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Syndax Pharmaceuticals

STATISTICAL ANALYSIS PLAN

A Phase 1/2, Open-Label, Dose Escalation and Dose Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Activity and Efficacy of SNDX- 6352 in Subjects with Active Chronic Graft Versus Host Disease who have Received at least 2 Lines of Prior Therapy

SNDX-6352-0503

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REVISION HISTORY

Version/Date	Section	Changes implemented
Final 1.0/01Mar2022	Not Applicable	Not Applicable
Final 2.0/04Jan2023	Section 3.3.1	Updated with additional summary on patients who started axatilimab taper
	Section 3.2.7	Clarified the application of Analysis Sets on tables and figures
	Section 3.6	Updated to reflect the taper dosing schedule
	Section 3.7	Added definition for time to response
	Section 3.8.4	Tabular summary of abnormal and normal findings of ECG was removed as listing will be sufficient
	Section 3.8.5	Additional details on ADA analysis were added to be consistent with other studies in the program
	Section 3.9	Additional details on PK analysis were added
	Appendix 6.2, 6.3	Removed Appendix 6.2 and 6.3 as CTCAE v5.0 will be used as reference

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LIST OF ABBREVIATIONS

Abbreviation Term	Description
AE	Adverse Event
ADA	Antidrug Antibody
ADaM	Analysis Dataset Model
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
$AUC_{0\text{-}inf}$	Area under the Plasma Concentration-Time Curve from Time 0 Extrapolated to Infinity
$AUC_{0\text{-}t}$	Area under the Plasma Concentration-Time Curve from Time zero to the Last Measurable Concentration
BAP	Bone Alkaline Phosphatase
BMI	Body Mass Index
BQL	Below the Quantifiable Limit
BUN	Blood Urea Nitrogen
cGVHD	Chronic Graft vs. Host Disease
CI	Confidence Interval
CIOMS	Internationals Organizations of Medical Sciences
C_{max}	Maximum Plasma Concentration
CR	Complete Response
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram

Abbreviation Term	Description
eCRF	electronic case report form
EOT	End of Treatment
FAS	Full Analysis Set
FFS	Failure Free Survival
HCT	Hematocrit
HGB	Hemoglobin
HR	Hazard Ratio
irAEs	Immune-Related Adverse Events
ITT	Intent-to-Treat
IV	Intravenous
Kg	Kilograms
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
MTD	Maximum-Tolerated Dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural Killer
OBD	Optimal Biologic Dose
ORR	Overall Response Rate
PK	Pharmacokinetic
PR	Partial Response

Abbreviation Term	Description
PT	Preferred Term
PT/INR	Prothrombin Time or International Normalized Ratio
RBC	Red Blood Cell
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class
$t_{1/2}$	Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time at which Maximum Plasma Concentration was Observed
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
λ_z	Terminal Elimination Rate Constant

1. INTRODUCTION

Clinical Trial SNDX-6352-0503 is an open-label Phase 1/2 dose escalation and dose expansion study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and efficacy of SNDX-6352 in subjects with active chronic Graft versus Host Disease (cGVHD) who have failed at least 2 prior lines of systemic therapy. The study will consist of a Screening period, a Treatment period, and a Safety Follow-up period.

This SAP contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report for Protocol SNDX-6352-0503. The statistical methods and analyses described here are based on those presented in the study protocol (Version 10.0, 12 Apr 2022).

2. STUDY SUMMARY

2.1 STUDY OBJECTIVES

Study objectives are summarized in protocol Section 3.

2.2 STUDY ENDPOINTS

2.2.1 Primary Endpoint of Phase 1

Optimal biologic dose (OBD) and recommended phase 2 dose (RP2D) of SNDX-6352

2.2.2 Secondary Endpoints of Phase 1

Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)

Plasma PK of SNDX-6352

Changes from baseline in CSF-1, IL-34 levels and their association with cGVHD response

Changes from baseline in circulating monocyte number and phenotype (CD14/16)

Changes from baseline in inflammation biomarkers that may include MCP1, CCL3 and CCL5 expression

Presence of ADA

2.2.3 Exploratory and Pharmacodynamic Endpoints of Phase 1

[redacted]

2.2.4 Primary Endpoint of Phase 2 Expansion

Proportion of subjects with CR or PR (ORR) at Cycle 7 Day 1 (Day 168)

2.2.5 Secondary Endpoints of Phase 2 Expansion

Frequency and severity of AEs and SAEs

Best Overall Response (BOR)

FFS

DOR

SRR (CR or PR ≥ 20 weeks)

Organ specific response based on 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD

Joints and fascia response based on refined NIH response algorithm for cGVHD

Changes in subject-reported symptom activity using the Lee cGVHD symptom scale

Proportion of subjects with a ≥ 7-point improvement in normalized score using the Lee cGVHD symptom scale.

