in Part B may be replaced if they do not receive the full 3 doses of study drug or do not complete the D22 visit, as long as the discontinuation was not due to a DLT. In the event that patients are unable to return to the clinic for protocol-specified visits, alternative methods for safety assessments and data collection may be employed to ensure the safety of the patients where appropriate.

Please see Table 2 for the complete schedule of assessments for Part B.

Figure 1: Overview of Study ANK-700-01



Single Ascending Dose (SAD) (Part A): 3 patients will be dosed IV with ANK-700 in each cohort. Initiation of the next dose cohort will commence once all patients in a cohort reach D15 and upon acceptable safety review and recommendation by SMC and approval by the Sponsor.

Multiple Ascending Dose (MAD) (Part B): the first MAD cohort (Cohort 4) will be initiated only after acceptable safety review of SAD Cohort 2, recommendation by the SMC, and approval by the Sponsor. Patients are randomized 2:1 to ANK-700 or PBO. Initiation of Cohort 5 will commence once all patients in Cohort 4 reach D22 and upon acceptable safety review of Cohorts 1 to 4, recommendation by the SMC, and approval by the Sponsor.

Abbreviations: D = day; IV = intravenously; MAD = multiple ascending dose; PBO = placebo; SAD = single ascending dose; SMC = Safety Monitoring Committee.

4.3. DOSING FREQUENCY

In Part A, patients will receive a single IV infusion of ANK-700 on D1.

In Part B, patients will receive a total of 3 IV infusions of either ANK-700 or PBO (double-blind). A single IV infusion will be administered on D1, D4, and D7.

4.4. BLINDING

Part A is open-label.

Part B is double-blinded, such that study personnel (e.g., investigators, site coordinators) and patients are blinded to treatment assignments and will remain blinded throughout the study.

Unblinded personnel include those involved in drug preparation and allocation (e.g., data systems support and pharmacists) and those involved in SMC data preparation, including the study pharmacokineticist, to allow for expedited review of PK data before SMC review.

The data reviewed for dose escalation in Part B will be presented and reviewed by the SMC in a blinded fashion.

[redacted]

If a medical emergency occurs, the site may be unblinded if knowledge of the study treatment is necessary to provide appropriate urgent medical care.

4.5. MONITORING OF ADVERSE EVENTS

Patients will be monitored continuously for AEs while on study. AE severity will be assessed using the NCI-CTCAE v5.0 or higher (Appendix 1).

4.6. DOSE-LIMITING TOXICITIES

Dose-limiting toxicities for Study ANK-700-01 include any Grade 2 AE not resolving within 14 days or any ≥ Grade 3 AE occurring during the dose-escalation safety monitoring period (D1 to D15 in Part A; D1 to D22 in Part B). DLTs do not include those AEs attributable solely to intercurrent illness or other concomitant medications. Any DLT experienced during the dose-escalation safety monitoring period will result in study pause and review by the SMC.

Any ≥ Grade 4 AE will result in notification to the Food and Drug Administration (FDA) in parallel with the SMC; all study dosing and enrollment will be paused pending review by FDA.

4.7. DOSE ESCALATION SAFETY MONITORING PERIOD

In Part A, the dose-escalation safety monitoring period is from the beginning of the IV administration of ANK-700 through the D15 clinic visit. Any AEs that meet the criteria defined in Section 4.6 but occur after the dose-escalation safety monitoring period of Part A, may be considered by the SMC in the evaluation for Part B dose selection.

The dose-escalation safety monitoring period in Part B is from the beginning of the first IV administration of ANK-700/PBO through the D22 clinic visit.

The monitoring period is supported by nonclinical animal data, which demonstrate:

- ANK-700 is cleared from circulation in < 7 minutes, ensuring that > 5 half-lives have elapsed during the safety monitoring period
- T-cell tolerance induction can be observed as early as 1 week after drug administration in nonclinical models, ensuring the mechanism of action will be active and robust during the safety monitoring period
- Immunologically active antigen cannot be detected in animals 7 days after GP-peptide administration, ensuring that any processed antigen will be cleared during the safety monitoring period

AEs and any abnormal clinical parameters, including laboratory findings, observed during this period will be used by the SMC to determine whether dose escalation should proceed.

No patient with a DLT will be replaced.

In both parts, patients will be monitored in the clinic for 8 hours after the completion the first IV administration of ANK-700/PBO. In Part B, patients will be monitored in the clinic for 4 hours after completion of their second and third dose.

4.8. SAFETY MONITORING COMMITTEE

This study will utilize an independent SMC that will meet regularly during dose escalation to review all accumulated and available data, including safety and PK. The SMC will be composed of 3 independent medical reviewers, including at least 1 medical expert in MS, as voting members. Non-voting members will include the study Medical Monitor, a medical representative from the Sponsor, and other relevant study and site staff as required to address study conduct. The SMC will make recommendations concerning dose escalation and/or any changes to the dosing paradigm based on review of the received data. The SMC will also make recommendations about the dose(s) selected for Part B. The final decisions related to dose escalation or the dosing paradigm will be made by the Sponsor.

4.9. INDIVIDUAL AND COHORT STOPPING RULES

During the dose-escalation safety monitoring period, any DLT will result in a pause in enrollment and a thorough review by the SMC before treating any additional patients. Any ≥ Grade 4 AE will result in notification of the FDA in parallel with the SMC, and study dosing and enrollment will be paused pending review by FDA.

For Part A, if 1 of the first 3 patients experiences a DLT within the safety monitoring period (D1 to D15) in a given cohort, 3 additional patients will be enrolled and evaluated in that cohort before dose escalation can occur if recommended by the SMC and only after consultation with the FDA for any ≥ Grade 4 AE. If 2 or more patients experience a DLT at a given dose level during the dose escalation evaluation period of Part A (D1 to D15), then that dose level will be considered to have exceeded the non-tolerated dose (NTD), and no further escalation will proceed.

