Statistical Analysis Plan

A PHASE 1 STUDY INVESTIGATING THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF KNX100 IN HEALTHY VOLUNTEERS

Protocol Number: KTX-101

SAP Version and date: Final v3.0 01-Sep-2023

STUDY DRUG:
KNX100

PREPARED FOR:

Kinoxis Therapeutics Pty Ltd (Kinoxis)
Suite 201, 697 Burke Road
Camberwell Victoria 3124 Australia

PREPARED BY:

Allucent
2000 Centergreen Way, Suite 300
Cary, NC 27513

Approval Signature Page Allucent

DocuSigned by:
Anna Tomkins
Signer Name: Anna Tomkins
Signing Reason: I approve this document
Signing Time: 01-Sep-2023 | 09:41 PDT

05-Sep-2023 | 11:17 PDT

Document Author: Anna Tomkins
Biostatistician II

Date

DocuSigned by:
Kris Chowning
Signer Name: Kris Chowning
Signing Reason: I approve this document
Signing Time: 11-Sep-2023 | 07:12 PDT
7BAD86AAA25B42048E19C98703ABE0AD

11-Sep-2023 | 07:13 PDT

Document Reviewer: Kris Chowning
Director, Biostatistics, Biostatistics

Date

Kinoxis Therapeutics Pty Ltd.

DocuSigned by:
Signer Name: Tina Soulis
Signing Reason: I approve this document
Signing Time: 01-Sep-2023 | 15:20 PDT

01-Sep-2023 | 15:21 PDT

Document Reviewer: Tina Soulis
VP, Clinical Strategy and Development

Date

DocuSigned by:
Sharon Hanegraaf
Signer Name: Sharon Hanegraaf
Signing Reason: I approve this document
Signing Time: 10-Sep-2023 | 22:32 PDT
E3070E6B343455AB8E77B267DAF7C50

10-Sep-2023 | 22:32 PDT

Document Reviewer: Sharon Hanegraaf
VP, Drug Development

Date

Biopharmaceutics Consultant

DocuSigned by:
Margaret Doherty
Signer Name: Margaret Doherty
Signing Reason: I have reviewed this document
Signing Time: 07-Sep-2023 | 14:39 AEST

07-Sep-2023 | 14:40 AEST

PK Section Author: Margaret Doherty
Consultant Pharmacokineticist

Date

Revision History

SAP Revision Chronology:

1.0	25-July-2022	Initial Version
1.1	14-Feb-2023	Update for protocol version 4.0
1.2	28-Apr-2023	Update for protocol version 5.0 and comments
2.0	04-May-2023	Second Version
2.1	03-Aug-2023	Update for protocol version 6.0
2.2	30-Aug-2023	Updated PK section additions and comments
3.0	01-Sep-2023	Third Version

Contents

ABBREVIATIONS

AE	Adverse event
ATC	Anatomic Therapeutic Class
BMI	Body mass index
BP	Blood pressure
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CRC	Cohort Review Committee
CRF	Case report form
CSR	Clinical study report
ECG	Electrocardiogram
EEG	Electroencephalogram
EOS	End of study
FAS	Full analysis set
FIH	First-in-human
ICH	International Council for Harmonization
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Medical Affairs
PP	Per Protocol
PK	Pharmacokinetics
PT	Preferred Term
RAC	Accumulation ratio
SAE	Serious adverse events
SAD	Single ascending dose
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
ULOQ	Upper limit of quantification

1 INTRODUCTION

The statistical analysis plan (SAP) details the planned statistical analysis methods required to address the study objectives as described in Kinoxis Therapeutics Pty Ltd's (Kinoxis) protocol KTX-101: A Phase 1 Study Investigating the Safety, Tolerability and Pharmacokinetics of KNX100 in Healthy Volunteers.

This SAP should be read in conjunction with the study protocol, case report form (CRF), and any other applicable study documents. This version of the SAP is based on the protocol version 6.0, dated 07 July 2023. Changes to the protocol may result in subsequent changes to the SAP. The final, sponsor-approved version of the SAP must occur prior to database lock.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
• The primary objectives of this study are to evaluate the safety and tolerability of KNX100 administered orally as a single ascending dose and multiple ascending doses in healthy volunteers.	• Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), related AEs, AEs leading to discontinuation, and AEs by severity • Clinical laboratory testing from protocol-specified standard urine and blood tests, including liver function tests (LFTs) and thyroid function tests (TFTs: triiodothyronine [T3], thyroxine [T4], thyroid stimulating hormone [TSH]) • Change in clinical observations from baseline, including body temperatures, vital signs, electrocardiograms (ECGs), electroencephalograms (EEGs)
Secondary	
• To determine the pharmacokinetic (PK) profile of KNX100 and its metabolites following administration of KNX100 as single and multiple oral doses administered once and twice daily in healthy volunteers.	• Maximum observed concentrations (C_{max}) following dose administration • Time of C_{max} (T_{max}) following dose administration • Area under the concentration-time curve (AUC) from time zero to last quantifiable concentration ($AUC_{0\text{-last}}$), from time zero to 24 hours post-dose administration ($AUC_{0\text{-}24}$), and, as data permit, from time zero to extrapolated to infinity ($AUC_{0\text{-}\infty}$)

	• As data permit, additional disposition parameters including terminal half-life ($t_{1/2}$), volume of distribution (V_z/F), and oral clearance (CL/F) may be calculated • Accumulation Ratio (RAC) for C_{max} and AUC_{0-24}; Day 7 vs Day 1 (MAD phase only) • Other PK parameters will be calculated as deemed appropriate and as referred to in Section 8.7 of the protocol

3 STUDY DESIGN

3.1 General Description

This is a Phase 1, first-in-human (FIH), single site, single treatment, two-part, double-blind, placebo-controlled, randomized, single ascending dose (SAD)/multiple ascending dose (MAD) study. The planned enrollment is approximately 64male and female subjects. The total number of subjects will depend on the number of dose levels assessed in dose-escalation. Completed subjects will have received either KNX100 (active study drug) or placebo. Subjects who discontinue will be replaced to achieve the targeted number of evaluable subjects in each cohort.