Percent reduction in average daily dose (or equivalent) of corticosteroid

Proportion of subjects who discontinue corticosteroid use after study entry

Percent reduction in average daily dose (or equivalent) of calcineurin inhibitor

Proportion of subjects who discontinue calcineurin inhibitor after study entry

2.2.6 Exploratory and Pharmacodynamic Endpoints of Phase 2

[redacted]

2.3 STUDY DESIGN

Phase 1 of Study SNDX-6352-0503 is the dose escalation phase and Phase 2 is the dose expansion phase. The dose escalation rules were defined in protocol Section 4.

2.3.1 Number of Subjects and Sample Size Considerations

Phase 1 Dose Escalation: Up to 30 subjects will be enrolled in this study.

Phase 2 Dose Expansion: A maximum of 22 subjects will be enrolled. A true ORR of 60% is hypothesized. A response rate greater than 30% is considered the lower threshold. The number of responders needed to declare the study a success was based on single proportion binomial test with 91% power and 1-sided significance level of 5%. Ninety percent 2-sided confidence interval of the observed one sample proportion will be calculated. The trial will be considered a success if the lower limit of 90% confidence interval is greater than 30%. Eleven responders out of 22 subjects will provide the lower limit of 90% confidence interval of 31.1% (90% CI [31.1%, 68.9%]).

2.3.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.2 of the protocol).

2.3.2.1 Response Determination according to 2014 NIH Consensus definitions

Overall physician- assessed responses will be evaluated as defined by the 2014 NIH Consensus Development Project on Clinical trials in cGVHD (Lee 2015). CR is defined as resolution of all manifestations in each organ or site, and PR is defined as improvement in at least 1 organ or site without progression in any other organ or site. Table 1 contains the Working Group proposed consensus definitions of CR, PR and progression for assessment of organ specific responses as well as a global response determination.

Table 1: Response Determination for Chronic GVHD Clinical Studies based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1

Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 ULN
Lungs	Normal %FEV1 after previous involvement If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	Increase by 10% predicted absolute value of %FEV1 If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	Decrease by 10% predicted absolute value of %FEV1 If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN = upper limit of normal.
Source: (Lee 2015)

2.3.2.2 Physician-Reported Global and Organ Specific cGVHD Activity Assessment

Changes in cGVHD severity as defined by the NIH 2014 Consensus Criteria will be evaluated using physician-reported global and organ-specific cGVHD activity assessment form (Appendix 1). The clinicians will provide a subjective assessment of current overall chronic GVHD severity on a 4-point scale (no chronic GVHD, mild, moderate, severe) independent of the recorded NIH global severity score (Table 1, last line) and their evaluations of cGVHD changes since the last assessment. Key organ assessments include skin, mouth, liver, upper and lower GI, esophagus, lung, eye, and joint/fascia .

2.3.2.3 Patient-Reported cGVHD Activity Assessment

Changes in patient-reported symptom activity will be evaluated using the cGVHD Lee symptom scale (Lee 2002), which has been recommended for use by the 2005 and 2104 National Institutes of Health (NIH) Consensus Conferences to capture cGVHD symptoms.

The Lee cGVHD symptom questionnaire asks subjects to indicate the degree of "bother" that they experienced during the past 7 days due to symptoms in 7 domains potentially affected by chronic GVHD (Lee, 2002). Published evidence supports its validity, reliability, and sensitivity to cGVHD severity (Lee, 2015; Merkel, 2016). Seven-point improvement in normalized score using the Lee cGVHD symptom scale is considered clinically meaningful.

For each subscale, if >=50% of the items are non-missing/complete, the total score is calculated as the sum of the non-missing item-level scores and use the following formula to transform the scores to 0-100:

$$Transformed\ score = (sum\ of\ item\ scores) * 100/(4 * m) * \left(\frac{m}{No.\ of\ nonmissing\ items}\right)$$

where m= total number of items in the subscale (see Section 10.5.2 of the protocol). If <50% of the items in the subscale are non-missing/complete, then set the total score for this subscale to be missing.

For the overall total score, if ≥4 subscale scores are non-missing/available, then the overall total score is calculated as the average of the non-missing/available subscale scores. If <4 subscale scores are non-missing/available, then the overall total score is set to be missing.

2.3.3 Pharmacokinetic Assessments

Plasma samples will be collected to assess the PK of SNDX-6352. SNDX-6352 levels in plasma samples will be determined using a validated enzyme-linked immunosorbent assay (ELISA). One (1) blood sample will be collected at the time points specified in the SoA (Section 1.2 of the protocol).

On each PK sample collection day, the time and date of SNDX-6352 administration, the start and stop time of SNDX-6352 administration, and the time and date of PK sample collection should be recorded in the eCRF.

2.3.4 Pharmacodynamics and Exploratory Endpoints

The details on pharmacodynamics and exploratory endpoints are specified in Section 8.6 of the protocol.

2.3.5 Biomarkers

The following blood samples will be collected from all subjects in this study and the immune correlate analyses biomarker research may be performed.

Levels of blood immune parameters that may include CSF-1, IL-34, IFN-gamma, IL-1beta, IL-2, IL-4, IL-5, IL-6, CXCL8/IL-8, IL-10, IL-12 (p70), IL-13, TNF-alpha and sCD163, CD204/206 and change from baseline compared to PK, safety endpoints

Levels of circulating classical and non-classical monocytes and change from baseline compared to PK, safety endpoints

Analysis of numbers of circulating immune cell subsets including CD8+ T cells, CD4+ T cells, B cells, natural killer (NK) cells and change from baseline compared to PK and safety endpoints

2.3.6 Safety Assessments

The following assessments will be performed to evaluate the safety profile of SNDX-6352 at the timepoints specified in SoA (Section 1.2 of the protocol).

Vital signs: temperature, pulse rate, respiration rate, blood pressure (systolic and diastolic), and weight

Body height (at Screening only)

Karnofsky/Lansky Performance Scale

Triplicate 12-lead ECGs

Neurological examination

AE and SAE recording

Safety laboratory assessments

2.3.7 Other Assessments

Other assessments include patient demographics, medical and disease history, prior medications, physical examinations, SNDX-6352 administration and accountability, concomitant medications and procedures, protocol deviations, post-treatment anti-cancer therapy, and clinical disease assessment, collected per Schedule of Activities

(Protocol Section 1.2).

3. STATISTICAL METHODS

3.1 General Methods

Phase 1 and Phase 2 will be summarized separately. For Phase 1, summary statistics will be provided at each dose level and all those dose levels combined. For Phase 2, summary statistics will be provided at 1 mg/kg Q2W. Summary of Phase 1 and Phase 2 combined may also be performed. In general, subject listings will be provided to support summary tables.

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher. Programming specifications will be prepared, which describe the datasets and variables created for this study. The datasets will be prepared using the most recent version of CDISC's Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM).

3.1.2 Reporting of Numerical Values

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables. Percentages will be based on the number of subjects with non-missing assessments. If there are missing values, the number missing will be presented, but without a percentage.

Means and medians will be reported to one decimal place more than the data reported in the clinical data management system. Standard deviations will be reported to two decimal places more than the data reported. Minimum and maximum will be reported to the same number of decimal places displayed in the clinical data management system.

3.1.3 Baseline Value and Change from Baseline

Baseline will be defined as the most recent, non-missing value obtained prior to the first dose of any study drug (SNDX-6352).

Change from baseline will be calculated by subtracting the baseline value from the on-study assessment for each patient (i.e., post-dose – baseline).

Percent change from baseline is calculated as (post-dose assessment – baseline value)/baseline value x 100.

3.1.4 Handling of Missing/Incomplete Values

Adverse events

Missing and incomplete adverse event start dates will be imputed based on the algorithm described below. The algorithm will be used only if the end date of the adverse event (if reported) indicates the event was not resolved before the first administration of study drug. The purpose of the imputation is to determine if an adverse event with a missing or incomplete start date is treatment emergent. Imputed adverse event dates will not be used to calculate the duration of adverse event episodes.

Case 1: if year portion of AE start date is missing, then missing AE start date = first dose date;

Case 2: if year portion of AE start date = year portion of first dose date, then,

> If month portion of AE start date is missing, then missing AE start date = first dose date.
> If month portion of AE start date = month portion of first dose date, then missing AE start date = first dose date.
> If month portion of AE start date is not equal to month portion of first dose date, then onset day of AE start date will be set to 1st day of the AE start month.

Case 3: if year portion of AE start date > year portion of first dose date, then,

> If month portion of AE start date is missing, then onset day and month of AE start date is set to January 1.
> If month portion of AE start date is not missing, then onset day of AE start date is set to 1st day of the AE start month.

Medications

When determining prior or concomitant medications, partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be

assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, medication will be assumed to be ongoing. In the case of complete missing start date, medication will be assumed to be prior medication.

Lee cGVHD Symptom Score

For handling of missing data in Lee cGVHD symptom questionnaire, please refer to Section 2.3.2.3.

cGVHD diagnosis

Missing date of cGVHD diagnosis will imputed based on the rule below:

If month and day are missing, the date is set to June 30
If day is missing, the date is set to the 15th of the month

3.2 Analysis Sets

3.2.1 Enrolled (Intent-to-treat) Set

The Enrolled Set is defined as all subjects who sign the ICF and were enrolled into the study.

3.2.2 Full Analysis Set

The Full Analysis Set (FAS) is a subset of all enrolled subjects, with subjects excluded for the following reasons:

- Failure to receive at least one dose of SNDX-6352
- Lack of baseline data for those analyses that require baseline data

3.2.3 Evaluable Analysis Set

The Evaluable Analysis Set is defined as all subjects who have received at least 1 dose of treatment and have at least one post baseline response assessment unless the subject drops out early due to progression or treatment related AE.

3.2.4 Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least one dose of study drug.

3.2.5 Pharmacokinetic Analysis Set

The PK Analysis Set will include all treated subjects who have at least one plasma concentration measured.

3.2.6 Pharmacodynamic Analysis Set

The PD Analysis Set will include all treated subjects who have evaluable PD samples at one or more scheduled collections.

For skin biopsy and lung biopsy specimens, subjects with baseline and/or post dose samples will be evaluated.

3.2.7 Applications of Analysis Sets

Unless otherwise noted, the analysis sets that will be used for table summaries of each type is provided in the following table.

Table 2: Application of Analysis Sets on Tables and Figures

Type	Safety	Enrolled	Evaluable
Summary of analysis sets		X	
Disposition	X		
Protocol deviations	X		
Demographics	X		
Baseline characteristics	X		
Medical history	X		
Treatment exposure	X		
Safety evaluations	X		
Efficacy evaluations			
Response-related analyses and Lee Symptom Scale analysis	X		X
Failure free survival and reduction in	X		

corticosteroid or calcineurin inhibitor use			

3.3 Disposition and Evaluability

3.3.1 Disposition

The numbers of subjects who were screened, enrolled, dosed, and the reasons for discontinuation of study intervention and reasons for discontinuation of study will be summarized.

The number of patients who started axatilimab taper, and reasons for discontinuation of study intervention for those who started axatilimab taper, will also be summarized.

3.3.2 Protocol Deviations

Protocol deviations will be presented in a subject listing.

3.4 Demographics and Baseline Characteristics

3.4.1 Demographics

Summary statistics will be presented for age, sex, race, ethnicity, weight (kg), height (cm), and body surface area (m^2) in Safety Analysis Set.

Body surface area will be calculated using the Mosteller formula:

$$\text{Body surface area} = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$$

3.4.2 Baseline Disease Characteristics

The following baseline disease characteristics variables will be summarized in Safety Analysis Set:

Number of transplants
Type of transplant
Type of donor
HLA matching of cell graft between donor and recipient

Stem cell source
Time from transplant
Time from transplant to diagnosis of cGVHD
Time from initial cGVHD diagnosis to first dose
Number of involved organs
Involved organ
Karnofsky/Lansky Performance Status
Number of prior lines of treatment of cGVHD
Systemic prednisone (or equivalent) dose at C1D1 (mg/kg)
Systemic calcineurin use at C1D1
Prior ibrutinib therapy
Prior ruxolitinib therapy
Prior belumosudil therapy

If the date of diagnosis is missing the day and/or month, the algorithm specified in Section 3.1.4 for incomplete dates will be used.

3.4.3 Medical History, Prior Medications, and Physical Exam

Data regarding medical history, prior medications, and clinically significant findings from the physical and neurological exam will be presented in subject listings for the Safety Analysis Set.

3.5 Concomitant Medications

Concomitant medications are defined as any medication that was taken on or after the first dose of study medication. If the start and stop dates of the concomitant medication do not clearly define the period during which a medication was taken, it will be assumed to be a concomitant medication.

All medications will be coded using the World Health Organization (WHO) Drug Dictionary (September 2020 or later). The numbers and percentages of subjects taking concomitant medication will be presented for the Safety Analysis Set for both Phase 1 and Phase 2.

3.6 Treatment Exposure

The Safety Analysis Set will be used for summarizing treatment exposure.

The total number of cycles started, and the total number of cycles started by category (≥1, ≥2, ≥3, so on) will be tabulated. The treatment duration and cumulative dose of SNDX-6352 administered (in mg/kg) will be calculated. These data will be further summarized by calculating the mean, standard deviation, median, and range of these values. Treatment duration is defined as (minimum of [last dose date + x, death date] – first dose date)/7, where x=14, 28, or 56 if the last dose occurred in a cycle with Q2W, Q4W, or Q8W dosing, respectively. The actual dose intensity is calculated as [actual cumulative dose/(treatment duration)]*100. Relative dose intensity (RDI) is defined as actual dose intensity / planned dose intensity * 100, where planned dose intensity is defined as total planned dose (i.e. starting dose * number of cycles * 2 for Q2W, or 1 for Q4W) divided by planned treatment duration (i.e. number of cycles started * 4). For patients who are on axatilimab taper, the taper dose during taper will be considered as planned dose. Relative dose intensity for the first 6 cycles will also be summarized. The number and proportion of subjects with one or more dosage modification (i.e., interruptions, reductions, or delay) will be tabulated along with the reasons for dosage modification.

3.7 Efficacy Analysis

For response related endpoints, the primary analysis set will be Safety Analysis Set and Evaluable Analyses set will be used as sensitivity analysis. Analysis for FFS and reduction in corticosteroid or calcineurin inhibitor use will be conducted in Safety Analysis Set.

ORR at Cycle 7 Day 1 (Day 168) and BOR

Responses by each organ (Skin, Eyes, Mouth, Esophagus, Upper GI, Lower GI, Liver, Lungs, Joints and Fascia and global) will be assessed using the NIH Consensus Development Project on Clinical trials (Table 1).The overall response at each visit will be derived using physician reported assessment for each organ based on the rule in Section 2.3.2.1. Best overall response will be derived based on response across all post-baseline visits. Best overall response will be categorized as complete response, partial response, no change, progression and other. ORR at Cycle 7 Day 1 is defined as CR and PR at Cycle 7 Day 1. Exact 95% confidence intervals (CIs) using binomial distribution will be calculated for ORR at Cycle 7 Day 1 at each dose and all those dose

levels combined for Phase 1 and at 1 mg/kg Q2W for Phase 2. Exact 90% CI for ORR at Cycle 7 Day 1 will also be calculated for Phase 2.

ORR by Cycle 7 Day 1 and ORR will be conducted as supportive analyses. ORR by Cycle 7 Day 1 is defined as CR or PR by Cycle 7 Day 1, and ORR is defined as CR or PR at any post-baseline visit. Exact 95% confidence intervals (CIs) using binomial distribution will be calculated.

Time to response is defined as the time from first dose of study intervention to the date of first CR or PR.

Failure Free Survival (FFS)

Failure Free Survival (FFS) is defined as the time from first dose of study intervention to unequivocal progression of cGVHD, or addition of another systemic immune suppressive therapy, or relapse of underlying malignancy, or discontinuation of study treatment due to toxicity, or death for any reason whichever date occurs first. Unequivocal progression of cGVHD is defined as treatment discontinuation due to clinical progression.

Subjects who either didn't start another treatment at the end of study or didn't progress/relapse or are alive or didn't discontinue study treatment due to toxicity (as of the data analysis cutoff date) will be censored at the last visit date.

The duration of FFS as determined by the NIH 2014 Consensus Criteria will be evaluated using organ-specific cGVHD activity assessment form and will be summarized descriptively using the Kaplan-Meier method. FFS at 6 months and 12 months will be estimated using Kaplan-Meier method.

Duration of Response (DOR)

Duration of response will be calculated for subjects who achieve CR or PR. For such subjects, DOR is defined as the time from the start date of the PR or CR (whichever response occurs first) to documented progression or start of another systemic treatment. The date of progression or censoring for DOR will be determined according to the conventions listed in Table 3. DOR will be summarized using the Kaplan-Meier method.

Table 3. Date of Progression or Censoring for Duration of Response

Situation	Date of Event or Censoring	Outcome
Documented progression	Date of documented progression	Event
Started another systemic treatment without documented progression	Date of first dose for another systemic treatment	Event
Without another systemic therapy and without documented progression	Date of last evaluable disease assessment	Censored

Sensitivity analysis for DOR, defined as the time from the start date of initial response of CR or PR to documented progression from best response or start of another systemic treatment, whichever is earlier will also be performed. The date of progression or censoring for DOR will be determined according to the conventions listed Table 3.

Sustained Response Rate

The proportion of subjects with sustained response, defined as CR or PR ≥ 20 weeks (at least 20 weeks from the time of initial response), will be summarized. Exact 95% confidence intervals (CIs) will be calculated.

Changes in Subject-Reported Symptom Activity

Changes in subject-reported symptom activity will be assessed using the Lee cGVHD Symptom Scale summary score (Section 2.3.2.3).

The proportion of subjects with a ≥ 7-point improvement in normalized score using the Lee cGVHD Symptom Scale in patients with baseline and at least one post-baseline assessment and exact 95% CIs using binomial distribution will be calculated.

Responses by Organ System

The proportion of subjects with a response (CR/PR) with skin, eyes, mouth, esophagus, upper GI, lower GI, liver, lungs, and joints and fascia will be summarized using the NIH Consensus Development Project on Clinical trials (See Table 1). Exact 95% confidence intervals (CIs) using binomial distribution will be calculated. Joints and fascia response based on refined NIH response algorithm for cGVHD (Inamoto, 2020)

will be summarized.

The proportion of subjects with a joint and fascia response based on refined NIH response algorithm for cGVHD and exact 95% CIs using binomial distribution will be calculated.

Reduction in Corticosteroid or Calcineurin Inhibitor Use

The best percent change in corticosteroid use (percent reductions in the average daily dose of prednisone (or equivalent) after study entry) will be summarized.

The proportion of subjects who discontinue corticosteroids after study entry and along with exact 95% CIs will be calculated. The same analysis will be repeated for calcineurin inhibitor use.

3.8 Safety Analysis

Safety analyses will be performed on the Safety Analysis Set.

3.8.1 Adverse Events

AEs are classified as related, possibly related, probably related, unlikely related or unrelated to study treatment. Any AEs with missing or unknown relationship will be considered as related to study treatment.

All AEs will be coded according to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 24.0 or later).

TEAEs are defined as any AE occurring or worsening in severity after the administration of study drug and within 90 days of last administration of study drug.

TEAEs will be summarized by system organ class (SOC) and preferred term (PT) by each dose level and all dose levels combined. All summaries will be ordered by decreasing frequency of total number of subjects in all dose levels combined category within SOC. In the case of equal frequency of number of patients, summaries of AEs will be sorted alphabetically.

If AE start dates are completely missing or partially missing, the date imputation rules described previously in Section 3.1.4 will be applied for the determination of treatment-emergence. This algorithm will be used only if the end date of the AE (if reported) indicates the event was not resolved before the first administration of study

drug. Imputed AE dates will not be used to calculate the duration of AE episodes.

For the phase 1, the observed DLT rate in each dose cohort will be calculated by the proportion of subjects who experienced DLT.

The following AEs will be summarized:

- TEAEs by SOC and PT
- TEAEs by PT
- Most common TEAEs (occurred in > 10% of patients) by PT
- Drug-related TEAEs by PT
- Most common drug-related TEAEs (occurred in > 10% of patients) by PT
- Grade ≥ 3 TEAEs by PT
- Drug-related grade ≥ 3 TEAEs by PT
- TEAEs leading to study drug discontinuation by PT
- Related TEAEs leading to study discontinuation by PT
- Serious TEAEs by SOC and PT
- Serious TEAEs by PT
- Drug-related serious TEAEs by PT
- AESI by PT
- Drug-related AESI by PT
- Fatal AE by PT
- TEAE by PT and severity

SOCs will be sorted alphabetically. Within an SOC, PTs will be presented by decreasing incidence overall. Incidences of SAEs, and incidence of related SAEs by PT only, will be presented by decreasing incidence overall.

For subjects experiencing the same PT at multiple severities, the occurrence of the AEs with the greatest severity will be used in the analysis of incidence by severity. For subjects experiencing the same PT at multiple relationship levels, the occurrence of the AEs with the strongest relationship to study drug will be used in the analysis of incidence by relationship to study drug.

All reported AEs, regardless of whether they were treatment-emergent, will be included in subject listings. Listings of all AEs leading to discontinuation of study drug will also be provided.

3.8.2 Laboratory Evaluations

The absolute values and change from baseline for each of these post-baseline values will be summarized.

Whenever available, laboratory values will be assigned toxicity grades using the NCI-CTCAE, version 5.0. Analyses will be performed for shifts in NCI CTCAE toxicity grades relative to the baseline toxicity grade. Similar analyses may be performed for shifts above or below the normal range for selected laboratory tests.

Percentages will be based on the total number of subjects with a baseline assessment and at least one post-baseline assessment for the given laboratory parameter. Laboratory test groupings and standard normal ranges are described in Appendix 6.1, and CTCAE toxicity grades for hematology and chemistry parameters are based on CTCAE v5.0, respectively.

3.8.3 Vital Signs

Change from baseline for vital signs (temperature, pulse, systolic/diastolic blood pressure, respiration rate, and weight) will be summarized over time.

3.8.4 ECG

Electrocardiogram results will be listed in terms of subjects with abnormal and normal findings, as reported by the Investigator, at the time points at which ECGs were assessed.

Change in from baseline for ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTcF will be summarized. QTc will be calculated using Fridericia's correction (QTcF).

Subject listings of ECG overall interpretation as well as all ECG parameters will be provided.

3.8.5 ADA

Negative ADA

A sample that has been evaluated as negative in the ADA screening assay will be

considered negative. Samples that are determined to be positive in the ADA screening assay, but the result is not confirmed in the ADA confirmatory assay, will be considered negative.

Positive ADA

A sample that has been evaluated as positive in both the ADA screening and confirmatory assays will be considered positive.

Positive Neutralizing ADA

A sample that has been evaluated as positive in the neutralizing ADA assay will be considered positive.

A patient is considered ADA positive if at least one post-baseline sample is ADA positive.

Treatment-induced ADA positivity is defined as detection of post-baseline ADA in patients negative at baseline.

Treatment-boosted ADA positivity is defined as detection of four-fold change in post-baseline ADA titers in patients who have detectable ADA at baseline.

The overall percentage of subjects with at least one ADA positive sample will be provided. The overall percentage of subjects with at least one neutralizing ADA positive sample will be provided. The overall percentage of ADA positive patients, treatment-induced ADA positive patients, and treatment-boosted ADA positive patients will also be provided.