If a patient experiences a DLT during the dose-escalation safety monitoring period of Part B, no additional doses will be administered to that patient. If 1 patient experiences a DLT during the dose-escalation safety monitoring period of Part B, the study will be paused to determine if any dose adjustments are needed and/or if the study should dose any additional patients. For any ≥ Grade 4 AE, the study will only continue after consultation with the FDA. If 2 or more patients experience a DLT during the dose-escalation safety monitoring period of Part B (D1 to D22), then that dose level will be considered to have exceeded the NTD, and no further escalation will proceed.

The maximum tolerated dose (MTD) will be defined as the proximal dose level below the dose exceeding the NTD administered during the study. Of note, dose escalation may not identify an NTD or MTD.

4.10. TREATMENT DISCONTINUATION

Patients will be discontinued from treatment for any of the after reasons:

- An AE that requires permanent discontinuation of study treatment*
- Noncompliance with the protocol

- Investigator decision
- patient becomes pregnant
- patient death
- patient lost to follow-up
- termination of the study by the Sponsor
- voluntary withdrawal of consent by patient

**AEs leading to the discontinuation of ANK-700 will be followed until resolution, resolution to baseline, or until the event is considered stable or chronic.*

The reason for treatment discontinuation will be documented.

All patients will have a final follow-up approximately 6 months (D182 ± 7) after the single dose of ANK-700 in Part A and approximately 1 year (D365 ± 14) after the first dose in Part B unless the patient withdraws from the study prematurely (Section 4.11).

4.11. STUDY WITHDRAWAL

Patients may voluntarily withdraw from the study at any time for any reason without prejudice.

Patients will be withdrawn from the study for any of the following reasons:

- Investigator's decision
- Patient death
- Patient lost to follow-up
- Termination of the study by the Sponsor
- Voluntary withdrawal of consent by patient

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

1. Male or female adults aged 18 to 60 years inclusive at screening
2. Diagnosed with RRMS per revised McDonald criteria (2017) with an EDSS score ≤ 6.5 at screening
3. Neurologically stable with no evidence of relapse within the 28 days prior to signing the informed consent form (ICF)

   Note: Patients who experienced relapse during the screening period (i.e., after signing the ICF but before dosing) may be rescreened after 28 days
4. Either not currently receiving disease modifying MS therapy **or** currently using fumarate drugs (i.e. dimethyl fumarate, diroximel fumarate)

   Note: Patients on fumarate drugs are only eligible if they have been on a stable dose ≥ 6 months before administration of study drug
5. Patients must use a highly effective method of birth control or are sterile or postmenopausal as confirmed by study Investigator for the first 3 months (through D90) of the study
6. Patient has signed and understands the ICF

5.2. EXCLUSION CRITERIA

1. Diagnosis of PPMS or SPMS
2. Uncontrolled or significant medical conditions (including active infection, chronic hepatitis, or Neuromyelitis Optica Spectrum Disorder) which, in the opinion of the Investigator, preclude participation
3. Has any of the following laboratory parameters at screening:
   a. Hemoglobin < 10 g/dL
   b. Platelet count < 100 x 10^9/L
   c. White blood cell count outside the normal range and assessed as clinically significant by the Investigator
   d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) > 1.5 × the upper limit of normal
   e. Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 based on the Cockcroft-Gault equation during screening
4. Positive for HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV)
5. Patients treated with glatiramer acetate, parenteral steroids or adrenocorticotropic hormone, β-interferon, or plasma exchange within the 3 months prior to first dose
6. Patients treated with sphingosine-1-phospate receptor modulators such as fingolimod, ozanimod, or siponimod within 6 months prior to first dose

7. Patients treated with cytotoxic agents (including but not limited to cladribine, mitoxantrone, cyclophosphamide, azathioprine, and methotrexate), laquinimod, teriflunomide, or IV gamma globulin within 12 months prior to first dose
8. Patients treated with monoclonal antibody (mAb) therapy (including natalizumab, daclizumab, rituximab, and ocrelizumab) within 24 months prior to first dose except anti-severe acute respiratory syndrome coronavirus 2 monoclonal antibodies
9. Patients receiving any vaccination within 28 days prior to first dose
10. Patients previously treated with alemtuzumab, total lymphoid irradiation, mesenchymal stem cell or hematopoietic stem cell transplantation, or tolerance-inducing therapies for MS
11. Patients with clinical signs and symptoms consistent with suspected COVID-19 or confirmed COVID-19 infection by appropriate laboratory test within the last 4 weeks prior to screening or on admission

    Note: Patients who experienced symptoms consistent with COVID-19 or confirmed infection during the screening period (i.e., after signing the ICF but before dosing) may be rescreened after 4 weeks
12. Patients with a prior severe course of COVID-19 requiring extracorporeal membrane oxygenation or mechanical ventilation
13. Patient does not agree to limit alcohol intake to 2 drink equivalents or less per day during the study
14. Contraindication to or inability to undergo gadolinium-enhanced MRI scan
15. Use of any investigational drug or experimental procedure within previous 6 months that would interfere with the assessment of ANK-700
16. Patients who are pregnant or breastfeeding

6. STUDY PROCEDURES AND ASSESSMENTS

Time points for assessments collected throughout the study can be found in the Schedule of Assessments (Table 1 and Table 2). A brief description of each assessment can be found below.

6.1. SCREENING AND TREATMENT PROCEDURES AND ASSESSMENTS

6.1.1. Informed Consent

An ICF must be signed by prospective patients before initiating any study-specific procedures. Standard of care assessments performed prior to ICF signing may fulfill study eligibility requirements if performed within the screening period. Patients will be required to sign ICF for rescreening.

