DOCUMENT:	Statistical Analysis Plan
PROTOCOL:	ANK-700-01
TITLE:	A Phase 1 Study of the Safety and Tolerability of Single and Multiple Doses of ANK-700 in Patients with Relapsing-Remitting Multiple Sclerosis Version 4
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Version No.	Effective Date	Summary of Change(s)
Final 1.0	[DD MMM YY]	New document

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LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATAS	All Treated Analysis Set
AUC	Area under the concentration-time curve
AUC_{inf}	AUC from time zero extrapolated to infinity
AUC_t	AUC from time zero to the last quantifiable concentration
$AUC_{\tau,ss}$	AUC over the dosing interval at steady state
$\%AUC_{ex}$	Percentage of $AUC_{0\text{-}inf}$ that is due to extrapolation beyond T_{last}
BLQ	Below the Limit of Quantification
C_{max}	Maximum observed concentration
$C_{max,ss}$	Maximum observed concentration at steady state
C_{last}	Last quantifiable concentration at t_{last}
C_{trough}	Concentration immediately prior to dosing
CI	Confidence interval
CL/F	Apparent clearance following oral administration
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
D	Study Day
DBL	Database Lock

Abbreviation / Acronym	Definition
DLT	Dose-Limiting Toxicity
DMT	Disease Modifying Therapy
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
[redacted]	[redacted]
EOS	End-of-Study
FIH	First-In-Human
HBV	Hepatitis B
HCV	Hepatitis C
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
[redacted]	[redacted]
IRB	Institutional Review Board
IRR	Infusion related Reaction
IV	Intravenous
LLQ	Lower Limit of Quantification
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic Ratio
MRT	Mean Residence Time
MRT(0-inf)	MRT extrapolated to infinity
MS	Multiple sclerosis
NA	Not Available
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation / Acronym	Definition
NCS	Not Clinically Significant
NTD	Non-tolerated dose
PBO	Placebo
[redacted]	[redacted]
PD	Pharmacodynamic
PDAS	Pharmacodynamic Analysis Set
PE	Physical exam
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PLT	Platelet
PT	Preferred Term
PTF	Peak Trough Fluctuation
Rac	Accumulation Ratio
RRMS	Relapsing-Remitting Multiple Sclerosis
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error of Mean
SMC	Safety Monitoring Committee
SOC	System Organ Class
SoA	Schedule of Assessments
$t_{½}$	Apparent terminal elimination half-life
t_{last}	Time of last quantifiable concentration
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Tables, Listings and Figures

Abbreviation / Acronym	Definition
ULQ	Upper Limit of Quantification
t_{max}	Time corresponding to occurrence of C_{max}
V_z/F	Apparent volume of distribution during terminal phase
WBC	White blood cell
WCBP	Women of child-bearing potential
WHO-DD	World Health Organization - Drug Dictionary
λ_z	Terminal elimination rate constant
$\%AUC_{ex}$	Percentage of AUC_{inf} obtained by extrapolation

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the analysis for protocol ANK-700-01. The statistical methods described herein are based on the analyses proposed in the Final Protocol V4 dated 06 June 2022 and the associated CRF (Case Report Form) dated 12Sept2022 This SAP supersedes the statistical considerations identified in the protocol. Any analyses that are substantially different will be identified in Section 10. This document is written with consideration of the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline (Guidance for Industry: Statistical Principles for Clinical Trials) and on the ICH E3 Guideline (Guidance for Industry: Structure and Content of Clinical Study Reports).

The SAP will be developed and finalized prior to database lock and unblinding of the clinical database. The analyses identified in this SAP were developed for regulatory submissions and/or future manuscripts. Additional exploratory analyses, not necessarily identified in this SAP, may be performed to support the clinical development program.

1.1 Background

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. 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.

ANK-700 is [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.

2. GENERAL STUDY DESIGN AND PLAN

2.1 Study Objectives

2.1.1 Primary

- Assess the safety and tolerability of escalating doses of ANK-700 in patients with RRMS (Relapsing Remitting Multiple Sclerosis)

2.1.2 Secondary

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

2.1.3 [redacted]

- [redacted]
- [redacted]

2.2 Study Population

The study population includes adults (18 to 60 years inclusive, at screening) 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. The population selected for this study (ie, 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.