3.9 Pharmacokinetic Analysis

PK analysis set will be used to describe the pharmacokinetic parameters of C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$, λ_z, as data permit. The PK parameters for the plasma concentrations of SNDX-6352 will be calculated via non-compartmental methodsusing the Phoenix WinNonlin™ software package. The PK parameters will be summarized using descriptive statistics to include mean, standard deviation, minimum, median, maximum, percent coefficient of variation (CV%), geometric mean, and geometric CV%.

The effects of patient factors (e.g., demographics, clinical chemistries, and disease) on SNDX-6352 PK may be evaluated. In addition, the relationship between SNDX-6352 exposure parameters and indicators of safety may be assessed. Descriptive analyses may be performed to summarize the PK of SNDX-6352 and ADA for time points at which both are collected.

All measurable plasma concentrations will be used for the analysis. For concentration values reported as no Results/not Reportable (NR), values will be treated as missing. Values below the quantifiable limit (BQL) that occur prior to the first measurable concentration will be treated as zero. All other BQL values will be treated as missing.

The mean plasma concentration over time by treatment and the individual subject plasma concentration versus time data will be plotted. Nominal times will be used for plotting the mean plasma concentrations over time by treatment.

The actual dose dates and times will be used to calculate the actual elapsed time from the start of the infusion for each PK plasma sample. Actual elapsed sampling times will be used for the individual figures and for the non-compartmental analysis.

3.10 Pharmacodynamic and Biomarker Analyses

Immune correlate values may be summarized in a descriptive manner. For immune correlates measured on a continuous scale, the number of subjects with non-missing data, mean, standard error or standard deviation, median, minimum, and maximum values will be presented. For discrete data, the frequency and percent distribution will be presented.

- Reduction of non-classical monocytes at the time of dose interval and plateaued increase of circulating CSF-1 levels that persist for an entire dose level
- Changes in CSF-1, IL-34, MCP-1, CCL3 and CCL5 from baseline to day 8, day 15, C2D1, C4D1 and end of treatment
- Changes in monocyte number and phenotype (CD14/16) from baseline to day 8, day 15, C2D1, C4D1 and end of treatment
- Changes from baseline in skin macrophages, Langerhans cells and dendritic cells in skin or pulmonary biopsy prior to SNDX-6352 and after 2 cycles of SNDX-6352 treatment

- Frequency of immune cells in peripheral circulation, including natural killer (NK) cells, T-cells, and B-cells
- Bone metabolism will be assessed by measuring changes in concentration of BAP and CTX in serum

4. CHANGES FROM PROTOCOL

ITT and FAS are removed as efficacy analysis population since evaluable population is more appropriate for an early phase study. Evaluable population definition is updated to include patients who discontinued treatment early due to progression or treatment related AE without any post-baseline response assessment.

PK analysis set definition is updated to be consistent with other studies in the program.

2-sided CI for DLT rate is removed.

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6. Appendix

Appendix 1: Global cGVHD Activity Assessment -Physician Report

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth								
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
			Total score for all mucosal changes					

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

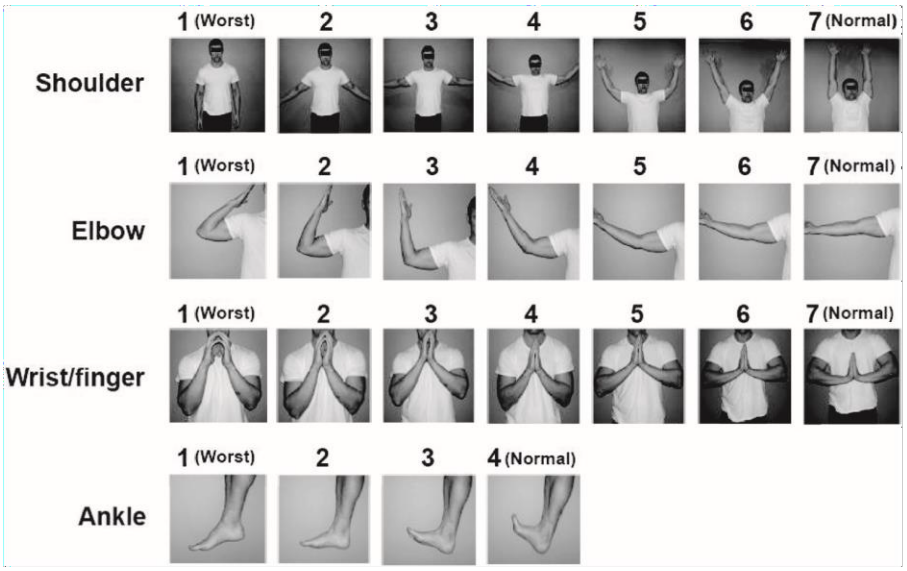
Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)	TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L / ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min	Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____ ☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____ ☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____				

Figure 1. Chronic GVHD Activity Assessment- Clinician Report.

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA*: **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE	SCORE
JOINTS AND FASCIA	☐ No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				



❑ Not done

❑ Not done

❑ Not done

❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Source:

cGVHD Lee Symptom Scale

Please let us know whether you have been bothered by any of the following problems in the past month.

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

Appendix 2:

6.1 Laboratory Test Groupings and Standard Normal Range

Analyte	Standard Unit	Significant Digits	Directional Change of Interest	Standard Normal Range†
Lab group = Hematology, WBC with Differential				
WBC count‡	10^9 cells/L	XX.X	Decrease	3.2 – 9.8
Basophil count	10^6 cells/L	XX	Decrease	15 – 50
Eosinophil count	10^6 cells/L	XXX	Decrease	50 – 250
Lymphocyte count‡	10^6 cells/L	XXXX	Decrease	1500 – 3000
Monocyte count	10^6 cells/L	XXX	Decrease	285 – 500
Neutrophil count‡	10^6 cells/L	XXXX	Decrease	3000 – 5800
Lab group = Hematology, Erythrocytes and Platelets				
Hematocrit	Fraction of 1.00	0.XX	Decrease	0.33 – 0.43 (female)
				0.39 – 0.49 (male)
Hemoglobin‡	g/L	XXX	Decrease	115 – 155 (female)
				140 – 180 (male)
RBC count	10^{12}/L	X.X	Decrease	3.5 – 5.0
Platelet count‡	10^9/L	XXX	Decrease	130 – 400
Lab group = Hematology, Coagulation				
PT	seconds	XX	Increase	9 – 12
PTT‡	seconds	XX	Increase	22 – 37

† Standard normal ranges are provided for reference and not will be used in analysis unless laboratory normal ranges are missing. Source: Laposta, M: *SI Unit Conversion Guide*, The New England Journal of Medicine Books, Boston, 1992.

‡ If present, indicates CTCAE toxicity grade is defined for the analyte.

Laboratory Test Groupings and Standard Normal Range (continued)

Analyte	Standard Unit	Significant Digits	Directional Change of Interest	Standard Normal Range†
Lab group = Chemistry, Hepatic				
Albumin‡	g/L	XX	Decrease	40 – 60
Alk Phos‡	U/L	XXX	Increase	30 – 120
ALT‡	U/L	XXX	Increase	0 – 35
AST‡	U/L	XXX	Increase	0 – 35
Lactic dehydrogenase	U/L	XXX	Increase	50 – 150
Total Bilirubin‡	micromol/L	XX	Increase	2 – 18
Total Protein	g/L	X.XX	Decrease	60 – 80
Lab group = Chemistry, Renal				
BUN	mmol/L of urea	X.X	Increase	3.0 – 6.5
Creatinine‡	micromol/L	XXX	Increase	50 – 110
Creatinine clearance	mL/min	XXX	Decrease	75 – 125
Creatinine kinase‡	U/L	XXX	Increase	50-200
Pancreatic				
Amylase	U/L	XXX	Increase	27-130
Lipase	U/L	XXX	Increase	0-160

† Standard normal ranges are provided for reference and not will be used in analysis unless laboratory normal ranges are missing.

Source: Laposta, M: *SI Unit Conversion Guide*, The New England Journal of Medicine Books, Boston, 1992.

‡ If present, indicates CTCAE toxicity grade is defined for the analyte.

Laboratory Test Groupings and Standard Normal Range (continued)

Analyte	Standard Unit	Significant Digits	Directional Change of Interest	Standard Normal Range†
Lab group = Chemistry, Electrolytes				
Bicarbonate‡	mmol/L	XX	Both	22 – 28
Calcium‡	mmol/L	X.XX	Both	2.20 – 2.56
Chloride	mmol/L	XXX	Both	95 – 105
Magnesium‡	mmol/L	X.XX	Both	0.80 – 1.20
Phosphorus	mmol/L	X.XX	Both	0.80 – 1.60
Potassium‡	mmol/L	X.X	Both	3.5 – 5.0
Sodium‡	mmol/L	XXX	Both	135 – 147
Lab group = Chemistry, Metabolic				
Glucose‡	mmol/L	XX.X	Both	3.9 – 6.1
Uric Acid	micromol/L	XXX	Increase	120 – 420

† Standard normal ranges are provided for reference and not will be used in analysis unless laboratory normal ranges are missing.

Source: Laposta, M: *SI Unit Conversion Guide*, The New England Journal of Medicine Books, Boston, 1992.

‡ If present, indicates CTCAE toxicity grade is defined for the analyte.

SNDX-6352-0503_SAP_2.0_Final_Signature

Final Audit Report 2023-01-05

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By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAAaVZvTc18muTXNf__kn8Tx89WP_4qOC2V

"SNDX-6352-0503_SAP_2.0_Final_Signature" History

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Agreement completed.

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