6.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5) will be reviewed for each potential patient. Eligibility will be documented in the electronic case report form (eCRF).

6.1.3. Medical History, Demographics, and Disease History

Complete medical history will be obtained, including demographics, previous therapies, and disease history. MS is considered part of medical history and should include:

- duration since MS symptom onset
- duration since MS diagnosis
- number of relapses within the last year and 3 years
- date of last relapse
- previous MS treatment(s)

6.1.4. Concomitant Medications and Procedures

At screening, concomitant medications will be recorded. Assessment of any change in concomitant medications, or procedures since the last visit will occur at all further patient visits through the final Follow-Up Visit.

6.1.5. Expanded Disability Status Scale (EDSS) Assessment

Assessment of EDSS score will be captured at the time points specified in the Schedule of Assessments (Table 1 and Table 2). The EDSS is based on a standard neurological examination, incorporating the pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, and cerebral [or mental] functional systems, and ambulation, rated and scored as functional system scores. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death) (Kurtzke 1983). The EDSS must be administered by a certified examiner. All patients with new

neurological symptoms suggestive of relapse may have an EDSS assessment performed during an unscheduled visit, if appropriate (see Section 11.1.2).

If the screening EDSS has been completed within 3 months of scheduled dosing it would not need to be repeated as long as the screen fail is not due to MS relapse. If the patient needs to re-screen due to experiencing an MS relapse during the screening period, the patient must wait at least 28 days from the relapse resolution and then a new screening EDSS should be obtained.

6.1.6. Physical Examination and Vital Signs

A full physical examination (PE) and vital signs check will be performed at the time points specified in the Schedule of Assessments (Table 1 and Table 2). PEs will also be conducted as clinically indicated.

The PE will include an assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory, abdomen, height, and weight (baseline only). Vital signs will include temperature, pulse rate, and diastolic and systolic blood pressure (sitting for 5 minutes). If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart.

Any new clinically significant (CS) abnormality from baseline should be recorded as an AE.

6.1.7. Electrocardiogram

At screening, a standard 12-lead electrocardiogram (ECG) will be obtained and interpreted by the Investigator to confirm eligibility. If the screening ECG has been completed within 3 months of scheduled dosing it would not need to be repeated

At screening, ECGs will be conducted after approximately 10 minutes of rest and obtained as outlined in Table 1 and Table 2.

6.1.8. Brain Magnetic Resonance Imaging

As outlined in Table 1 and Table 2, screening and post-dose brain MRIs will be performed. Scans will be performed by trained and certified MRI technicians. The MRI will include the acquisition of scans at each time point with and without IV administered gadolinium contrast enhancement.

The following time windows apply:

- "Screening/baseline" MRI should be performed on or after the Screening Visit, but ≥ 10 days before the D1 visit.
- The MRI obtained for the Part A D15 Visit and Part B D22 Visit should be performed up to 3 days before or on the scheduled visit day.
- MRI at Part B visit D90 should be performed within 2 weeks of the scheduled visit.

MRIs will be performed for assessment of safety only and will be reviewed locally.

If a relapse occurs at the time of a scheduled MRI, the MRI should be obtained before initiation of corticosteroid therapy or the MRI should be postponed by 1 month.

If the screening MRI has been completed within 3 months of scheduled dosing it would not need to be repeated as long as the screen fail is not due to MS relapse. If the patient needs to re-screen due to experiencing an MS relapse during the screening period, the patient must wait at least 28 days from the relapse resolution and then a new screening MRI should be obtained (and the re-screening MRI must be at least 28 days from last MRI assessment).

All patients with new neurological symptoms suggestive of MS relapse should have an MRI performed (which may include the spinal column) during an unscheduled visit, if clinically necessary, but before the initiation of steroids (see Section 11.1.2).

Additional details on MRI acquisition procedures are described the imaging acquisition guidelines.

6.1.9. Clinical Laboratory Tests

The following laboratory parameters will be measured at screening and at the time points specified in the Schedule of Assessments (Table 1 and Table 2) and will be analyzed locally by a certified laboratory:

- A serum pregnancy test during screening for all women of childbearing potential (WCBP)
- Serum or urine pregnancy testing for all WCBP before each dose
- Hematology laboratory parameters include white blood cell (WBC) count, hemoglobin, hematocrit, platelet count, and WBC differential
- Blood chemistry laboratory parameters, including blood urea nitrogen, creatinine, glucose, AST, ALT, ALP, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), amylase, lipase, albumin, magnesium, calcium, and phosphorus
- Coagulation laboratory parameters, including prothrombin time, partial thromboplastin time or activated partial thromboplastin time, and international normalized ratio
- Complete urinalysis with qualitative analysis for protein (dipstick)
- HIV, HBV (hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody), and HCV testing (screening only)

Unscheduled assessments should be performed as clinically indicated.

For any out-of-range laboratory findings during screening, repeat laboratory testing may be performed at the discretion of the Investigator. Abnormal laboratory findings at screening should be recorded as medical history only if considered CS.

Clinical laboratory assessments should be performed before ANK-700/PBO infusion when applicable.

Laboratory findings assessed by the Investigator as CS, including but not limited to, those findings resulting in a drug interruption/hold/reduction/discontinuation or medical intervention, should be repeated to verify the out-of-range findings, followed to a satisfactory clinical resolution, and reported as an AE(s) (see Section 11.1.1 for definition of an AE).

6.1.10. ANK-700 Administration

Detailed instructions on the administration of ANK-700 can be found in Section 10.

6.1.11. Pharmacokinetic Sampling

PK sample collection time points are shown in Table 1 and Table 2.

The exact date and time of each sample collection must be recorded for all collected samples.

Refer to the ANK-700-01 Laboratory Manual for details on processing, storage, and shipment of PK samples.

6.1.12. Antidrug Antibody Sampling

Blood sample collection time points are shown in Table 1 and Table 2.