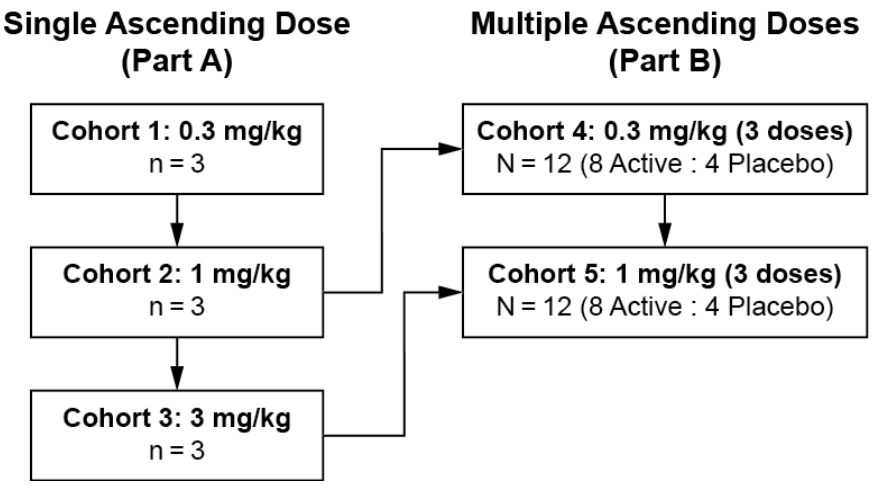
Patients receiving a stable dose of a fumarate drug (ie, dimethyl fumarate, diroximel fumarate) for ≥ 6 months will be allowed to remain on stable doses of fumarates (dimethyl fumarate or diroximel fumarate) during the study because fumarate drugs do not interfere with the mechanism of action of ANK-700. Patients using any other disease modifying therapies (DMT) to treat MS will be excluded.

2.3 Study Design

Study ANK-700-01 is a Phase 1, FIH (First in Human) study designed to evaluate the initial safety, tolerability, and activity of ANK-700 in patients with RRMS.

A graphic overview of the 2 parts (Part A: Single Ascending Dose (SAD) and Part B: Multiple Ascending Doses (MAD)) is presented below.

Figure 1: Overview 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.

2.3.1 PART A: SAD (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.

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. 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 plasma samples will be collected for PK and anti-drug antibody (ADA) assessments during Part A. 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.

2.3.2 PART B: MAD (Multiple Ascending Doses)

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 as described in Section 3.2. Patients will arrive at the clinic on the morning of dosing and will be monitored in-clinic for 24 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 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.

Initiation of Cohort 5 will only commence after review of the safety, tolerability, and laboratory test 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 study drug, 1 dose administered on D1, D4, and D7. Blood and plasma samples will be collected for PK and ADA assessments during Part B of the study. 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.

2.4 Study Drug Dosage and Administration

[redacted]. Administration of study drug in 100 mL normal saline will be by IV infusion over approximately 30 minutes.

For Part A, patients will receive a single IV infusion of ANK-700 only (i.e. no PBO). The following doses will be given:

Part A (SAD)

- ANK-700 0.3 mg/kg
- ANK-700 1 mg/kg
- ANK -700 3 mg/kg

For Part B, patients will receive 3 IV infusions; each administered 3 days apart, of a given dose of either ANK-700 or PBO. Dosing groups in Part B will be as follows:

Part B (MAD)

- PBO
- ANK -700 0.3 mg/kg
- ANK -700 1 mg/kg

3. SAMPLE SIZE, RANDOMIZATION AND BLINDING

3.1 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. If 1 of the first 3 patients in a given 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 under this model, Part A may enroll 9 to 18 patients across 3 treatment groups, depending upon the toxicities observed. No formal hypothesis testing is planned for 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 assessed to be related to study drug.

In Part B, the total sample size of 24 patients (n=8 ANK-700 0.3 mg/kg; n=8 ANK-700 1 mg/kg; n=8 PBO) was chosen to allow for a comparison of safety between ANK-700 and PBO, however no sample size calculation was performed.

In Part B, patients may be replaced if they do not complete all 3 doses and the D22 visit as long as they did not discontinue the study because of a related AE. No patient with a DLT will be replaced.

3.2 Randomization and Blinding

Once a patient has met all entry criteria, he or she will be assigned a distinct subject identifier. If a patient discontinues from the study, the subject identifier will not be reused, and the patient will not be allowed to reenter the study. Patients not eligible during the screening period, may be rescreened after 4 weeks. Patients who experience a relapse during screening may be rescreened after 28 days.

3.2.1 Part A (SAD) – Open Label

Part A is open-label. 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.

3.2.2 Part B (MAD) – Double Blind

Part B is double-blinded, such that study personnel (eg, 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 (eg, data systems support and pharmacists) and those involved in SMC data preparation, including the study pharmacokinetic scientist, to allow for expedited review of PK data before SMC review. [redacted]

The MAD part of the study includes two cohorts, Cohort 4 (ANK-700 0.3 mg/kg) and Cohort 5 (ANK-700 1 mg/kg). In each cohort, randomization is stratified based upon a patient's use of fumarate at study entry within the interactive response technology (IRT) system.

After completion of the sentinel dosing in each cohort, the remaining patients will be randomized to ensure an overall 2:1 allocation to either ANK-700 or PBO, respectively. A total of 12 patients will be enrolled per each dose cohort (ANK-700 n = 8; PBO, n = 4).

For the sentinel dosing, the following constraints will occur for the **first randomization block** only (the first block contains the first 3 patients in each stratum):

- Within a cohort/fumarate stratum, the first 2 treatments will not be the same treatment.
- Within each cohort, Fumarate yes stratum will not be the same order of treatments as the fumarate no stratum.