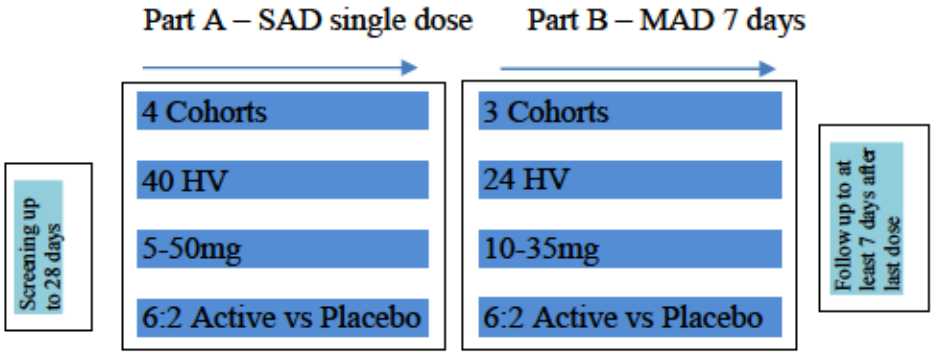
Healthy subjects who meet all eligibility criteria will be sequentially enrolled and assigned to a single cohort in Cohorts 1-4 in Part A (SAD) of the study or in Cohorts 1-3 in Part B of the study. Each cohort selected will evaluate 8 subjects who will be randomly assigned with a ratio of 6:2 to receive either KNX100 or placebo. Each cohort will be enrolled sequentially, and the subsequent dose increase will be based on the Cohort Review Committee (CRC) evaluation of data known to date. Additional cohorts may be added as required, based on safety profile and CRC authorization.

Part A (SAD) will initially dose two sentinel subjects (one assigned to KNX100 and one assigned to placebo)in Cohort 1. The center will review safety and tolerability up to and including the 48-hour timepoint for the sentinel subjects before dosing the remaining subjects in the dose cohort. The CRC will be informed and authorize the decision to continue with the remainder of the cohort dosing. Each subject will receive one dose, administered orally, of study drug. All subjects in each cohort will have their data, up to and including the 30-hour post-dose timepoint, evaluated for safety and tolerability by the CRC before opening the next dose cohort based on assessment of all available data. The dosing schedule may be extended if additional observations are needed at a particular cohort. In the absence of unacceptable AEs, the CRC may decide to open the next cohort before they have reviewed all data from all 8 evaluable subjects who have completed up to and including the 30-hour post-dose timepoint. Subjects will be housed in the clinic from Day -3 prior to study drug administration and will remain in-house for 30 hours post-dose (Day 2) for PK and safety assessments.

Part B (MAD) will evaluate up to 3 doses based on the doses established during Part A (SAD). Each subject in Cohorts 1 and 2 will receive study drug for 7 days, administered once daily. Subjects in Cohort 3 will receive study drug for 7 days, administered twice daily. All subjects in each Part B (MAD) cohort will have their AE, PK, and electroencephalography (EEG) data, acquired up to and including Day 8, evaluated for safety and tolerability by the CRC before opening the next higher dose cohort. Subjects will be housed in the clinic from Day -3 prior to study drug administration and will remain in-house for 24 hours post morning dose (Day 8) for PK and safety assessments.

The study will be comprised of 3 periods: Screening (up to 28 days); Treatment (1 day for Part A (SAD) subjects and 7 days for Part B (MAD) subjects); and Follow-up. Subjects will have a follow-up visit 7 days after the last dose. As SAD dosing is a single dose on Day 1, follow-up will occur on Day 7. Part B (MAD) Cohorts 1 and 2 dosing involves single daily dosing on Days 1 to 7, with a follow-up visit occurring on Day 14. Part B (MAD) Cohort 3 dosing involves twice daily dosing on Days 1 to 7, with a follow-up visit occurring on Day 14.

Figure 1. Study Phases and Activities



3.2 Randomization and Blinding

Subjects will be centrally randomized to treatment in a 6:2 ratio within each assigned cohort. The first 2 sentinel subjects will be assigned to treatment in a 1:1 ratio such that 1 subject receives KNX100 and the other receives placebo. Once eligibility is re-confirmed (Day -1), subjects will be randomized via a randomization list.

The study will be performed in a double-blind fashion. The investigator and study staff (including lab personnel), the subjects, the monitors, and the Sponsor's staff will remain blinded to treatment assignment until database lock. The investigator will receive sealed envelopes with the individual randomization per subject to be opened in the case of emergency only. To ensure study blinding, the active and placebo will be provided in identical capsules and an equivalent number of capsules will be administered to subjects receiving placebo.

The site pharmacy staff will be unblinded. Additionally, the following roles may be unblinded: Unblinded biostatistics team that prepares the randomization materials and handles treatment-revealing data prior to database lock; selected study Sponsor personnel who are not directly involved in the conduct of the study; and the drug-reconciliation clinical research associate (CRA). A list of unblinded individuals will be maintained in study files.

Subjects may be unblinded in the event that an AE of Grade 3 or greater is reported in 2 or more subjects to support CRC data review and decisions regarding dose escalation or stopping criteria. If deemed necessary, the CRC may be required to break the randomization code.

3.3 Sample Size

The sample size for this study is planned for approximately 64 subjects. The sample size for this study has been selected without performing a formal sample size calculation.

3.4 Cohort Review Committee

An independent CRC will oversee the progress of the study and periodically review the accruing safety data. The CRC is intended to ensure that treatment does not pose undue risk to subjects. The CRC will include an appropriate group of professional specialties, including at a minimum, the following: blinded primary investigator (PI) or delegate (must be a physician), blinded medical monitor or delegate (must be a physician), blinded neurologist with expertise in EEG analysis and interpretation, and a blinded pharmacokineticist.

For Part A (SAD), the CRC will review all safety and PK data of the sentinel subjects, collected up to the 30-hour post-dose timepoint, to enable the decision to enroll the rest of the cohort. Any AE in a sentinel subject assessed as related to study medication may trigger the need for a safety evaluation by the CRC to determine if additional subjects in the cohort may be dosed. The CRC will also conduct a blinded, cohort-escalation review after the final subject in a cohort has been dosed, using safety data from all subjects through at least the 30-hour post-dose timepoint, as well as all available blinded PK and safety data from the current and previous cohorts.

For Part B (MAD), the CRC will review all safety and PK data from each cohort collected up to and including the 24-hour post-dose timepoint on Day 8. Additionally, the frequency and severity of the following events and findings will be used to determine the acceptability of escalation to the next cohort:

- Serious AEs
- AEs leading to study discontinuation
- AEs
- Clinically significant laboratory, EEG, and ECG findings
- Study medication sensitivities and reactions

3.5 Interim Analysis

There is no formal interim analysis planned for this study. Ongoing cohort reviews will be performed for dose escalation decisions as described in section 3.4.

The final analysis will occur once all subjects complete their end of study (EOS) visit or discontinue from the study.

4 ANALYSIS SETS/POPULATIONS

4.1 Safety Set

The Safety Set (SAF) will include all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the treatment received. The SAF will be used for all safety summaries.

4.2 Per Protocol Set

The Per Protocol Set (PP) will include all subjects who received at least one dose of any amount of KNX100 and do not have major protocol violations as defined in Section 9.9 of the protocol. A final determination of inclusion in the PP will be made by a blinded team prior to database lock and unblinding. The PP may be used on select biomarker endpoints. Subjects will be analyzed according to the randomized treatment assignment.

4.3 Pharmacokinetic Set

The Pharmacokinetic (PK) Set will include all subjects who received at least one dose of any amount of KNX100 and had sufficient plasma KNX100 concentration data for calculation of at least one PK parameter (among AUC0-24, Cmax or Tmax).

Subjects with protocol violations will be assessed on a participant-by-participant basis for inclusion in the PK Population.

5 GENERAL CONSIDERATIONS

5.1 General Data Handling

All safety analyses will be conducted based on SAS 9.4 or higher.

Placebo subjects will be pooled across cohorts.

Data in the clinical database as well as vendor data will be presented in by-subject data listings.

Continuous data will be summarized by study part and cohort based on n, mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum value, and maximum value.

Categorical data will be summarized by study part and cohort using frequency counts and percentages. Unless otherwise stated, the denominator of percentages will be the number of participants in the population/cohort or the number with non-missing data.

- In summaries pertaining to subject demographics and subject disposition, the number of missing values will be presented as a separate category with no percentage, but only if one or more subjects are missing data.
- Counts of zero will be presented without percentages.

No inferential statistics will be produced for any safety endpoints.

Relative to the number of digits after the decimal in the raw data, summary statistics will have the following number of digits after the decimal:

- Minimum and Maximum: same number of significant digits as the raw data
- Mean, Median, Q1, and Q3: one additional significant digit
- SD: two additional significant digits
- Percentages <100% will be reported to one decimal place and percentages of 100% will be reported with no decimal place. The number and percentage will be presented in the form of XX (XX.X%). Percentage values of less than 0.1% will be presented as XX (<0.1%).
- Summary statistics will not exceed four digits after the decimal. Some laboratory parameters or other data may require deviation from this rule.

For clinical laboratory data, results reported as below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) will be replaced by the LLOQ and ULOQ, respectively, to ensure inclusion in applicable tables and figures, but will be presented in applicable listings as originally reported.

All data up to the time of study completion/withdrawal from the study will be included in the analysis, regardless of duration of treatment.

Numbering for data displays will be based on International Council for Harmonization (ICH) E3.

5.2 General Definitions

Variable	Definition
Study Day	• Study Day = date of interest – treatment start date + 1, when the date of interest >= treatment start date; • otherwise, Study Day = date of interest – treatment start date. Note: if either date is missing, Study Day calculations will not be performed. Should imputation be performed, then Study Day may be computed, where appropriate.
Baseline	For ECG data, baseline is defined as the average of up to three measurements taken at the pre-dose timepoint on the Day 1 Visit if available; otherwise, baseline is defined as the last single tracing measurement taken prior to the first dose of study treatment. For EEG data, baseline is defined as the assessment collected at the Screening Visit (Day -2) in which the patient was in a sleep deprived state. For all other endpoints, baseline is defined as the last non-missing value collected prior to receiving the first dose of study treatment (based on date and time of administration as applicable). For endpoints with both planned pre-dose and post-dose timepoint assessments on Day 1, only pre-dose assessments will be considered as a candidate for baseline. For MAD Cohort 3, vital signs

	assessments on Day 1 associated with the second dose (i.e., evening) will not be considered as a candidate for baseline.
Post-baseline	Defined as values collected after receipt of the first dose of study treatment (based on date and time of administration as applicable)
Change from Baseline	Defined as: Post-baseline value – Baseline value
Duration on Study (in days)	End of study date – randomization date + 1
BMI (kg/m^2)	BMI is collected in the clinical database
Age (yr)	Age is collected in the clinical database
Study Completion	Defined as attendance at the End of Study (EOS) Visit.

5.3 Data Imputation Rules

Generally, missing data will not be imputed, and will be presented as collected in the study database.

In cases where adverse event or medication dates are missing, the imputation methods described in Appendix 1 will be used to determine flags for treatment-emergent events and concomitant medications.

Other missing data methods will be described within the respective analysis section, as appropriate.

5.4 Visit Windows

Data will be summarized using the recorded nominal visit values in the CRF; no visit date windowing will be conducted. Unscheduled visit data may be included in summaries of baseline, minimum/maximum post-baseline, and incidence of subjects with potentially clinically significant post-baseline results. Unscheduled visits will also be presented in applicable data listings.

In general, if multiple non-missing values are available at the same visit/timepoint then the later value will be used in the analysis. In cases where multiple non-missing values are on the same date and time, the value with the larger Study Data Tabulation Model (SDTM) record sequence number will be used in the analysis.

6 ANALYSIS METHODS

6.1 Study Subject Data

6.1.1 Subject Disposition

The number and percentage of subjects in each analysis population and final subject status (completed or withdrawn), including study discontinuation reasons, will be produced based on the number of randomized subjects. Data will be presented by study part and cohort.

Subjects contributing to each analysis population and final disposition status will be listed. Failed eligibility criteria for screen failures will also be included in a data listing. Alcohol breath test and drug screening results will be included in a data listing.

6.1.2 Protocol Deviations

Protocol deviations will be identified and classified as minor or major on the CRF before the database is locked. Major protocol deviations will be summarized by part, cohort, and deviation category using the SAF population.

A listing of all protocol deviations will be provided.

6.1.3 Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized and listed. These will include age (as collected in the clinical database at the Screening visit), age category (18-<30, 30-<40, 40-<50, 50-55) sex (Male / Female), ethnicity (Hispanic or Latino / Not Hispanic or Latino), race (American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or Pacific Islander / White / Other / Not Reported), baseline height (cm), baseline weight (kg), BMI (kg/m^2), and smoking status (Never Smoked / Current Smoker / Former Smoker). Subjects reporting multiple race categories will be summarized under the "Multiple" category. Data will be presented by study part and cohort for the SAF population.

A listing of demographics and baseline characteristics will be provided.

6.1.4 Medical History

General medical history (including clinically significant diseases and surgeries) will be summarized by Medical Dictionary for Medical Affairs (MedDRA) System Organ Class (SOC) and Preferred Term (PT) by study part and cohort for the SAF population. A subject will be counted only once at each level of reporting. SOC will be ordered in accordance with the international agreed upon sort order for SOC followed by descending order of overall PT incidence. The MedDRA version used for reporting will be described in the relevant table and listing footnotes.

General medical and surgical history will be presented in a by-subject data listing for the SAF population.

6.1.5 Prior and Concomitant Medication

The incidence of concomitant medication use will be summarized by WHO Drug Dictionary (WHODD) anatomic therapeutic chemical (ATC) Level 2 classification (i.e., therapeutic main group) and preferred name. The WHODD version used for reporting will be provided in the relevant table and listing footnotes.

A subject will be counted only once at each level of reporting. Prior medications are those which have been identified to have been discontinued prior to the treatment start date (e.g., taken exclusively during the pre-therapy period). Concomitant therapies are defined as all therapy

ongoing at the time of enrollment and all therapy other than study drug received during the study. Concomitant medication use will be summarized and presented by study part and cohort for the SAF population. Partial start/end dates will be imputed according to Appendix 1 for the determination of concomitance. Medications will be sorted by decreasing frequency of ATC classification based on overall subjects. Preferred drug names will be sorted in descending order by frequency within each ATC classification based on overall subjects.

All prior and concomitant medication data will be listed including the verbatim and preferred drug name and ATC Level 2.

6.1.6 Study Drug Exposure and Compliance

Study drug administration information recorded on the CRF will be presented in a data listing for the SAF population.

6.2 Efficacy

This study enrolls healthy volunteers; efficacy will not be evaluated.

6.3 Pharmacokinetics

6.3.1 Plasma Pharmacokinetic Parameters

The plasma PK parameters described in this section will be derived for KNX100 and metabolites (data permitting) based on the plasma concentration-time profiles as observed after the study drug administrations. Derivations will be based on the actual elapsed time (hours) since the study drug administration.

The pharmacokinetic concentrations will be processed using standard non-compartmental analytical approach to derive the required parameters. The software used for the analysis will be Phoenix™ WinNonlin® v8.3 (Pharsight Corporation, USA).

The PK parameters described in Table 4 will be derived provided that the required concentrations data are available. Concentrations below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the standard deviation (SD) and coefficient of variation (CV) will be reported as not applicable. Missing concentrations will be excluded from the calculations.

Table 4 Plasma PK Parameters

Where possible, the following PK parameters of KNX100 and any measurable metabolites will be determined.

SAD

Parameter (Unit)	Method
Cmax (ng/mL)	Maximum plasma concentration obtained directly from the observed concentration versus time data
AUC0-∞ (h*ng/mL)	Area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinity (units) calculated by linear trapezoidal rule and extrapolated to infinity by the addition of the last quantifiable concentration divided by the terminal rate constant: AUC0-last + Clast/λz
AUC0-last (h*ng/mL)	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration at time "t" (units), calculated by linear trapezoidal rule
AUC0-8 (h*ng/mL)	Area under the plasma concentration-time curve from time zero to 8 hours after dosing, calculated by linear trapezoidal rule
Tmax (h)	Time to maximum plasma concentration obtained directly from the observed concentration versus time data
CL/F (L/h)	Plasma clearance estimated as dose divided by AUC0-∞
Vz /F (L)	volume of distribution estimated by dividing the apparent clearance by λz
λz (h-1)	Apparent terminal elimination rate constant estimated by log-linear least-squared regression of the terminal part of the concentration-time curve profile
t½ (h)	Elimination half-life, calculated as ln(2)/λz.
Residual area	Percentage of AUC0-∞ due to extrapolation from the time of last non-zero concentration to infinity.
DN AUC	Dose-normalized AUC, calculated as AUC/ Dose where AUC is AUC0-8 and AUC0-last
DN Cmax	Dose-normalized Cmax, calculated as Cmax / Dose

MAD

Parameter (Unit)	Method
Cmax (ng/mL)	Maximum plasma concentration obtained directly from the observed concentration versus time data, Day 1 and Day 7
AUC0-∞ (h*ng/mL)	Area under the plasma concentration-time curve from time zero (pre-dose) extrapolated to infinity (units) calculated by linear trapezoidal rule and extrapolated to infinity by the addition of the last quantifiable concentration divided by the terminal rate constant: AUC0-last + Clast/λz. Day 7 only
AUC0-last (h*ng/mL)	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration at time "t" (units), over the whole plasma profile on Days 1 and 7, calculated by linear trapezoidal rule. Cohorts 1, 2 and 3
AUC0-8h (h*ng/mL)	Area under the plasma concentration-time curve from time zero to 8 hours after dosing, calculated by linear trapezoidal rule. Days 1 and 7, Cohorts 1, 2 and 3
AUC8-16h (h*ng/mL)	Area under the plasma concentration-time curve from time 8 hours to 16 h after first dose, calculated by linear trapezoidal rule. Days 1 and 7, Cohort 3
Tmax (h)	Time to maximum plasma concentration obtained directly from the observed concentration versus time data. Day 1 and Day 7
CL/F ss(L/h)	Plasma clearance estimated as dose divided by AUC0-tau. Day 7 only where data permits
Vz /F (L)	volume of distribution estimated by dividing the apparent clearance by λz. Day 7 only
λz (h-1)	Apparent terminal elimination rate constant estimated by log-linear least-squared regression of the terminal part of the concentration-time curve profile. Day 7 only
t½ (h)	Elimination half-life, calculated as ln(2)/λz. Day 7 only
Residual area	Percentage of AUC0-∞ due to extrapolation from the time of last non-zero concentration to infinity. Day 7 only
RA AUC	Accumulation Ratio for AUC, calculated as AUCDay 7/ AUCDay 1, Cohorts 1, 2 and 3 (note the time interval over which the AUC will be determined will be dependent on the quantifiable data).

Parameter (Unit)	Method
RA Cmax	Accumulation Ratio for Cmax, calculated as Cmax Day 7/ Cmax Day 1
MR AUC	Metabolite to parent ratio for AUC, calculated as Ratio of [AUC (metabolite)/AUC (parent)] *[mw (parent)/mw (metabolite)] where AUC is AUC0-8
MR Cmax	Metabolite to parent ratio for Cmax, calculated as ratio of [Cmax (metabolite)/ Cmax (parent)]*[mw (parent)/mw (metabolite)] on Day 7 only

For non-compartmental analysis, λz will be the negative of the estimated slope of the linear regression of the log transformed concentration (natural logarithm) versus time profile in the terminal elimination phase.

At least three concentration points will be used in estimating λz. The time point where log-linear λz calculation begins (λz Lower), and the actual sampling time of the last quantifiable concentration used to estimate the λz (λz Upper) will be reported with the correlation coefficient from the linear regression (R2 adjusted) to calculate λz.

Rsq adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λz must be ≥ 0.8.

If the λz cannot be measured (e.g.: fewer than 3 non-zero concentrations in the terminal elimination phase), then elimination related PK parameters (λz, λz Lower, λz Upper, AUC0-∞, Rsq adjusted, Residual area, T1/2, CL/F, and Vz/F) will not be reported for PK profiles. If Rsq adjusted < 0.8, then λz, and its related PK parameters (λz, λz Lower, λz Upper, AUC0-∞, Rsq adjusted, Residual area, T1/2, CL/F, and Vz/F) will be flagged in individual listings, and excluded from analyses.

6.3.2 Dose Proportionality (for SAD only)

An assessment of dose proportionality will not be based strictly on statistical criteria, but rather several factors will be considered when assessing dose proportionality, such as results derived from a Power Model (Gough et al, 1995) (e.g., the slope estimate, and the width of the 90% confidence interval [CI]) and descriptive statistics.

Details are as follows:

Power Model: The power model will be used to estimate the slope parameter and its 90% CI. The general form of the power model is described as:

$$\ln(PK\ Parameters) = \beta_0 + \beta_1 ln(Dose) + \varepsilon$$

This approach is usually referred to as a power model because after exponentiation:

$$PK\ Parameters = \alpha Dose^{\beta_1}$$

where α only depends on the β0, ε and represents the intercept of the line and β1 represents the slope of the line.

Dependent Variables (PK Parameters):

- Cmax, AUC0-t

Independent Variables:

- The regression above is a univariable regression. The only independent variable in this model is natural logarithm transformation of dose level (e.g., ln(dose)). No other covariates will be controlled for.

Dose proportionality can generally be concluded if the 90% CIs around the slope estimate (i.e., β1) include the value of 1.

6.4 Safety

All safety analysis reporting will be based on the Safety Population.

6.4.1 Adverse Events

An adverse event (AE) is recorded if it is a new event that was not present at Screening, or is the worsening of an event present at Screening. A treatment-emergent adverse event (TEAE) is defined as any AE that starts or worsens after first dose of study drug. Partial start dates will be imputed according to Appendix 1 for the determination of treatment-emergence. Any AEs with missing start time that occur or worsen on study day 1 will be assumed to be treatment-emergent.

AEs will also be assessed for outcome, severity, relationship to study drug, and seriousness. Any missing severity assessments will be assumed to be Grade 3 (severe) and missing relationship assessments will be assumed to be related. Expected AEs related to KNX100 treatment are provided in the KNX100 Investigator's Brochure. Adverse events will be coded based on the MedDRA for reporting by SOC and PT. SOCs will be ordered in accordance with the international agreed upon sort order for SOC followed by descending order of overall incidence. The MedDRA version used for reporting will be described in the relevant table and listing footnotes.

An overview of TEAEs will be produced, including counts and percentages of subjects as well as number of events by study part and cohort with any incidences of: TEAEs, TEAEs grade 3 or higher, TESAEs, TEAEs related to study treatment, and TESAEs related to study treatment.

Summaries of adverse events by SOC and PT will present the number and percentage of total subjects and number of events (where noted below) by study part and cohort and will include the following types:

- TEAEs (including number of events)

- TEAEs by maximum severity
- TEAEs by highest relationship to study treatment
- Treatment-emergent SAEs

When calculating the incidence of AEs, each AE will be counted only once for a given subject within a MedDRA category (e.g., overall, system organ class, or preferred term), but all occurrences of the same event will be counted in the number of events. When AEs are summarized within levels of another AE assessment (e.g., relatedness or severity), AEs will be counted once per subject at the worst/highest level of the assessment (e.g., highest relationship to study drug or greatest severity).

A comprehensive listing of all adverse events will be provided in a by-subject data listing. In addition, a listing of all treatment-emergent SAEs will be provided.

6.4.2 Clinical Laboratory Evaluations

Serum chemistry, hematology, coagulation, and urinalysis parameters reported as numeric values will be summarized based on SI units. The following laboratory tests will be included in data summaries:

- Serum chemistry: Alanine Aminotransferase (ALT), Albumin, Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Bicarbonate, Bilirubin, Urea, Calcium, Chloride, Creatinine, Gamma-Glutamyl Transferase, Glucose, Lactate Dehydrogenase, Phosphate, Potassium, Protein, Sodium
- Hematology: Hematocrit, Hemoglobin, Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Basophils, Basophils/Leukocytes, Eosinophils, Eosinophils/Leukocytes, Lymphocytes, Lymphocytes/Leukocytes, Monocytes, Monocytes/Leukocytes, Neutrophils, Neutrophils/Leukocytes
- Coagulation: Activated Partial Thromboplastin Time, Prothrombin Time
- Urinalysis: Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrite, PH, Protein, Specific Gravity, Urobilinogen
- Thyroid function tests: Thyroxine, Free; Triiodothyronine, Free; Thyroid Stimulating Hormone

Observed values and changes from baseline for laboratory evaluations will be summarized by study part and cohort at each visit/timepoint as well as minimum and maximum post-baseline. Serum chemistry and hematology will also be summarized in shift from baseline tables by visit/timepoint and normal reference range (low, normal, high).

Liver function tests using various thresholds above the upper limit of normal will be summarized, including any subjects meeting the criteria for potential Hy's Law defined as (AST >= 3 x ULN or ALT >= 3 x ULN) and (Total Bilirubin > 2 x ULN) and (ALP < 2 x ULN) at the same visit.

Potentially clinically significant post-baseline thyroid function test results will be summarized by study part and cohort at each visit.

Thyroid Function Test	Criteria
Triiodothyronine, Free [T3]	< 3.5 pmol/L

Thyroid Function Test	Criteria
	> 7.2 pmol/L
Thyroxine, Free [T4]	< 9 pmol/L > 25 pmol/L
Thyroid Stimulating Hormone	< 0.4 mIU/L > 4.0 mIU/L

All laboratory parameters will be provided in by-subject data listings and values that are outside normal ranges (high vs. low; normal vs. abnormal) will be flagged. Serum chemistry, hematology, coagulation, urinalysis, and viral serology laboratory parameters with results determined by the investigator to be clinically significant will also be listed by subject and visit.

6.4.3 Vital Signs

Vital signs and body measurements include: height (cm); weight (kg); BMI (kg/m^2); systolic and diastolic blood pressure (mmHg); heart rate (beats/min); respiratory rate (breaths/min); oxygen saturation (%); temperature (°C); and the highest of 3 peak flow measurements (L/min) taken on Day 1 will be recorded on the CRF. Observed values and changes from baseline for vital signs will be summarized by study part and cohort at each visit and time point.

Potentially clinically significant post-baseline results will be summarized by study part and cohort at each visit and timepoint.

Vital Sign	Criteria
Systolic BP	> 150 mmHg > 200 mmHg ≤ 80 mmHg
Diastolic BP	> 100 mmHg > 110 mmHg
Heart Rate	< 50 bpm > 120 bpm ≥ 30 bpm increase from baseline ≥ 30 bpm decrease from baseline
Respiratory Rate	< 8 breaths/min > 24 breaths/min
Oxygen Saturation	< 95%
Temperature	> 38.3°C increase of ≥ 1.1°C from baseline

All vital signs results will be provided in by-subject data listings.

6.4.4 Telemetry

Telemetry results will be presented in by-subject data listings.

6.4.5 Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters include: HR (beats/min), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec), QTcB interval (msec), QTcF interval (msec), P wave (msec), and T wave (msec). Observed values and changes from baseline for ECG parameters

will be summarized by study part and cohort at each visit and time point. If triplicate reads are taken, the mean of the reads will serve as the observed value at the specific visit and timepoint.

Investigator-reported ECG findings shifts from baseline to each post-baseline visit/timepoint and maximum post-baseline will be summarized by study part and cohort. Categories of Normal, Abnormal – Not Clinically Significant, and Abnormal – Clinically Significant will be included.

Subjects meeting the following potentially clinically significant criteria post-baseline will also be presented:

- 450 msec <QTcF / QTcB ≤ 480 msec
- 480 msec < QTcF / QTcB ≤ 500 msec
- 500 msec < QTcF / QTcB
- 30 msec < QTcF / QTcB change from baseline ≤ 60 msec
- 60 msec < QTcF / QTcB change from baseline

All ECG parameter results will be provided in by-subject data listings.

6.4.6 Electroencephalogram (EEG)

Frequency and percentage of subjects showing any seizure activity and any interictal epileptiform activity in EEG results will be summarized by study part and cohort at each visit and timepoint. All EEG results recorded on the CRF will be presented in by-subject data listings.

6.4.7 Gastrointestinal Symptoms

Frequency and percentage of subjects in Part B (MAD) cohorts experiencing any gastrointestinal symptoms will be summarized by study part and cohort at each visit and any post-baseline. All gastrointestinal symptom assessment results recorded on the CRF will be presented in by-subject data listings.

Gastrointestinal symptom assessments will not be performed for Part A (SAD) subjects.

6.4.8 Columbia Suicide Severity Rating Scale (C-SSRS)

At the Screening Visit, the Baseline/Screening Version of the C-SSRS will be administered to Part B (MAD) subjects to assess lifetime and recent history. The Since Last Visit Version of the C-SSRS will be administered to subjects at each subsequent visit (Day 4 and Day7).

Data from the Baseline/Screening Version and from the Since Last Visit Version of the C-SSRS will be summarized by cohort. The number of subjects with any post-baseline occurrence of suicidal ideation (C-SSRS items 1-5), suicidal behavior (C-SSRS items 6-11), as well as occurrence of individual items at each visit will be summarized by study part and cohort.

C-SSRS results will be presented in by-subject data listings.

C-SSRS assessments will not be collected for Part A (SAD) subjects.

6.4.9 Physical Examinations

Physical examination findings will be presented in by-subject data listings.

6.4.10 Neurological Examinations

Neurological examination findings will be presented in by-subject data listings.

7 REFERENCES

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH E3 Guideline: Structure and content of clinical study reports questions & answers (R1). 2012. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf. Accessed 13 Jan 2016.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports E3. Step 4. 1995. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf. Accessed 13 Jan 2016.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH E9: Statistical principles for clinical trials. 1998. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf . Accessed 15 June 2016.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. 2005. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf. Accessed 17 February 2017.

Hamilton S, Bernstein AB, Blakey G, Fagan V, Farrow T, Jordan D, Seiler W, Shannon A, Gertel A, Budapest Working Group: Developing the Clarity and Openness in Reporting: E3-based (CORE) Reference user manual for creation of clinical study reports in the era of clinical trials transparency. Research Integrity and Peer Review. (2016) 1:4.

PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group. Analyses and Displays Associated with Demographics, Disposition, and Medications in Phase 2-4 Clinical Trials and Integrated Summary Documents. 2014. http://www.phusewiki.org/wiki/images/c/c9/CSS_WhitePaper_DemoDispMed_v1.0.pdf . Accessed 03 Jan 2017.

PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group. Analyses and Displays Associated to NonCompartmental Pharmacokinetics – With a Focus on Clinical Trials. 2014. http://www.phusewiki.org/wiki/images/e/ed/PhUSE_CSS_WhitePaper_PK_final_25March2014.pdf . Accessed 31 Dec 2016.

PhUSE CSS Development of Standard Scripts for Analysis and Programming Working Group. Analyses and Displays Associated with Thorough QT/QTc Studies. 2016.

http://www.phusewiki.org/docs/CSS%20White%20Papers%202016/230316%20CS_WhitePaper_TQTStudies_v1.0.pdf. Accessed 03 Jan 2017.

8 APPENDICES

8.1 APPENDIX 1: Partial Date Conventions

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

Incomplete Adverse Event Start Date

If *year* and *day* are present but *month* is missing, assume that only *year* is present in the steps below.

If the start date is completely missing: set the date to the first dose date.

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

If *year* = year of first dose: set the date to the first dose date.

If *year* < year of first dose: set *month* and *day* to December 31st.

If *year* > year of first dose: set *month* and *day* to January 1st.

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

If *year* = year of first dose, and:

If *month* = month of first dose: set *day* to day of first dose.

If *month* < month of first dose: set *day* to last day of *month*.

If *month* > month of first dose: set *day* to 1st day of *month*.

If *year* < year of first dose: set *day* to last day of month.

If *year* > year of first dose: set *day* to 1st day of month.

Should the imputed start date based on the rules above be after a complete end date, use the end date instead of the date that would otherwise be imputed.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

Incomplete Prior/Concomitant Medication Start Date

If *year* and *day* are present but *month* is missing, assume that only *year* is present in the steps below.

If the start date is completely missing: set the date to the first dose date.

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

Set *month* and *day* to January 1st.

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

Set *day* to 1st day of the month.

Should the imputed start date based on the rules above be after a complete end date, use the end date instead of the date that would otherwise be imputed.

Incomplete Prior/Concomitant Medication End Date

If *year* and *day* are present but *month* is missing, assume that only *year* is present in the steps below.

If the end date is completely missing and ongoing is checked: set the date to the last dose date.

If the end date is completely missing and ongoing is not checked: do not impute.

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

Set *month* and day to December 31st.

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

Set *day* to last day of the month.

Should any of the imputed end dates come before the start date (either complete or imputed) then use the start date instead.

DocuSign

Certificate Of Completion

Envelope Id: 36ADACFC083A43CEA32C3DBD68A90FF8
Status: Completed
Subject: Complete with DocuSign: KTX-101_SAP_v3.0_01SEP2023.docx
Source Envelope:
Document Pages: 28
Signatures: 5
Certificate Pages: 6
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-08:00) Pacific Time (US & Canada)

Envelope Originator:
Anna Tomkins
450 N. Sam Houston Parkway E.,
Suite 250
Houston, TX 77060
anna.tomkins@allucent.com
IP Address: 136.54.38.79

Record Tracking

Status: Original
9/1/2023 9:34:44 AM
Holder: Anna Tomkins
anna.tomkins@allucent.com
Location: DocuSign

Signer Events	Signature	Timestamp
Anna Tomkins anna.tomkins@allucent.com Biostatistician I Allucent Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: DF9122CE-95F1-4F65-A641-742B8CBEA101 Using IP Address: 136.54.38.79 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2023 9:40:12 AM Viewed: 9/1/2023 9:40:55 AM Signed: 9/5/2023 11:17:39 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Kris Chowning kris.chowning@allucent.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 7BAD86AA-A25B-4294-8E19-C98703ABE0AD Using IP Address: 67.197.102.194 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2023 9:40:15 AM Resent: 9/11/2023 6:53:33 AM Viewed: 9/11/2023 7:10:59 AM Signed: 9/11/2023 7:13:06 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
Margaret Doherty mmdherty@bigpond.net.au Security Level: Email, Account Authentication (Required)	DocuSigned by: Margaret Doherty Signer Name: Margaret Doherty Signing Reason: I have reviewed this document Signing Time: 07-Sep-2023 | 14:39 AEST 4E39EEBE639D4B2BA39D2AD8E2B2D74D Signature Adoption: Pre-selected Style Signature ID: 4E39EEBE-639D-4B2B-A39D-2AD8E2B2D74D Using IP Address: 138.130.34.245 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 9/1/2023 9:40:13 AM Viewed: 9/6/2023 9:39:26 PM Signed: 9/6/2023 9:40:17 PM
Electronic Record and Signature Disclosure: Accepted: 9/6/2023 9:39:26 PM ID: 11ad89ef-f6c4-4a72-bbc1-754197e78566		
Sharon Hanegraaf shanegraaf@kinoxistherapeutics.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Sharon Hanegraaf Signer Name: Sharon Hanegraaf Signing Reason: I approve this document Signing Time: 10-Sep-2023 | 22:32 PDT E7070EEDB3434EFAB8E77B267DAF7C50 Signature Adoption: Pre-selected Style Signature ID: E7070EED-B343-4EFA-B8E7-7B267DAF7C50 Using IP Address: 101.182.36.8 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2023 9:40:14 AM Viewed: 9/10/2023 10:31:49 PM Signed: 9/10/2023 10:32:46 PM
Electronic Record and Signature Disclosure: Accepted: 9/10/2023 10:31:49 PM ID: bd0aa5ea-d927-4d8b-ac09-e165fb1a2f8b		
Tina Soulis tina.soulis@kinoxistherapeutics.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Signer Name: Tina Soulis Signing Reason: I approve this document Signing Time: 01-Sep-2023 | 15:20 PDT 36CBF7C99E42455A833E326D6D6A1F8A Signature Adoption: Drawn on Device Signature ID: 36CBF7C9-9E42-455A-833E-326D6D6A1F8A Using IP Address: 101.181.69.56 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2023 9:40:15 AM Viewed: 9/1/2023 3:20:14 PM Signed: 9/1/2023 3:21:42 PM
Electronic Record and Signature Disclosure: Accepted: 9/1/2023 3:20:14 PM ID: 5f6b6c32-edb8-41aa-a5f6-39451c5715f7		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	9/1/2023 9:40:15 AM
Certified Delivered	Security Checked	9/1/2023 3:20:14 PM
Signing Complete	Security Checked	9/1/2023 3:21:42 PM
Completed	Security Checked	9/11/2023 7:13:06 AM
Payment Events	**Status**	**Timestamps**
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Allucent - Regulated Account (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Allucent - Regulated Account:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: Liaty.Port@allucent.com

To advise Allucent - Regulated Account of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at Liaty.Port@allucent.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Allucent - Regulated Account

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to Liaty.Port@allucent.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Allucent - Regulated Account

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to Liaty.Port@allucent.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Allucent - Regulated Account as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Allucent - Regulated Account during the course of your relationship with Allucent - Regulated Account.

DocuSigned by:
Margaret Doherty
Signer Name: Margaret Doherty
Signing Reason: I have reviewed this document
Signing Time: 07-Sep-2023 | 14:39 AEST

07-Sep-2023 | 14:40 AEST

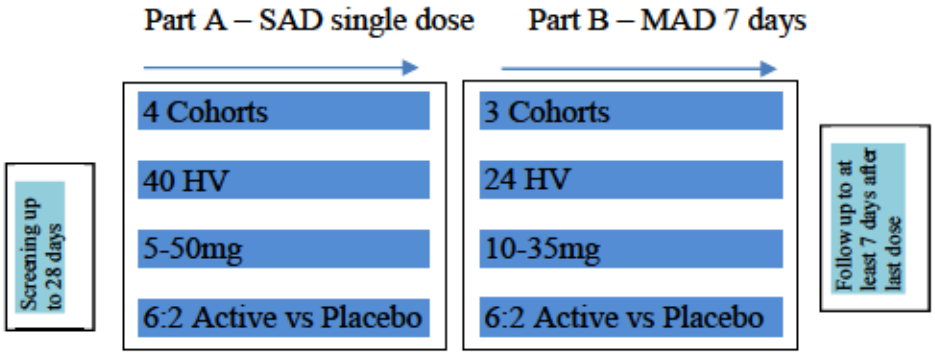
PK Section Author: Margaret Doherty
Consultant Pharmacokineticist

Date

Part B (MAD) will evaluate up to 3 doses based on the doses established during Part A (SAD). Each subject in Cohorts 1 and 2 will receive study drug for 7 days, administered once daily. Subjects in Cohort 3 will receive study drug for 7 days, administered twice daily. All subjects in each Part B (MAD) cohort will have their AE, PK, and electroencephalography (EEG) data, acquired up to and including Day 8, evaluated for safety and tolerability by the CRC before opening the next higher dose cohort. Subjects will be housed in the clinic from Day -3 prior to study drug administration and will remain in-house for 24 hours post morning dose (Day 8) for PK and safety assessments.

The study will be comprised of 3 periods: Screening (up to 28 days); Treatment (1 day for Part A (SAD) subjects and 7 days for Part B (MAD) subjects); and Follow-up. Subjects will have a follow-up visit 7 days after the last dose. As SAD dosing is a single dose on Day 1, follow-up will occur on Day 7. Part B (MAD) Cohorts 1 and 2 dosing involves single daily dosing on Days 1 to 7, with a follow-up visit occurring on Day 14. Part B (MAD) Cohort 3 dosing involves twice daily dosing on Days 1 to 7, with a follow-up visit occurring on Day 14.

Figure 1. Study Phases and Activities



3.2 Randomization and Blinding

Subjects will be centrally randomized to treatment in a 6:2 ratio within each assigned cohort. The first 2 sentinel subjects will be assigned to treatment in a 1:1 ratio such that 1 subject receives KNX100 and the other receives placebo. Once eligibility is re-confirmed (Day -1), subjects will be randomized via a randomization list.

The study will be performed in a double-blind fashion. The investigator and study staff (including lab personnel), the subjects, the monitors, and the Sponsor's staff will remain blinded to treatment assignment until database lock. The investigator will receive sealed envelopes with the individual randomization per subject to be opened in the case of emergency only. To ensure study blinding, the active and placebo will be provided in identical capsules and an equivalent number of capsules will be administered to subjects receiving placebo.

The site pharmacy staff will be unblinded. Additionally, the following roles may be unblinded: Unblinded biostatistics team that prepares the randomization materials and handles treatment-revealing data prior to database lock; selected study Sponsor personnel who are not directly involved in the conduct of the study; and the drug-reconciliation clinical research associate (CRA). A list of unblinded individuals will be maintained in study files.

Signer Events	Signature	Timestamp
Margaret Doherty mmdherty@bigpond.net.au Security Level: Email, Account Authentication (Required)	DocuSigned by: Margaret Doherty Signer Name: Margaret Doherty Signing Reason: I have reviewed this document Signing Time: 07-Sep-2023 | 14:39 AEST 4E39EEBE639D4B2BA39D2AD8E2B2D74D Signature Adoption: Pre-selected Style Signature ID: 4E39EEBE-639D-4B2B-A39D-2AD8E2B2D74D Using IP Address: 138.130.34.245 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document	Sent: 9/1/2023 9:40:13 AM Viewed: 9/6/2023 9:39:26 PM Signed: 9/6/2023 9:40:17 PM
Electronic Record and Signature Disclosure: Accepted: 9/6/2023 9:39:26 PM ID: 11ad89ef-f6c4-4a72-bbc1-754197e78566		
Sharon Hanegraaf shanegraaf@kinoxistherapeutics.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Sharon Hanegraaf Signer Name: Sharon Hanegraaf Signing Reason: I approve this document Signing Time: 10-Sep-2023 | 22:32 PDT E7070EEDB3434EFAB8E77B267DAF7C50 Signature Adoption: Pre-selected Style Signature ID: E7070EED-B343-4EFA-B8E7-7B267DAF7C50 Using IP Address: 101.182.36.8 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2023 9:40:14 AM Viewed: 9/10/2023 10:31:49 PM Signed: 9/10/2023 10:32:46 PM
Electronic Record and Signature Disclosure: Accepted: 9/10/2023 10:31:49 PM ID: bd0aa5ea-d927-4d8b-ac09-e165fb1a2f8b		
Tina Soulis tina.soulis@kinoxistherapeutics.com Security Level: Email, Account Authentication (Required)	DocuSigned by: Signer Name: Tina Soulis Signing Reason: I approve this document Signing Time: 01-Sep-2023 | 15:20 PDT 36CBF7C99E42455A833E326D6D6A1F8A Signature Adoption: Drawn on Device Signature ID: 36CBF7C9-9E42-455A-833E-326D6D6A1F8A Using IP Address: 101.181.69.56 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/1/2023 9:40:15 AM Viewed: 9/1/2023 3:20:14 PM Signed: 9/1/2023 3:21:42 PM
Electronic Record and Signature Disclosure: Accepted: 9/1/2023 3:20:14 PM ID: 5f6b6c32-edb8-41aa-a5f6-39451c5715f7		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**