The exact date and time of each sample collection must be recorded for all collected samples.

Refer to the ANK-700-01 Laboratory Manual for details on processing, storage, and shipment of ADA samples.

6.1.13. [redacted]

[redacted]

6.1.14. [redacted]

[redacted]

6.1.15. Adverse Events

All AEs should be captured on the source documentation and eCRF from the time of signing of ICF through the final Follow-Up Visit/phone call. AEs leading to treatment discontinuation and those considered at least possibly related to ANK-700 should be followed until resolution, return to baseline, or deemed chronic or stable.

All serious adverse events (SAEs) will be immediately reported to the Sponsor from the time of signing the ICF through the Follow-Up Visit/phone call or until the patient has been deemed to be a screen failure. After completion of the AE reporting period (i.e., through the final Follow-Up Visit/phone call), only SAEs attributed to ANK-700 must be reported to the Sponsor.

See Section 11.2 for a full description of the collection and reporting of AEs during this study.

6.2. SAFETY FOLLOW-UP VISIT

All patients in Part A will have a final Follow-Up Visit at D182 (±7 days), 6 months after the single administration of ANK-700.

All patients in Part B will have a final Follow-Up Visit at D365 (±14 days), approximately 1 year after the first administration of ANK-700.

Ongoing AEs considered at least possibly related to ANK-700 treatment should be followed until resolution, return to baseline, or are considered stable or chronic.

7. CONCOMITANT MEDICATIONS

7.1. PROHIBITED CONCOMITANT THERAPIES

During the first 3 months of the study period, any DMTs not listed as a permitted concomitant therapy to treat RRMS (Section 7.2) or other investigational agents are prohibited, including biologic or nonbiologic therapies. All vaccines are prohibited within 4 weeks before dosing and for 2 months after dosing. Patients should avoid taking biotin-containing dietary supplements throughout the duration of the study.

Patients previously treated with any of the following DMTs must adhere to the washout periods outlined below:

- 3-month washout
  - glatiramer acetate, parenteral steroids, or adrenocorticotropic hormone, β-interferon, plasma exchange
- 6-month washout
  - fingolimod, ozanimod, or siponimod
- 12-month washout
  - cytotoxic agents (including but not limited to cladribine, mitoxantrone, cyclophosphamide, azathioprine, and methotrexate), laquinimod, teriflunomide, or IV gamma globulin
- 24-month washout
  - mAb therapy (including natalizumab, daclizumab, rituximab, and ocrelizumab)

After patients have completed the 3-month visit (D90), they may receive alternative DMTs for their MS if judged clinically appropriate by their treating physician or the Investigator.

7.2. PERMITTED CONCOMITANT THERAPIES

Patients currently on a stable dose of fumarate (dimethyl fumarate or diroximel fumarate) for ≥ 6 months will be allowed to remain on fumarate throughout the study. The dose should remain stable during the screening period and for the first 3 months of the study unless medically necessary to alter.

Any medication considered necessary for the patient's welfare, including non-DMTs used to treat symptoms of MS (e.g., antispasmodics or antidepressants), that is not expected to interfere with the clinical evaluation of ANK-700 may be given at the discretion of the Investigator. In cases involving concomitant therapies whose predicted interference with ANK-700 is unknown to the Investigator, the Sponsor should be contacted for discussion.

Any medication (including over the counter or prescription medications, vitamins, and/or herbal supplements) that the patient receives after enrollment through the last study visit must be recorded on the eCRF.

7.3. TREATMENT FOR SYMPTOMS OF MS

Patients who experience a relapse during the treatment period may receive treatment with IV methylprednisolone or oral corticosteroids, if judged to be clinically appropriate by the Investigator. If a relapse occurs at the time of a scheduled MRI, the MRI should be obtained before initiation of corticosteroid therapy or should be postponed by 1 month.

See Section 11.1.2 for the protocol-defined criteria for an MS relapse.

8. CONTRACEPTION AND PREGNANCY

The effects of ANK-700 on conception, pregnancy, and lactation are unknown.

At screening, all patients who are not surgically sterile or postmenopausal must agree to use a medically acceptable methods of birth control as confirmed by study Investigator (e.g., use of an intrauterine device, a barrier method with spermicide, condoms, any form of hormonal contraceptives, or partner sterility) for the first 3 months of the study (through D90). Hormonal forms of birth control must have been in continuous use for ≥ 3 months prior to screening to ensure their effectiveness. Complete sexual abstinence is only acceptable when it is the usual/preferred lifestyle of the patient and has been so for ≥ 3 months before screening. Periodic abstinence, calendar timing methods of contraception, or withdrawal are NOT acceptable methods of contraception.

A serum pregnancy test will be administered during screening for all WCBP. A serum or urine pregnancy test will be administered to all WCBP before each dose of study drug and must be confirmed negative before administration of study drug.

9. OTHER RESTRICTIONS RELATED TO COVID-19

Patients will be advised to adhere to local requirements for reduction of the public severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure while ambulatory. All patients should be called 1 day prior to every visit for assessing COVID-19 signs and symptoms and asked not to attend the site if infection is suspected. In addition, patients will be asked whether they have had any contact with a person who has a confirmed infection. If applicable, patients will be referred to the local health care system. Physical distancing and person-to-person contact restrictions should be applied and explained to patients while staying at the study site, if required by local requirements. Where physical distancing is not possible, study participants will be asked to use face masks and/or gloves, if deemed appropriate by the Investigator and site staff and guided by local requirements.

10. ANK-700 MATERIALS AND MANAGEMENT

10.1. ANK-700 AND PLACEBO

[redacted] dministration of ANK-700 [redacted] will be by IV infusion over approximately 30 minutes. For Part A, patients will receive a single IV infusion of ANK-700. For Part B, patients will receive a total of 3 IV infusions, administered 3 days apart, of either ANK-700 or PBO.

Additional information is provided in the ANK-700-01 Pharmacy Manual.

10.2. DOSAGE AND ADMINISTRATION

[redacted]

Administration will be by IV infusion over approximately 30 minutes.

For Part A, patients will receive a single IV infusion of ANK-700 only (no PBO).

For Part B, patients will receive 3 IV infusions, each administered 3 days apart, of a given dose of either ANK-700 or PBO. All doses will be prepared as outlined in the ANK-700-01 Pharmacy Manual by an unblinded pharmacist.

Study treatment (ANK-700 or PBO) should be administered over approximately 30 minutes under the supervision of a physician or other medically qualified study personnel experienced in the use of IV agents and in a facility equipped to manage medical emergencies. The prepared saline bag and infusion line should be weighed before and after administration. These weights should be recorded using any available scale with a precision to at least one tenth of a gram (0.1 grams). Both weight measurements should be conducted using the same scale to reduce variability. In the event of a Grade 3 infusion-related reaction (IRR), the total infusion duration may be increased to 2 hours or 50% of the rate at which the reaction occurred (please see Section 10.5 for more information). In cases where a temporary interruption is required, the total infusion should be completed within 6 hours of saline bag preparation. See Section 10.5 for detailed guidance regarding infusion administration interruptions because of infusion reactions.

Please refer to the ANK-700-01 Pharmacy Manual for detailed administration instructions.

10.3. STORAGE

ANK-700 is supplied in vials for single use. ANK-700 is to be stored at -20°C and protected from light in a temperature-monitored, locked freezer. Additional details on storage conditions are available in the ANK-700-01 Pharmacy Manual.

10.4. POST-INFUSION MEDICATIONS

No specific post-infusion medications are required for ANK-700, but appropriate medications may be administered at the discretion of the Investigator.

10.5. INFUSION-RELATED REACTIONS

If an IRR occurs during ANK-700 administration, the following treatment recommendations are provided and may be modified per local treatment standards and guidelines as appropriate.

- Grade 1 (mild): Infusion rate modification not indicated. Administer symptomatic treatment (e.g., antihistamines, antipyretics, antiemetics) as needed. Closely monitor patient until resolution. Prophylaxis with diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg is recommended ≥ 30 minutes prior to future ANK-700 infusions.
- Grade 2 (moderate): Slow infusion to ≤ 50% of the original infusion rate and treat symptoms with appropriate medical therapy, including but not limited to antihistamines, antipyretics, and analgesics. Increase monitoring of vital signs as medically indicated until patient is deemed stable. Prophylaxis with diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg is recommended ≥ 30 minutes prior to future ANK-700 infusions.
- Grade 3 (severe): Stop infusion and institute appropriate symptom-directed therapy, including but not limited to antihistamines, antipyretics, corticosteroids, bronchodilators, and oxygen. Increase monitoring of vital signs as medically indicated until patient is deemed stable. If the reaction has not resolved within 6 hours, the remainder of the infusion will not be administered, and ANK-700 will be permanently discontinued. After the completion or termination of a restarted infusion because of an IRR, all patients must be monitored until resolution of symptoms or for 2 hours in the absence of additional symptoms. Prophylaxis with diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg is required ≥ 30 minutes before future ANK-700 infusions. The next infusion should initiate at a rate of 2 hours per dose, or 50% of the rate at which the reaction occurred. If no IRRs are observed within the first 30 minutes, the infusion rate may increase to the 1-hour-per-dose rate as outlined in Section 10.2. Permanently discontinue ANK-700 upon a second occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life-threatening): Stop infusion and immediately institute appropriate symptom directed therapy and supportive measures as necessary, including, but not limited to, corticosteroids, bronchodilators, oxygen/respiratory support, and vasopressors. Hospitalization and/or intensive care unit admission may be indicated. Permanently discontinue treatment.

10.6. DRUG ACCOUNTABILITY

The Investigator or designee is responsible for taking an inventory of each shipment of ANK-700 received and comparing it with the accompanying drug order form. All unused ANK-700 will be retained at the site. After full drug accountability and reconciliation, the Investigator will either dispose of any unused ANK-700 at the clinical study site per site procedures or return unused ANK-700 to the Sponsor or its designee. Disposition of all ANK-700 should be documented, including any ANK-700 that is lost or damaged.

10.7. ASSIGNMENT TO TREATMENT

Once a patient has met all entry criteria, he or she will be assigned a distinct patient identifier. If a patient discontinues from the study, the patient identifier will not be reused, and the patient will not be allowed to reenter the study.

In Part A, patients will be assigned to receive open-label ANK-700 at a dose level based on the next available spot in the cohort(s) currently being enrolled. Patients in Part A may be replaced if they do not receive the full dose of study drug or do not complete the D15 visit, as long as the discontinuation was not due to a DLT

In Part B, patients will be stratified based upon their use of fumarate at study entry within the IRT system. For the sentinel group, the first 2 eligible patients within each cohort will be randomized through IRT in a 1:1 ratio to receive either ANK-700 or PBO. After completion of the sentinel dosing in each cohort, the remaining 10 patients will be randomized to ensure an overall 2:1 randomization to ANK-700 and PBO. Patients in Part B may be replaced if they do not receive the full 3 doses of study drug or do not complete the D22 visit, as long as the discontinuation was not due to a DLT.

11. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

11.1. ADVERSE EVENTS

11.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug, or with study participation, whether or not consider related to study treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include worsening of a pre-existing medical condition, including MS, as well as CS changes from baseline laboratory values/conditions. Worsening of the preexisting medical condition (e.g., diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study is not considered an AE.

11.1.2. Protocol-Defined MS Relapse

Patients who present with suspected clinical relapse should be assessed by EDSS and/or MRI (with and without contrast and may include spinal cord), as appropriate. Protocol-defined MS relapse for this study is:

- Sudden episode of new symptoms or worsening existing MS symptoms that lasts for ≥ 24 hours and occurs ≥ 30 days after conclusion of previous relapse (patient must be stable or improving for the 30 days immediately preceding relapse) and for which there is no other cause such as infection or environmental triggers. Episodic spasms, sexual dysfunction, fatigue, mood change, or bladder or bowel urgency or incontinence will not suffice to establish the diagnosis of a relapse.

11.1.3. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is immediately life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (documented as medical history on the eCRF) is not considered an SAE.
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE.
- results in persistent or significant disability/incapacity

- results in congenital anomaly/birth defect
- is considered an important medical event
  - If an AE does not meet 1 of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as an SAE under the criterion of an "Important Medical Event." Examples of such medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or convulsions that do not result in inpatient hospitalization.

11.2. PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS

11.2.1. Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs and SAEs occurring in patients will be recorded in the eCRF from the time of signing the ICF through the Final Study Visit/phone call. An AE will be followed until it is resolved, has returned to baseline, or is determined to be a stable or chronic condition.

At each protocol-required visit (including safety follow-up phone call) during the study, all AEs that have occurred since the previous visit must be reviewed by the Investigator. The Investigator must determine if the AE is serious or nonserious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
  - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained
- dates of onset and resolution
- severity as defined per protocol
- assessment of relatedness to ANK-700/PBO
- action taken with each ANK-700/PBO dose because of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (e.g., for dehydration because of diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (e.g., for sepsis secondary to pneumonia, both events should be recorded).

Confirmed and suspected SARS-CoV-2 infections and/or COVID-19 cases will be recorded in the AE eCRF.

11.2.2. Relationship to ANK-700

The Investigator must assess whether the AE may be related to ANK-700 (study drug) or any protocol mandated procedure, when applicable. The relationship is defined below:

Relationship assessments that indicate the event is "Not Drug Related":

- None: The event is related to an etiology other than the study product administration (the alternative etiology must be documented in the study patient's medical record).
- Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate the event is "Drug Related":

- Possible: There is an association between the event and the administration of ANK-700, and there is a plausible mechanism for the event to be related to the study product; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of ANK-700, there is a plausible mechanism for the event to be related to ANK-700, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of ANK-700, there is a plausible mechanism for the event to be related to the ANK-700, and causes other than ANK-700 have been ruled out and/or the event re-appeared on re-exposure to ANK-700.

11.2.3. Adverse Event Severity

The Investigator will assess the Grade of the AE per the NCI-CTCAE v5.0 or higher (Appendix 1). Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 11.1.3.

11.2.4. Abnormal Laboratory Values

The Investigator is responsible for reviewing clinical laboratory tests determining whether an abnormal value represents a CS change from the patient's baseline value. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should

not be recorded as AEs. In general, an abnormal laboratory test result should be reported as an AE if the laboratory result:

- requires an adjustment or discontinuation of ank-700
- requires treatment with or adjustment to concomitant medications
- is considered to be an AE by the Investigator

11.2.5. Medication Errors, Misuse, and Abuse of ANK-700

Overdose, medication error, off-label use, misuse, abuse, and occupational exposure are defined as follows:

- Overdose: refers to the administration of a quantity of ANK-700 given per administration or cumulative that is above the maximum dose according to the protocol
- Medication error: refers to an unintentional error in dispensing or administration of ANK-700 not in accordance with the protocol
- Off-label use: relates to situations where ANK-700 is intentionally used for medical purpose not in accordance with the protocol
- Misuse: refers to situations where ANK-700 is intentionally and inappropriately not used in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of ANK-700, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to exposure to ANK-700 because of one's professional or nonprofessional occupation

Overdoses, medication errors, abuse, or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

11.2.6. Reporting of Serious Adverse Events

SAEs will be recorded on the appropriate eCRF and reported to the Sponsor within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to ANK-700, from the time of signing ICF through the final Follow-Up Visit/phone call.

The initial SAE eCRF must be as complete as possible and include details of the current illness and SAE as well as an assessment of the relationship between the event and ANK-700. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor or designee, to provide clarifications or additional information.

If the Investigator becomes aware of an SAE considered related to ANK-700 occurring more than 30 days after the last dose of ANK-700, the SAE must be reported as described above.

11.2.7. Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committee, and Institutional Review Board

The Sponsor or designee will determine expectedness of the Sponsor's product for each reported SAE based on the appropriate reference safety information per local country requirements. The Sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, per local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AE(s) submitted to the regulatory agencies, per local country requirements.

The Investigator will notify the appropriate Institutional Review Board (IRB)/Local Ethics Committees (LECs) of serious, related, and unexpected AE(s), or significant risks to patients, per local country requirements. The Investigator must keep copies of all AE information on file, including correspondence with the Sponsor or IRBs/LECs.

11.2.8. Pregnancy and In Utero Drug Exposure

ANK-700 has not been evaluated in pregnant or nursing women. Thus, pregnant women or WCBP who are not using effective contraception are excluded from this study (see Section 8 and Section 6.1.9 for instructions on birth control and pregnancy testing, respectively).

Pregnancies occurring in patients or partners of male patients are considered immediately reportable events if the pregnancy occurs during the study treatment through the Safety Follow-Up Visit (D15 in Part A; D22 in Part B) after the patient's last dose of ANK-700. If a pregnancy occurs in a patient, ANK-700 must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy by recording it on the appropriate eCRF.

The Investigator will follow the pregnancy (the patient or the patient's partner) until completion of the pregnancy and must notify the Sponsor of the pregnancy outcome within 24 hours of the Investigator's knowledge of the outcome. The Investigator will provide this information by recording it on the appropriate eCRF. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant patient/patient's pregnant partner experiences an SAE during pregnancy, or the outcome of the pregnancy meets any of the serious criteria (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to the Sponsor or designee within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor or designee. In addition, any infant death or

congenital anomaly occurring after 30 days that the Investigator suspects is related to the in utero exposure to ANK-700 should also be reported to the Sponsor or designee.

12. STATISTICAL METHODS

Details of the statistical methods for this study will be documented in a Statistical Analysis Plan (SAP). When there is a difference between the final approved SAP and the protocol, the methods described in the final SAP will prevail.

Statistical methods will be primarily descriptive in nature. No hypothesis will be formally tested. Placebo from each cohort will be pooled for analysis. Part A and Part B will be pooled together for the first dose to provide additional tables and listings for all of the patients in the study. Summary statistics will be provided for Part A, Part B, and Part A and Part B combined for disposition, demographic, and PK analysis. Additional tables will be provided for Part B with details included in the SAP. Continuous data will be summarized in terms of the total number of subjects, mean, StD, median, minimum, maximum, and number of observations, unless otherwise stated. For log transformed data, the geometric mean will be provided along with the other summary statistics. Categorical data will be presented by frequency and percent of patients.

Protocol deviations (missing assessments/visits) related to COVID-19 will be listed separately.

12.1. SAMPLE SIZE

In Part A, the number of patients enrolled into a treatment group will be based on safety and tolerability within a traditional 3+3 design. Under this model, Part A may enroll approximately 9 patients across 3 treatment groups, depending upon the toxicities observed. No formal hypothesis testing is planned for Part A.

In Part B, the total sample size of 24 patients (n=16 ANK-700; n=8 PBO) across 2 treatment groups was chosen to allow for a comparison of safety, PK, and PD between ANK-700 and PBO.

12.2. ANALYSIS SETS

The main analysis sets are defined in this section.

- **The All-Treated Analysis Set** is defined as all patients who receive any amount of ANK-700. This analysis set will be the primary analysis set for all safety endpoints.
- **The PK Analysis Set** will include all enrolled patients who receive ≥ 1 complete dose of ANK-700 and have ≥ 1 pre-dose and1 post-dose measurement. This analysis set will be used for the analysis of PK parameters as further defined in the protocol.

Additional analysis sets may be defined in the SAP.

12.3. BACKGROUND CHARACTERISTICS

12.3.1. Patient Disposition

The number and percentage of patients in each disposition category (e.g., enrolled, included in each analysis set, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized.

12.3.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by treatment group (PBO and dose group) for the All-Treated Analysis Set: sex, race, age, concomitant fumarate use, and years since MS diagnosis for Part A and Part B. Part A and Part B will be combined. Additional parameters may be provided in the SAP.

12.4. ANK-700 EXPOSURE

Exposure will be calculated for study Part A and Part B by dose level; all exposure data will be listed for both parts. The exposure variables include:

- the cumulative number of days of exposure
- the number of IV infusions completed
- the relative dose intensity

All variables are predefined:

- The relative dose intensity is defined as the percentage of the planned treatments completed. It is the ratio of the cumulative actual dose (mg) and cumulative planned dose (mg), multiplied by 100. In this definition,
  - the cumulative actual dose (mg) is the sum of the actual doses (mg) that the patient receives during the study
  - the cumulative planned dose (mg) is the cumulative number of days of exposure multiplied by the planned dose level (mg)

12.5. SAFETY ANALYSES

For Part A, all safety data will be listed. For Part B, the number and percentage of AEs and TEAEs experienced by patients will be summarized for each dose level and PBO group, accompanied by a by-patient listing of potential DLTs for both Part A and Part B.

The listing will include the description, severity, and relationship of the events to ANK-700 for each Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term and include details for relation to study drug, discontinuation because of study drug, and severity.

For Part A and Part B, safety data, including vital signs, ECGs, laboratory test results, PEs, disease relapses per MRI and EDSS evaluations, and AEs will be listed by dose and assessment time points, as appropriate.

12.6. ADVERSE EVENTS

AEs will be coded using the MedDRA v22.0 (MedDRA March 2019) or higher and will be graded according to the NCI-CTCAE v5.0 or higher (Appendix 1).

A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment to the final Follow-Up Visit/phone call after the last dose of ANK-700 or PBO.

12.7. CLINICAL LABORATORY ASSESSMENTS

Presentation of laboratory values will be performed using International System units. All statistical summaries for laboratory values, including change from baseline, will be by dose/treatment group for Part B. Part A will be listed.

Abnormal laboratory findings will be also listed by number and percentage of patients with values ≥ Grade 3 in severity.

A listing of individual patient hematology (including coagulation) and serum chemistry values outside the clinical reference ranges will be provided.

12.8. PHARMACOKINETIC ANALYSES

Blood samples will be collected for measurement of ANK-700, as specified in Table 1 and Table 2. The timing of sampling may be altered based on the emerging PK data. The adjustment of the PK sampling schedule is not considered to be a substantial amendment so long as the total number of plasma PK samples and the total blood volume to be collected from each participant will not change. Any adjusted sampling time points will be documented appropriately.

PK parameters of ANK-700 will be determined from the serum concentration-time data. Parameters will be calculated by noncompartmental modeling methods, using actual sampling times where relevant. The parameters that will be calculated are defined in Table 3 and will be calculated for single or multiple dosing of ANK-700, as appropriate. Not all listed parameters may be calculable, and additional parameters may be calculated, if needed, to fully characterize the available data. PK parameters and concentration data will be summarized for Part A and Part B and will be combined for doses with more than 2 patients in each dose group.

Table 5: Pharmacokinetic Parameter Definitions

Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time to first occurrence of maximum observed plasma concentration
C_{trough}	Pre-dose plasma concentration
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the last measurable time point
AUC_{inf}	Area under the plasma concentration-time curve extrapolated to infinity
AUC_{tau}	Area under the plasma concentration-time curve over the dosing interval
$t_{1/2}$	Terminal elimination half-life
CL	Clearance
V_z	Volume of distribution after a single dose
$R_{acc,AUC}$	Accumulation ratio based on AUC
$R_{acc,Cmax}$	Accumulation ratio based on C_{max}

Statistical evaluations of PK data will include dose proportionality assessment using C_{max}, AUC_{last}, and AUC_{inf}.

For cohort by cohort PK analysis, not all PK parameters may be calculated, and noncompartmental analysis may be done using nominal times.

Additional details on noncompartmental PK analyses for calculation of PK parameters and statistical analyses of PK parameters for dose proportionality will be provided in a PK analysis plan.

12.9. ANALYSIS OF ANTIDRUG ANTIBODIES

Blood samples for assessment of ADAs will be collected at the time points outlined in Table 1 and Table 2. The raw ADA dataset will be listed by visit and dose.

12.10. [redacted]

[redacted]

12.11. [redacted]

[redacted]

13. STUDY ADMINISTRATION

13.1. GOOD CLINICAL PRACTICE STATEMENT

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and all applicable local regulatory requirements.

13.2. INFORMED CONSENT

The Sponsor or designee will provide a sample patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/Independent Ethics Committee (IEC) requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or designee will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the patient prior to enrollment. The Investigator or designee will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. After the discussion regarding the study, a patient will be asked if he/she is willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local country requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent or if there is an amendment to the protocol that necessitates a change to the content of the patient's informed consent. The Investigator will inform the patients of changes in a timely manner and will ask the patients to confirm continuation of their participation in the study by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

13.3. PATIENT CONFIDENTIALITY

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative(s) will be identified by patient number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, and an IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include patient medical history.

The Investigator must ensure that patient anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by

their assigned patient number and study code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

13.4. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE REQUIREMENTS

The final study protocol including the final version of the ICF must be approved or given a favorable opinion in writing by an IRB/IEC at each clinical study site. The Principal Investigator (PI) must submit written approval from the IRB to the Sponsor before he or she can enroll any patient into the study.

The PI is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IRB/IEC annually or as required by the IRB, regulations, and guidelines.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

13.5. CASE REPORT FORMS AND SOURCE DOCUMENTATION

eCRFs will be provided for the recording of all data. The PI/Sub-Investigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by the Sponsor.

13.6. STUDY MONITORING

Before the first patient signs the ICF to participate in the study, the Sponsor or designee will visit or remotely assess the study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities related to the protocol and the responsibilities of the Sponsor or designee
- Confirm that the Investigator(s) (and other personnel involved with the study) have not invoked sanctions or demonstrated any scientific misconduct or fraud

During the conduct of the study, the Sponsor or designee will maintain regular contact, perform remote monitoring including data review, and visits to the clinical study site to:

- Provide information and support the Investigator
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

13.7. QUALITY ASSURANCE

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, and regulatory agencies or IRB/IECs may conduct quality assurance audits at any time during or after 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/her time and the time of the study staff to the auditors to discuss findings and issues.

Monitoring visits at site will be limited to a minimum required as deemed appropriate during the COVID-19 pandemic.

13.8. STUDY OR CLINICAL SITE TERMINATION

The Sponsor, or designee, reserves the right to terminate the study or a clinical study site at any time. Conditions that may warrant termination of the study include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- Decision on the part of the Sponsor to suspend or discontinue testing the study treatment

Conditions that may warrant termination of a study site include, but are not limited to:

- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the clinical study site to the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, the Sponsor and the Investigator(s) will assure that adequate consideration is given to the protection of the patients' interests.

13.9. DURATION OF THE STUDY, EXPECTED DURATION OF PATIENT PARTICIPATION, AND END OF STUDY

The study is planned to initiate enrollment in September 2020 with the last study visit in September 2023.

In Part A of the study, enrolled patients will receive a single IV infusion of ANK-700 on D1. The maximum duration of study participation for patients in Part A is approximately 210 days, which includes a screening period of up to 28 days, followed by a single dose of ANK-700 on D1, and clinic visits on D4, D15, D29, and at 3 and 6 months.

In Part B of the study, enrolled patients will receive 3 IV infusions of ANK-700, each on D1, D4, and D7. The maximum duration of study participation for patients in Part B is approximately 393 days, which includes a screening period of up to 28 days, followed by 3 doses of ANK-700 or PBO on D1, D4, and D7, and clinic visits on D22, D43, and at 3, 6, and 12 months.

13.10. RECORDS RETENTION

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, eCRFs, ANK-700 inventory, IRB, and Sponsor or designee correspondence pertaining to this study must be kept on file. All study documents must be kept secured for a period of 2 years after a marketing application is approved for ANK-700, or for 2 years after the last shipment and delivery of ANK-700 for investigational use on study, or as long as required by local regulations, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted before removing or relocating study records for any reason.

13.11. PUBLICATIONS

Publication by the clinical study site(s) of any data from this study must be carried out in accordance with the Clinical Site Agreement.

14. REFERENCES

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APPENDIX 1. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0 (CTCAE)

CTCAE Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA Lowest Level Term.

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

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

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Selfcare ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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APPENDIX 2. EXPANDED DISABILITY STATUS SCALE (EDSS)

Score	Description
1.0	No disability, minimal signs in 1 functional system (FS)
1.5	No disability, minimal signs in more than 1 FS
2.0	Minimal disability in 1 FS
2.5	Mild disability in 1 FS or minimal disability in 2 FS
3.0	Moderate disability in 1 FS, or mild disability in 3 or 4 FS. No impairment to walking
3.5	Moderate disability in 1 FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting
6.5	Requires 2 walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair, though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS