NCT #: NCT04514367

ANX005-HD-01
Statistical Analysis Plan

A Phase 2a Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous ANX005 in Subjects with, or at Risk for, Manifest Huntington's Disease

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Version 2.0

16aug2022

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LIST OF ABBREVIATIONS/DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ADA	Antidrug (ANX005) antibodies
AUC	Area under the curve
[redacted]	[redacted]
C1q	Component of complement complex
C4a	Component of complement complex
CAG	Cytosine-adenine-guanine
CAP	CAG age product
CH50	50% hemolytic complement activity
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
[redacted]	[redacted]
FAS	Full analysis set
HD	Huntington's Disease
ICH	International Conference on Harmonisation
IRR	Infusion-related reaction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NfL	Neurofilament light chain
PD	Pharmacodynamic or pharmacodynamics
PK	Pharmacokinetic or pharmacokinetics
PP	Per protocol set
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
Stat X24 Wireless EEG System	Proprietary EEG system provided by Advanced Brain Monitoring
[redacted]	[redacted]
WHO-DD	World Health Organization Drug Dictionary

Version History

This statistical analysis plan (SAP) for Study ANX005-HD-01 is based on the protocol version 6 dated 16 December 2020.

SAP Version	Date	Change	Rationale
1.0	31Mar2022	Not applicable	Original version
2.0	16Aug2022	1). Added information defining windowing of visits for the serum NfL and the CSF NfL data to section 6.4.2.3 Pharmacodynamics Endpoints. 2). Updated figure numbers and titles in section 8.3 List of Figures based on input from medical writing and from PKAP (Pharmacokinetic Analysis Plan).	Sponsor decided to add visit windowing based on Study Day to only the serum NfL and the CSF NfL data in order to maximize quantity of NfL data presented in outputs.

1 Introduction/Background

This statistical analysis plan (SAP) describes data analysis specifications for the ANX005-HD-01 protocol (version 6, dated on 16 December 2020) entitled "A Phase 2a Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Intravenous ANX005 in Subjects with, or at Risk for, Manifest Huntington's Disease". The SAP follows the International Council on Harmonisation (ICH) Guidelines E3 and E9. All statistical analyses will be performed using SAS®, Version 9.4 or higher. In cases in which the analyses in this SAP differ from those in the study protocol, the analyses in the SAP supersede those in the protocol. Should differences exist, these will be described in Section 6.2 of this document.

2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of intravenous ANX005 administered for up to 22 weeks in subjects with, or at risk for, manifest Huntington's Disease	• Incidence of treatment-emergent AEs, SAEs, AEs related to ANX005, SAEs related to ANX005, Grade 3 and higher AEs, Grade 3 and higher AEs related to ANX005, AEs leading to study discontinuation, and AEs leading to discontinuation of study medications • Incidence of ANX005 infusion-related reactions • Concomitant medications and procedures • Observed laboratory assessments and change from baseline (serum chemistry, hematology, urinalysis) • Observed vital signs assessments and change from baseline (body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures) • Observed Columbia Suicide Severity Rating Scale results and change from baseline • Study medication administration
• To assess the pharmacokinetics (PK) of ANX005 in the serum and cerebrospinal fluid (CSF).	• Details of the PK analysis will be presented in a separate PK analysis plan.

Objectives	Endpoints
• To assess the pharmacodynamic (PD) effects of ANX005 in blood and/or CSF through the assessment of C1q, C4a, and neurofilament light chain (NfL) levels	• CSF free C1q and serum free C1q • NfL (plasma NfL, CSF NfL) • CSF C4a • Details of the C1q serum and CSF evaluation will be presented, along with the PK analysis details, in a separate PK analysis plan.
Exploratory	
[redacted]	

3 Study Design

3.1 Overview

This is a multi-center, open label, proof-of-biology study of intravenous ANX005 in subjects with, or at risk for, manifest Huntington's Disease.

3.2 Treatment Administration

Subjects will receive induction dosing of ANX005 at 75 mg/kg administered by IV infusion on Days 1 and 5 or 6 (5/6), followed by maintenance dosing at 100 mg/kg every 2 weeks (Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22) with follow up visits on Weeks 24, 28, and 36. All ANX005 infusions will be administered at in-clinic visits. The first infusion will be given over approximately 21 hours with subsequent infusions

expected to be completed in approximately 4 hours (Day 5/6) or up to 5 hours (Weeks 2 through 22).

3.3 Sample Size Calculation

Approximately 24 total subjects will be treated in the study. The sample size for this study is determined by practical clinical methods rather than statistical considerations. Descriptive statistics will be used to characterize the results, with a focus on the percent change from the pre-treatment values. A sample size of 24 will provide 2-sided 95% confidence interval half-widths of 6 to 12%, assuming observed SD of 15 to 30%.

Subjects who do not receive their complete assigned doses of ANX005 may be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator. Similarly, if a subject discontinues from the study prior to the Week 36 (end-of-study) visit, an additional subject may be enrolled at the discretion of the Sponsor to replace the discontinued subject. Up to 5 replacement subjects may be enrolled.

4 Analysis Sets

Membership of each subject in the analysis sets will be determined prior to database closure.

4.1 Safety Population

The safety population (SAF) includes all subjects who received any amount of ANX005 and will be the population for safety and immunogenicity endpoints.

4.2 Full Analysis Set

The full analysis set (FAS) includes all subjects who received at least 1 completed infusion of ANX005 and have at least one post-infusion assessment. The FAS will be the population for clinical and functional assessments and biomarker endpoints.

4.3 Per Protocol Analysis Set

The per protocol set (PP) includes all subjects who completed all 13 infusions of ANX005 and do not have major protocol violations. A final determination of inclusion in the PP will be made prior to database lock. The PP set will be used for clinical and functional assessments and biomarker endpoints as a supplement to the FAS results.

4.4 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PK) includes all subjects who received any amount of ANX005 and have evaluable ANX005 concentration data. The PK set will be the population for pharmacokinetic endpoints.

5 Protocol Deviations

Major protocol violations may include, but are not limited to, violations of eligibility criteria, receipt of incorrect dose of ANX005, use of prohibited medications, and non-compliance with study assessments. All protocol deviations will be listed by subject.

6 Statistical Methodology and Analyses

6.1 General Considerations

All statistical analyses will be performed using SAS® Version 9.4 or higher.

Descriptive summaries for the categorical variables will include frequency counts and percentages. Descriptive summaries for the continuous variables will include means, medians, standard deviations, 25th and 75th quartiles, and minimum and maximum values. Summaries may include 95% confidence intervals (CIs) for point estimates.

Data will be summarized at each scheduled time point. Additional unscheduled data will not be included in the summaries at each time point, but adverse events or abnormal laboratory results will be included in subject level summaries. Unless specified otherwise, all data will be listed for all subjects.

Unless otherwise specified, the baseline assessment will be the latest, valid assessment available prior to the first infusion.

6.2 Changes from Protocol-Specified Analyses

This SAP may be amended before database closure to reflect any changes found to be needed. SAP changes from the protocol will take precedence over the protocol.

6.3 Hypotheses Testing and Multiple Comparisons

There is no planned formal hypothesis testing. Descriptive statistics will be used to describe the results of this study.

Since this is a proof-of-biology study, no adjustments for multiple comparisons will be performed.

6.4 Primary Endpoint Analysis

6.4.1 Definition of Endpoints

6.4.1.1 Safety and Tolerability Endpoints

- Incidence of treatment-emergent AEs, AESIs, SAEs, AEs leading to study discontinuation, and AEs leading to death
- ANX005 infusion-related reactions
- Safety laboratory assessments (serum chemistry, hematology, urinalysis)
- Vital signs (body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures)
- Columbia Suicide Severity Rating Scale results
- Concomitant medications and procedures
- Study medication administration

6.4.1.2 Pharmacokinetics Endpoints

Details for the serum ANX005 PK analysis, CSF ANX005 concentrations evaluation, and serum and CSF C1q concentrations evaluation will be presented in a separate PK analysis plan.

6.4.1.3 Pharmacodynamics Endpoints

Plasma NfL, CSF NfL, and CSF C4a.

6.4.2 Main Analytical Approach

6.4.2.1 Safety and Tolerability Endpoints

6.4.2.1.1 Adverse events

Adverse event data will be coded to system organ class and preferred term using MedDRA version 23.1 September 2020. Treatment emergence is defined as any AE with an onset on or after the day of infusion through Week 36 (EOS). The number and percentage of subjects experiencing any treatment-emergent AE (TEAE) by system organ class and preferred term will be tabulated. Similar tabulations will be presented by severity and relationship to ANX005.

Each TEAE will be counted only once for a given subject at each level of summarization. In analyses of grade and causality, if the same TEAE occurs on multiple occasions, the highest grade and strongest relationship to ANX005 will be used in the applicable summaries. Infusion-related and immune reactions will be summarized as the number and percentage of subjects with these reactions, and will be presented in data listings. Summaries will also be provided for AESIs, SAEs, Grade 3 and higher AEs, Grade 3 AEs and higher related to ANX005, AEs leading to study discontinuation, and AEs leading to discontinuation or dose interruption of ANX005. The number and percentage of subjects that died in study, from any cause, will be summarized.

AESIs include events such as hypersensitivity and infusion-related reactions, evidence of an infection, hemolytic anemia, autoimmune disorder.

All AE data will be presented in data listings.

6.4.2.1.2 Concomitant and Study Medications

Concomitant medications are considered medications that are taken during or after infusion up through Week 36 (EOS). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) WHODRUG GLOBAL B3 September 1, 2020 and will be summarized by anatomical-therapeutic-chemical level (ATC Level 2) and preferred term, using frequency and percentage of subjects. All concomitant medications will be presented in by-subject listings.

ANX005 administration will be summarized with number and duration of infusions, volume administered, and dose administered. The number of subjects with an infusion

interruption or incomplete administration will also be summarized. Extent of exposure will be assessed as the total dosage relative to planned exposure of ANX005.

6.4.2.1.3 Vital Signs

Results and changes from baseline in vital signs will be tabulated at each visit (and time point as applicable). All vital sign data will be presented in data listings.

6.4.2.1.4 Safety Laboratory Parameters

Results and changes from baseline in hematology and clinical chemistry parameters will be tabulated at each visit. Shift tables from baseline to each post-baseline time point will be presented. Laboratory values above or below the normal range will be flagged as such in the data listings. All laboratory results will be listed individually by subject and time point.

6.4.2.1.5 Additional Safety Considerations

Other safety data will be presented in data listings only, including C-SSRS, physical examinations, pregnancy tests, and illicit drug tests.

6.4.2.2 Pharmacokinetics Endpoints

Details for the serum ANX005 PK analysis, CSF ANX005 concentrations evaluation, and serum and CSF C1q concentrations evaluation will be presented in a separate PK analysis plan.

6.4.2.3 Pharmacodynamics Endpoints

Observed values, changes and percent changes from baseline will be summarized at each visit (and time point where applicable).

Special visit windowing based the half-width rule will be applied only to the serum NfL and CSF NfL data. Details for the windowing are provided in Appendix 9.1 and Appendix 9.2.

6.4.2.4 Handling of Missing Data

In general, data will not be imputed for safety parameters, except as follows for adverse events. If AE grade or relationship is missing in analyses of grade and causality, the missing grade will be set to Grade 3 and relationship will be set to related for tabulation purposes. Missing or partial AE start and end dates will be imputed as described in the following table:

AE date type	**If missing…**	**Condition**	**Impute to…**
Start Date	Full date/time	NA	Date/time of first dose
	Time only	If date is same as first dose date	Time of first dose
		If date is after first dose date	Midnight (00:00)

	Year only	If month is same as or after first dose month	Year of first dose date
		If month is prior to first dose month (e.g., first dose in Dec, AE starts in Jan)	Year of first dose date + 1
	Month only	If year is same as first dose year	Month of first dose date
		If year is after first dose year	January
	Day only	If month and year are same as first dose month and year	Day of first dose date
		If month and year are after first dose month and year	01
	Month and day only	If year is same as first dose year	Month and day of first dose
		If year is after first dose year	January 01
End Date	Full date/time	NA	No imputation necessary as this is an ongoing AE
	Time only	NA	23:59
	Year only	If month is same or after start month (through December)	Year of start date
		If month is prior to start month (e.g., AE starts in Dec, ends in Jan)	Year of start date + 1
	Month only	NA	December
	Day only	If month and year are same as or after start month and year	28, 29, 30, or 31 (depending on month)
	Month and day only	NA	December 31

For concomitant medications, the same imputation method described above for AEs will be used to compare to the date and time of the first infusion to determine if a medication is considered prior or concomitant.

Missing safety data will otherwise not be imputed.

Missing values for pharmacodynamic endpoints will not be imputed.

6.5 Exploratory Endpoint Analysis

[redacted]

6.5.1 Definition of Endpoints

6.5.1.1 [redacted]

6.5.1.2 [redacted] *to ANX005*

[redacted]

6.5.1.3 Efficacy Endpoints

[redacted]

6.5.2 Main Analytical Approach

6.5.2.1 [redacted]

6.5.2.2 [redacted] *to ANX005*

[redacted]

6.5.2.3 Efficacy Endpoints

[redacted]

[redacted]

6.5.2.4 Handling of Missing Data

Missing values for exploratory endpoints will not be imputed.

6.5.2.5 Sensitivity Analyses

Sensitivity and subgroup analyses may be performed on selected endpoints.

For the [redacted] endpoint, a sensitivity analysis of incomplete assessments will be conducted using multiple imputation assuming missing at random (MAR).

The Fully Conditional Specification (FCS) method will be used in SAS® PROC MI to create fifty imputed datasets. Each timepoint will be treated as a separate variable and

additional variables for some baseline characteristics may be included. The seed used in the PROC MI procedure will be 20220118.

Each of the 50 complete datasets will be used to generate estimates for the mean [redacted] values at each timepoint and corresponding 95% confidence intervals.

6.6 Interim Analyses, Final Analyses, and Unblinding

This is an open-label study so unblinding considerations are not applicable.

Safety data will be reviewed on an ongoing basis by a safety review team to evaluate the frequency and severity of AEs and SAEs, study discontinuation due to AEs. PK and PD data may also be reviewed. No formal interim analyses are planned. The final analysis will occur when the last subject completes the end-of-study visit (Week 36).

6.7 Other Analyses

6.7.1 Subject Disposition

Subject disposition, including receipt of intended ANX005, early discontinuation, and reason for discontinuation will be summarized using all enrolled subjects.

6.7.2 Demographic and Baseline Characteristics

Subject demographics (gender, age, ethnicity, and race) and clinical baseline characteristics (height, baseline weight, HD type, baseline CH50, baseline serum and CSF C1q, and baseline CSF C4a) will be summarized using the SAF and PP. If the SAF and FAS differ, the summaries will be repeated in the FAS.

Baseline disease characteristics, including baseline scores for [redacted] and C-SSRS will be summarized as described above.

Medical history and prior medications will be listed.

7 References

None at this time.

8 Tables, Listings and Figures

Tables, Listings and Figures shells will be finalized before database lock.

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9 Appendices

9.1 Half-width Rule Windowing Applied to Serum NfL Data

Based on the Study Day, analysis visits will be assigned as follows:

Protocol Specified Schedule of Assessments Visit Windows	Target Study Day	Is serum NfL Sample Expected at this Visit?	Half Width Rule Minimum Study Day	Half Width Rule Maximum Study Day
Screening Week -6, 42 (+/- 3 days prior to D1)	-42			

Screening Week -2, 14 (+/- 3 days prior to D1)	-14	Yes	<=-1	-1
Day 1	1	Yes	1	1
Day 3&4		Yes	NA	NA
Day 5/6		Yes	NA	NA
Week 2 (Day 15) (+/-2 days)	15	Yes	8	21
Week 4 (Day 29) (+/-2 days)	29	Yes	22	35
Week 6 (Day 43) (+/-2 days)	43	Yes	36	49
Week 8 (Day 57) (+/-2 days)	57	Yes	50	63
Week 10 (Day 71) (+/-2 days)	71	Yes	64	77
Week 12 (Day 85) (+/-2 days)	85	Yes	78	91
Week 14 (Day 99) (+/-2 days)	99	Yes	92	105
Week 16 (Day 113) (+/-2 days)	113	Yes	106	119
Week 18 (Day 127) (+/-2 days)	127	Yes	120	133
Week 20 (Day 141) (+/-2 days)	141	Yes	134	147
Week 22 (Day 155) (+/-2 days)	155	Yes	148	161
Week 23 (Day 157-166)	162	Yes	NA	NA
Week 24 (+/-3 days)	169	Yes	162	182
Week 28 (+/-3 days)	197	Yes	183	223
Week 36 EOS/ET (+/-5 days)	253	Yes	224	>=224
6 M after EOS (+/-2 weeks)				

Note: Study Day = Date of Visit – Date of Beginning of First Infusion + 1 for visits on or after the day of the beginning of the first infusion. Study Day = Date of Visit – Date of Beginning of First Infusion for visits before the day of the beginning of the first infusion.

9.2 Half-width Rule Windowing Applied to CSF NfL Data

Based on the Study Day, analysis visits will be assigned as follows:

Protocol Specified Schedule of Assessments Visit Windows	Target Study Day	Is CSF NfL Sample Expected at this Visit?	Half Width Rule Minimum Study Day	Half Width Rule Maximum Study Day

Screening Week -6, 42 (+/- 3 days prior to D1)	-42			
Screening Week -2, 14 (+/- 3 days prior to D1)	-14	Yes	<=-1	-1
Day 1	1			
Day 3&4				
Day 5/6				
Week 2 (Day 15) (+/-2 days)	15			
Week 4 (Day 29) (+/-2 days)	29			
Week 6 (Day 43) (+/-2 days)	43	Yes	1	64
Week 8 (Day 57) (+/-2 days)	57			
Week 10 (Day 71) (+/-2 days)	71			
Week 12 (Day 85) (+/-2 days)	85	Yes	65	127
Week 14 (Day 99) (+/-2 days)	99			
Week 16 (Day 113) (+/-2 days)	113			
Week 18 (Day 127) (+/-2 days)	127			
Week 20 (Day 141) (+/-2 days)	141			
Week 22 (Day 155) (+/-2 days)	155			
Week 23 (Day 157-166)	162			
Week 24 (+/-3 days)	169	Yes	128	211
Week 28 (+/-3 days)	197			
Week 36 EOS/ET (+/-5 days)	253	Yes	212	>=212
6 M after EOS (+/-2 weeks)				

Note: Study Day = Date of Visit – Date of Beginning of First Infusion + 1 for visits on or after the day of the beginning of the first infusion. Study Day = Date of Visit – Date of Beginning of First Infusion for visits before the day of the beginning of the first infusion.