The below two examples for cohort 4 show what **is not permitted** to occur in the randomization of the first blocks of Cohort 4, nor Cohort 5.

Patient Order	Block	Cohort	Fumarate	Treatment

NOT PERMITTED: The order of treatments for the fumarate yes group is the same as the fumarate no group.

1	1	4	Yes	PBO
3	1	4	Yes	ANK 0.3
5	1	4	Yes	ANK 0.3
2	1	4	No	PBO
4	1	4	No	ANK 0.3
6	1	4	No	ANK 0.3

Or

Patient Order	Block	Cohort	Fumarate	Treatment
2	1	4	Yes	ANK1
3	1	4	Yes	PBO
6	1	4	Yes	ANK1
1	1	4	No	ANK 1
4	1	4	No	ANK 1
5	1	4	No	PBO

NOT PERMITTED: The first two treatments are the same.

After completion of each dose group in Part B, the data will be presented and reviewed by the SMC in a blinded fashion. If a medical emergency occurs, the site may be unblinded for that patient, if knowledge of the study treatment is necessary to provide appropriate urgent medical care.

3.3 Withdrawal Criteria

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:

- Adverse event
- Noncompliance with the protocol
- Lost to follow-up
- Physician decision
- Study terminated by sponsor
- Withdrawal by subject
- Other

Treatment may be terminated but patient may be still followed in the study for the following reasons:

- Adverse event
- Physician decision
- Pregnancy
- Death
- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- Protocol deviation
- Other

4. CLINICAL PROCEDURES AND ASSESSMENTS

The assessments collected in the study are outlined in Appendix 1 Table 1 (Part A), Table 2 (Part B, Cohort 4) and Table 3 (Part B, Cohort 5).

5. STUDY OBJECTIVES

Below is an outline of the study objectives

5.1 Primary

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

5.2 Secondary

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

5.3 [redacted]

- [redacted]
- [redacted]

6. ASSESSMENTS

6.1 Safety Assessments

The safety and tolerability of ANK-700 will be assessed by AE and other safety assessments as detailed in Appendix 1 Table 1 (Part A), Table 2 (Part B, Cohort 4) and Table 3 (Part B, Cohort 5).

6.1.1 Adverse Events (AE)

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 (eg, 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 Clinically Significant (CS) changes from baseline laboratory values/conditions. Worsening of the preexisting medical condition (eg, 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.

All AEs are collected from the time of signing of Informed Consent Form (ICF) through the final Follow-Up Visit/phone. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (MedDRA Sep 2020) or higher. 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.

6.1.2 Treatment Emergent Adverse Events (TEAE)

TEAEs are defined as AEs that emerge or worsen in the period from the first dose of study treatment to the final Follow-Up Visit/phone call after the last dose study drug.
The incidence and severity of TEAEs as assessed by the CTCAE v5.0 or higher is considered the primary endpoint.

6.1.3 Adverse Event Severity

The Investigator will assess the Grade of the AE per the NCI-CTCAE v5.0 or higher (Appendix 2). 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

6.1.4 Serious Adverse Event (SAE)

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 in patient hospitalization.

6.1.5 AE Relationship to Study Medication

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":

- Not Related
- Unlikely Related

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

- Possibly Related
- Related

6.1.6 Dose-Limiting Toxicity (DLT)

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.

6.1.7 Clinical Laboratory Endpoints

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

- A serum pregnancy test during screening for all women of child-bearing potential (WCBP)
- Serum or Urine testing for all WCBP prior to 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 (hepatitis C) testing (screening only)

6.1.8 Expanded Disability Status Scale (EDSS)

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). See Appendix 3 for score details.

6.1.9 Brain Magnetic Resonance Imaging

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. Data collected for each MRI will include number of FLAIR lesions, number of enhancing lesions, and presence of restricted diffusion. For post-baseline scans there will be an assessment of whether there was improvement or worsening from prior scans.

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.

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.

6.1.10 Other Safety Assessments (Physical Exam, Vital Signs and ECG)

The Physical exam 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 systolic and diastolic 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.

At screening, a standard 12-lead electrocardiogram (ECG) will be obtained at baseline and interpreted by the Investigator to confirm eligibility.

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

6.2 Pharmacokinetic Assessments

Blood samples will be collected for measurement of ANK-700 as specified in Appendix 1 Table 1 (Part A), Table 2 (Part B, Cohort 4) and Table 3 (Part B, Cohort 5). 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 plasma concentration-time data. Parameters will be calculated by non-compartmental modeling methods, using actual elapsed time from start of infusion based on the actual mg administered. The parameters that will be calculated are defined in the table below and will be calculated for single or multiple dosing of ANK-700, as appropriate. Not all listed parameters may be calculable for every patient, and additional parameters may be calculated, if needed, to fully characterize the available data. PK parameters and concentration data will be summarized by Part, by Dose, and by Day (Single dose Day 1, Multiple dose Day 1, Multiple dose Day 4, Multiple dose Day 7, Single and Multiple Dose Day 1 for common doses.

Table 1 Pharmacokinetic Parameters for Part A and Part B After Each Dose

Parameter	Definition	Method of Determination
C_{max}	Maximum observed plasma concentration	Obtained directly from the concentration-time data
T_{max}	Time to first occurrence of C_{max}	Obtained directly from the concentration-time data
λ_z	Terminal elimination rate constant	Terminal phase rate constant calculated by linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression. A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope) and including C_{last}, t_{last}. The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the PK Scientist's best knowledge and judgment. An appropriate number of decimal places should be used for λ_z to enable the reported value of $t_{½}$ to be calculated.
$t_{1/2}$	Terminal elimination half-life	$Log_e(2)/ \lambda_z$
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the last measurable time point	The linear-log trapezoidal method will be employed to calculate AUCs. The linear method will be used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations. $AUC_t = \int_0^t \mathbf{C(t)dt}$.
AUC_{inf}	AUC from time zero extrapolated to infinity	$AUC_{inf} = \int_0^t \mathbf{C(t)dt} + \int_t^\infty \mathbf{C(t)dt} =$ $AUC_t + C_t/\lambda_{z,}$ where C_t is last observed quantifiable concentration.
$\%AUC_{ex}$	Percentage of $AUC_{(0\text{-inf})}$ obtained by extrapolation	$(1 - [AUC_t/AUC_{inf}])\times 100$
CL	Clearance	$dose/AUC_{inf}$
V_z	Volume of distribution during terminal phase	$CL/F/\lambda_z$
R_{acc},AUC	Accumulation ratio based on AUC	
R_{acc},C_{max}	Accumulation ratio based on Cmax	
C_{trough}	Predose plasma concentration	

For cohort by cohort PK analysis, not all PK parameters may be calculated, and non-compartmental analysis may be done using nominal times from start of infusion.

6.3 Antidrug Antibody

Anti-drug antibody (ADA) sampling will be performed at the time points shown in Appendix 1 Table 1 (Part A), Table 2 (Part B, Cohort 4) and Table 3 (Part B, Cohort 5). ADA-positive or ADA-negative will be determined for each time point. If the first test comes back positive then the reactivity to the pgal and peptide will be assessed separately. Titers will be determined for ADA positive sample if the quantity is sufficient for the determination.

6.4 [redacted]

[redacted]

6.4.1 [redacted]

[redacted]

6.5 Other Assessments

Additional assessments will be collected for demographics, medical history, concomitant medication, informed consent inclusion/exclusion, study drug administration will be explained in more detail in Section 8.

7. ANALYSIS SETS

Enrolled Analysis Set is defined as all patients in Part A and Part B who were enrolled in the study and signed informed consent form.

All-Treated Analysis Set (ATAS) is defined as all patients who receive any amount of study drug. This analysis set will be the primary analysis set for all safety and exploratory endpoints.

PK Analysis Set (PKAS) will include all enrolled patients who receive ≥ 1 complete dose of study drug and have ≥ 1 pre-dose and 1 post-dose measurement. This analysis set will be used for the analysis of PK parameters as further defined in the protocol.

Patients who receive at least one full dose out of the three doses will be included in this population; if a patient misses a dose or does not complete a dose then the PK concentration data, for that observation, will be considered missing.

8. STATISTICAL METHODS

All outputs will be produced using SAS® version 9.4 or a later version.

No hypothesis will be tested.

Summary statistics will be presented for all variables of interest for the ATAS population unless otherwise specified. Categorical variables will be summarized using numbers and percentages and be presented by dose level received. Continuous variables will be summarized by total number (n), mean, standard deviation (SD), median, and range (minimum and maximum). 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 in the treatment group.

Listings will be sorted by Study Part, subject ID, Treatment, study visit, date and time, where applicable, unless otherwise specified.

Summary statistics for Part A and B will be presented in the following manner:

- For Part A, summary statistics will be provided for subject disposition with the following tables summarized:
    - Disposition
    - Analysis populations
    - Demographics
    - Protocol Deviations
    - PK analysis
    - Summary of TEAE
    - Summary of TEAE by System Organ Class and Preferred Term

- For Part B alone, summary statistics will be provided by treatment group, pooling the placebo group from each cohort for all tables.
- For Part A and B pooled, summary statistics will be provided by pooling the treatment groups with only the following tables summarized:
    - Disposition
    - Analysis Populations
    - Demographics
    - PK analysis

8.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

8.2 Subject Disposition and Screen Failures

The number and percentage of patients in each disposition category (eg, enrolled, analysis sets, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized by treatment group for all patients.

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to end of study participation. Number and percentage of patients screened, enrolled/randomized, patients completed treatment, patients discontinued from the study and discontinuation reasons (including reasons for early withdrawal).

The summary tables will be provided by treatment group for subject disposition on enrolled patients. Listing will consist of ICF date, enrollment details (last contact date, reason of

screened failure), randomization codes, visit dates, and withdrawal details (including reason for discontinuation and duration of treatment prior to discontinuation).

A by-subject listing will be provided by study part and treatment group for study treatment/ randomization codes, study drug completion status, study completion status and subject disposition on enrolled patients. Screen failures, and patients who did not meet study eligibility criteria listings will be on listing of screened patients.

8.3 Prior and Concomitant Medication

Medication start and stop dates will be compared to the date of first dose of ANK-700 to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications will be assigned to a time period (prior and /or concomitant) as follows:

- If medications that start and stop prior to the date of first dose of ANK-700, the medications will be classified as Prior only.
- If the start date is missing and the stop date is before the first dose of study drug, the medication will be counted as prior.
- If a medication starts before the date of first dose of ANK-700 and stops on or after the date of first dose of ANK-700, then the medication will be classified as both Prior and Concomitant.
- If the start date is missing and the stop date is after the first dose of study drug or the medication is continuing, the medication will be counted as concomitant only.
- If they have a start date on or after the date of first dose of ANK-700, medications will be classified as Concomitant only.
- If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of ANK-700.

All concomitant medication and concurrent therapies as documented by the investigator, will be coded using the most current version of the WHO drug dictionary (WHO DD) available at the time of database lock.

If a patient has taken concomitant medications more than once, the patient will be counted only once in the total. The number and percentage of patients taking prior and concomitant medications will be summarized by WHO Drug Name.

For Part A and B, summary tables (as described in Section 7) will be provided by treatment group for prior and concomitant medications by ATC Levels and PT.

By-subject listings of concomitant medication and concurrent therapies including dose, route, unit frequency of administration, and indication for administration and dates of medication will be provided on enrolled patients and sorted by part, subject ID and date of medication start.

After patients have completed the 3-month visit (D90), they may receive alternative DMTs (Disease modifying Therapy) for their MS if judged clinically appropriate by their treating physician or the Investigator. Summary statistics for observations after 90 days may be presented in a sample size report, stratified by medication, if sample size permits.

8.4 Demographics, Baseline Characteristics, Disease History and Medical History

Patient listings will be presented for all enrolled patients for Part A and Part B, by treatment group, center, and subject ID for enrolled patients unless otherwise specified. Listings will be sorted by part and subject id unless otherwise specified.

Demographics and baseline characteristics will be summarized by treatment (PBO and dose group) for the All-Treated Analysis Set: sex, race, age, ethnicity, height, weight, BMI .

All medical history will be coded using Version 23.1 or higher of the Medical Dictionary for Regulatory Activities (MedDRA). A count and percentage will be presented for all medical history, including disease history and previous therapies. MS history is considered part of medical history and the following will be summarized (as stated in Section 7): concomitant fumarate use, duration since MS symptom onset, duration since MS diagnosis, number of relapses within the last year, number of relapses within the past 3 years, duration since last relapse, and use of previous MS treatments.

8.5 Study Drug Administration and Compliance

A by-subject listing for study drug administration and compliance will be provided by study part and treatment group on enrolled patients

The treatment compliance (%) at a study part and treatment group will be calculated as total received dose (mg) *100/sum of total intended dose (mg) during the treatment.

8.6 Dosing and Extent of Exposure

Exposure will be calculated for study Part A and Part B by dose level; all exposure data will be listed (for details see Section 7) for both parts. The exposure variables include:

- the cumulative number of days of exposure- count of days of treatment
- 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) times 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 times the planned dose level (mg)

8.7 Protocol Deviations

Protocol deviations will be reviewed and assessed before database lock. The major protocol deviations are defined as those deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis.

A summary of the number and percentage of patients with a major/minor protocol deviation as well as by type of deviation will be provided. Also, a by-subject listing of major/minor protocol deviations will be provided by treatment part, subject ID, and visit.

8.8 SAFETY ANALYSES

Safety analysis will be performed among patients who received at least a partial dose of study drug. If a patient experiences the same adverse event more than once, then the patient will be counted only once for that adverse event for frequency counts. Similarly, if a patient has more than one adverse event in a single SOC, then the patient will be counted only once for that SOC.

If a patient has taken the same concomitant medication (as coded to World Health Organization (WHO) PT) more than once, then the patient will be counted only once for that concomitant medication.

8.8.1 Adverse Events

The AE terms will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA™) Dictionary (Version 17.1 or later). AEs will also be presented by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (National Cancer Institute) NCI (Version 5.0) from Grade 1-Grade 5 of mild, moderate, severe, Life-threatening and death and by relationship to study drug. AEs will be presented by severity only when the CTC grade is not collected.

The Following Tables will be Provided for Part A .

- Overall summary of TEAE will include the number of patients with any TEAEs, drug-related TEAEs, ≥ Grade 3 TEAEs, treatment-emergent serious AEs (TESAEs), TEAEs leading to discontinuation (treatment and study);
- A summary of the number and percentage of patients reporting a TEAE by system organ class (SOC) and PT;

For Part B (MAD) only, the following AE summaries (as described in Section 7) will be provided:

- Overall summary of TEAE will include the number of patients with any TEAEs, drug-related TEAEs, ≥ Grade 3 TEAEs, treatment-emergent serious AEs (TESAEs), TEAEs leading to discontinuation (treatment and study);
- A summary of the number and percentage of patients reporting a TEAE by system organ class (SOC) and PT;
- A summary of the number and percentage of patients reporting a TEAE by severity, SOC and PT.
- A summary of the number and percentage of patients reporting a TEAE by causality, SOC and PT;
- A summary of the number and percentage of Maximum CTCAE recorded
- A summary of the number and percentage of patients reporting a Serious TEAE by system organ class (SOC) and PT;

AE summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the Total group, and then alphabetically for SOC, and PT within SOC.

For each subject and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries.

For Part A and Part B, by-subject listings of AEs will be presented by study part and treatment group for the following listings:

- All DLT events
- All TEAEs
- All SAEs
- All TESAEs
- TEAEs Leading to Study Discontinuation
- TEAEs Leading to Permanent Discontinuation of Study Drug
- TEAEs Leading to Death
- Non-TEAEs

The following information will be included in the listings: verbatim (reported term), PT, SOC, AE onset date (and time), AE end date (and time), AE duration, relationship to study drug, AE outcome, severity, and SAE indicator flag. Confirmed and suspected SARS-CoV-2 infections and/or COVID-19 cases will be recorded in the AE eCRF.

Pandemic related Impact of COVID-19 will be presented in listing, detailing the category of impact (example: Missed Visit, Missed Assessment, Early termination, Screen Failure, Adverse Event, Withdrawal of consent, Death, Replacement subject).

8.8.2 Physical Examination

Physical exam results will be listed for Part A and B, sorted by study Part, subject ID, body system and date of exam.

8.8.3 Vital Signs

Vital signs (temperature, pulse rate, and diastolic and systolic blood pressure will be summarized (as described in Section 7) for observed values and change from baseline, at each visit measured.

8.8.4 Clinical Laboratory Evaluation

For Part B only, clinical laboratory summary statistics (as described in Section 7) will be provided for serum chemistry, hematology, coagulation and urinalysis (specific gravity and pH only) for observed values and change from baseline by study visit.

A shift table will be provided to evaluate the change from baseline to each post-baseline visit in the lab value status (abnormal high, normal, abnormal low) for serum chemistry, hematology, and coagulation.

The following by-subject laboratory listings (values and change from baseline if applicable) will be provided by study part and treatment group using the enrolled patients and sorted by subject ID, laboratory evaluation and date measured:

- Serum Chemistry
- Hematology
- Coagulation
- Urinalysis
- Virus Serology (screening only)
- Serum and Urine Pregnancy test
- Lab abnormality ≥ Grade 3 in Severity.

Toxicity, in reflection of safety laboratory results will be graded locally according to NCI-CTCAE v5.0 or higher and included in separate listings.

8.8.5 ECGs

Screening data collected on ECG (normal/abnormal) will be listed by patient number.

8.8.6 Medication for Infusion Reaction

A by-subject listing will be provided by study part and treatment group for any medications to treat infusion reactions by ATC levels and PT on enrolled patients.

8.8.7 MRI of Brain

Summaries of MRI scans will include:

- Number and percentage of patients with Screening scans classified as normal or abnormal
- For post-baseline scans: number and percentage of patients with scans classified as improved, worsened, or unchanged since previous scan, by visit
- Number and percentage of patients with any FLAIR lesions found, by visit
- Number and percentage of patients with any enhancing lesions found, by visit
- Number and percentage of patients with evidence of restricted diffusion present, by visit

By-subject listings of MRI findings also will be provided.

8.9 Efficacy Analysis

There is no efficacy analysis.

8.10 Pharmacokinetics

Non-compartmental PK parameters will be determined using Phoenix® WinNonLin (WNL) version [8.3] or a later version in a secure and validated environment. All pharmacokinetic data analysis will be performed on the PKAS set.

8.10.1 Pharmacokinetic Concentration Tables, Figures, and Listings

For Part A (SAD) and Part B (MAD), separately, plasma concentrations for ANK-700 will be summarized by treatment group, day of dose, and nominal protocol time point for PKAS. Additionally, Part A and B will be pooled for a combined summary concentration table by dose on the first (Day 1) dose only for PKAS.

A by-subject listing for plasma concentration data for ANK-700, will be listed by study part, treatment group, patient, and day/time of dose for PKAS. Listings will include nominal and protocol time, actual sampling time relative to start of infusion, actual infusion duration, scheduled infusion duration (30 minutes), and difference between scheduled and actual infusion duration.

All individual as well as summary concentration data (mean, SD, minimum, median, maximum, and geometric mean) will be reported in Table, Figures, and Listings to the same precision as the data provided by the Bioanalytical Lab, e.g, if concentrations are provided as 3 significant digits, TFLs will also report individual and summary concentration data as 3 significant digits. N will represent number of subjects in the treatment group, n will represent number of concentrations available at a nominal time, n(blq) will represent number of concentrations available at a nominal time that are blq, and n (ND) will represent number of concentrations available at a nominal time that were not drawn, not analyzed, or analyzed but not reportable. N and n's will be reported as whole number. Pharmacokinetic Parameters Tables, Figures, and Listings

Following figures will be presented for Part A and B, separately, and for Day 1 combined parts A and B (except for individual separate plots for each patient):

- Linear mean (+/- SD) plasma concentration-time profiles for ANK-700 (all doses on one plot)
- Semilogarithmic mean (+/- SD) plasma concentration-time profiles for ANK-700 (all doses on one plot)
- Linear individual concentration-time profiles for ANK-700 (all patients on same dose on one plot)
- Semilogarithmic individual concentration-time profiles for ANK-700 (all patients on same dose on one plot)
- Linear individual concentration-time profiles for ANK-700 (separate plot for each patient)
- Semilogarithmic individual concentration-time profiles for ANK-700 (separate plot for each patient)

8.10.2 Pharmacokinetic Parameters Tables, Figures, and Listings

For Part A and Part B separately, and Part A and Part B, Day 1 (combined), summary tables of ANK-700 calculable pharmacokinetic parameters will be provided that were calculated using concentrations available in PKAS.

A by-subject listing for PK parameters for ANK-700 will be listed by study part, by treatment group, by patient and day of dose using the PKAS.

Following rules will be followed for reporting PK parameters:

For t_{max}, only median, minimum and maximum values will be presented.

For all other parameters N, n, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV% will be presented. N will represent the number of subjects in the treatment group and n will represent calculable PK parameter in the treatment group.

Lambda z dependent PK parameters, i.e. λz, AUC_{inf}, CL, Vz will not be summarized if r^2adjusted is <0.90, and/or span of the terminal phase is <1.3 times the half-life and/or the %extrapolation to calculate AUC_{inf} is >30%, unless otherwise determined by the PK scientist. Such parameters will be flagged in parameters listing, and if flagged parameters are not used for calculation of descriptive summaries, it will be footnoted in the PK parameters listing. For summarizing or calculating the summary PK parameters, the individual parameter values as provided by the Phoenix® software will be used without any truncation.

In tables, figures, and listings, individual and summary C_{max} will be reported to the same precision as that provided by the Bioanalytical Lab, T_{max} will be reported in 3 decimal places in hours and all other PK parameters will be reported as 3 significant figures. N and n will be reported as whole number and CV% will be reported in 2 decimal places.

Box plots for C_{max}, AUC_{last}, and AUC_{inf} and corresponding dose normalized parameters will be created to visually assess dose proportionality.

8.10.2.1 Assessment of Dose Proportionality

No formal dose proportionality assessment will be performed. Informal assessment of dose proportionality will be done using Box plots, displaying minimum, Q25, median (Q50), Q75 and maximum will be provided for NK-700 C_{max} and AUCs by visit/day and dose level.

8.10.2.2 Antidrug Antibodies

For Part B (MAD) only, immunogenicity summaries will be provided by treatment group on ATAS. Patients with any ADA positive samples, screening (ADA status) and confirmatory assay (titer, specificity, and ADA status) results will be included. The results for 3-Tiers will be displayed. If the sample is ADA-positive then the reactivity to the pgal and peptide will be included.

A by-subject listing of immunogenicity will be provided by study part and treatment group on enrolled patients.

[redacted]

8.12 [redacted]

[redacted]

9. ADJUSTMENTS FOR COVARIATES

There will be no adjustment for covariates in this study.

10. DATA HANDLING AND MISSING DATA

All missing or partial data will be presented in the patient data listing, as they are recorded on the eCRF. Patients lost to follow-up or withdrawn will be included in statistical analyses up to the point of their last evaluation.

10.1 Missing Start and Stop Dates/Time for Adverse Events

Due diligence will be done to obtain accurate AE information. If all planned methods to obtain accurate time AE information have failed, missing and partial AE onset and end dates will be imputed. Imputed dates will be flagged in the individual supportive patient listings. Unless otherwise specified, the following conventions will be used:

Missing and Partial AE onset dates:

- If onset date is completely missing, then onset date is set to date of first dose.
- If onset year is present and

  - month and day are missing:
    - If onset year = year of first dose, then set onset date to date of first dose.
    - If onset year < year of first dose, then set onset month and day to December 31st.
    - If onset year > year of first dose, then set onset month and day to January 1st.

  - month is missing:
    - If onset year = year of first dose, then set onset date to date of first dose.
    - If onset year < year of first dose, then set onset month to December.
    - If onset year > year of first dose, then set onset month to January.

- If onset month and year are present and day is missing:

  - If onset year = year of first dose and
    - onset month = month of first dose then set onset date to date of first dose.
    - onset month < month of first dose then set onset date to last day of month.
    - onset month > month of first dose then set onset date to 1st day of month.

  - If onset year < year of first dose, then set onset date to last day of month.

  - If onset year > year of first dose, then set onset date to 1st day of month.

- For all other cases, set onset date to date of first dose.

Missing and Partial AE end dates:

- If end date is completely missing, end date is not imputed and the AE is flagged as "ongoing".
- If year is present and

  - month and day are missing:

    - If year = year of last dose, then set end date to the date of last dose.
    - If year < year of last dose, then set end month and day to December 31st.
    - If year > year of last dose, then set end month and day to January 1st.

  - month is missing:

    - If year = year of last dose, then set end date to date of last dose.
    - If year < year of last dose, then set end month to December.
    - If year > year of last dose, then set end month to January.

- If month and year are present and day is missing:

  - If year = year of last dose and

    - month = month of last dose then set day to day of last dose.
    - month < month of last dose then set day to last day of month.
    - month > month of last dose then set day to 1st day of month.

  - If year < year of last dose, then set end date to last day of the month.

  - If year > year of last dose, then set end date to 1st day of month.

- For all other cases, set end date to date of last dose.
- Screen failures are collected in EDC and will be a part of SDTM. Screen failure data are not analyzed and will not be included in the ADaM except for demographics (ADSL) and inclusion/exclusion criteria (ADIE).

Any AEs with incomplete start and end dates/times will be treated as follows:

- Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK: NK in the listings (where NK = Not Known).

10.2 Missing Start and Stop Dates for Prior and concomitant Medication

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication starts and stop dates will be imputed as follows:

- If year and month are present and day is missing, then set day to first day of month for start date and set day to last day of month for end date.
- If year and day are present and month is missing, then set month to January for start date, and set month to December for end date.

- If year is present and month and day are missing, then set month and day to January 1 for start date and set month and day to December 31 for end date.
- Completely missing date will not be imputed.

The partial dates will be provided as such in the patient data listings (with the imputed dates).

When imputing a start date, the programmer will ensure that the new imputed date is sensible i.e. it is before the end date of prior and concomitant medications.

10.3 Concentrations Below the Limit of Quantification (BLQ)

For PK data, all concentrations BLQ will be labeled as "BLQ" in the concentration data listings. Values that are BLQ will be substituted by for the calculation of descriptive statistics of concentration tables and for the individual and mean concentration-time plots.

For non-compartmental PK analysis, all below the limit of quantification (BLQ) values pre-dose to the first dose, and prior to the first quantifiable concentration will be substituted by zeros. BLQ values between non-BLQ concentrations will be considered missing before the calculation of the PK variables. Terminal BLQ values will be considered missing.

10.4 Labs [redacted] (BLQ and ULQ)

For relevant labs [redacted], BLQ will be labeled as "BLQ" in the data listings. Values will be replaced with ½ LLQ (Lower Limit of Quantification) when summarized in tables. Values will also be labeled when they are above the ULQ (upper limit of quantification) and will be replaced with the ULQ when summarized in tables.

11. INTERIM ANALYSES AND DATA MONITORING

No Interim analysis will be performed.

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.

11.1 Pooling Centers

Patients will be pooled together for analysis from all study sites. No site adjustment will be made. The placebo patients will be pooled from each cohort.

12. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

Changes in statistical methods as compared to those stated in the protocol will be documented in the CSR.

13. APPENDIX 1: SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments Part A (SAD)

Assessment	Screening	Study Period						Early Term.
Study Day	**-28 to 0**	**1**	**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	X							X
Pregnancy test	X	X[f,]						
Vital signs	X	X[g]		X				X
Concomitant medications and procedures	X	X	X	X	X	X	X	X
EDSS	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			X				
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] 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	Screening	Treatment Period			Study Period					Early Term.
Study Day	**-28 to 0**	**1**	**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	X									X
Pregnancy test	X	X[f,-]	X[f, g]	X[f, g]						
Vital signs	X	X[g]			X					
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X
EDSS	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				X		X			
Study Drug Administration										
Randomization		X								
ANK-700 or PBO administration		X[,q]	X[,q]	X[o,q]						
Additional Blood Samples										
PK blood sample		X	X[g]	X	X					
ADA samples		X[g]			X		X	X	X	X
[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; [redacted]; PK = pharmacokinetics; [redacted].

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

Assessments	Screening	Treatment Period			Study Period					Early Term.
Study Day	-28 to 0	1	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	X									X
Pregnancy test	X	X[f,-]	X[f, g]	X[f, g]						
Vital signs	X	X[g]			X					
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X
EDSS	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				X		X			
Study Drug Administration										
Randomization		X								
ANK-700 or PBO administration		X[,r]	X[,r]	X[o,r]						
Additional Blood Samples										
PK blood sample		X	X[g]	X	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]	[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] [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; E[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; [redacted]; PK = pharmacokinetics; [redacted]

14. APPENDIX 2: 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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15. APPENDIX 3 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

Score	Description
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS