NCT03938636

Statistical Analysis Plan (SAP)

Evaluation of the Precision and Sensitivity of Tilmanocept Uptake Value (TUV) on Tc 99m Tilmanocept Planar Imaging

Study No: NAV3-31

Version 1.1

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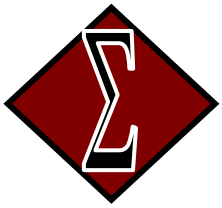

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Approval Page

By entering into this Statistical Analysis Plan (SAP), the parties acknowledge and agree that this SAP shall be incorporated into and subject to the terms of the Master Services Agreement (MSA). Any changes requested by Client to this SAP shall be subject to Section I.C of the MSA requiring a mutually agreed upon "Change Order" prior to any modification of the procedures set forth herein.

I agree to the format and content of this document.

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Revision History

Version 1.0 to 1.1:

- Updated the TUV prediction algorithms 1 and 4 in Section 4.2.2 to include a 10% decrease as a predicted responder. The prior SAP version defined a responder as one with a strictly greater than 10% decrease.
- Added clarification in Section 4.2.2 that the TUV prediction algorithms are to be implemented after rounding the change in TUV calculations to the nearest integer percentage (i.e., nearest hundredths place for a proportion).

List of Abbreviations and Definitions of Terms

Term	Definition
Δ	Greek letter delta, used to represent the change in a particular variable
µg	microgram
ACPA	anti-citrullinated protein/peptide antibody
ACR/EULAR	American College of Rheumatology/ European League Against Rheumatism
AE	adverse event
Anti-TNF-α bDMARD	Anti-Tumor Necrosis Factor α biological Disease Modifying Anti-Rheumatic Drug
CDAI	Clinical Disease Activity Index
CFB	change from baseline
CI	confidence interval
CRF	case report form
CSR	clinical study report
CT	X-ray computed tomography
CV	coefficient of variation
DAS28	Disease activity score used with the ACR/EULAR 2010 RA guidelines
ECG	electrocardiogram
FDA	Food and Drug Administration
HAQ-DI	Health Assessment Questionnaire Disability Index
HC(s)	healthy control(s)
ICH	International Conference on Harmonization
ITD	intent-to-diagnose
IV	intravenous
mCi	milliCurie ($37x10^6$ becquerels; 37megabecquerels)
MCP	metacarpophalange
MedDRA	Medical Dictionary for Regulatory Activities
NPV	Negative Predictive Value
OA	Osteoarthritis or Overall Accuracy, depending on context
PIP	proximal interphalange
PP	per protocol
PPV	Positive Predictive Value
RA	rheumatoid arthritis
ROI	region of interest
RR	reference region
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SPECT	single photon emission computed tomography

Term	Definition
Tc 99m	technetium-99m metastable isotope; γ-emitting (half-life 6.02 h)
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
tilmanocept	DTPA Mannosyl Dextran (the US Adopted Name for the drug substance of Lymphoseek)
TUV	Tilmanocept uptake value
US	United States
$\bar{X}_{BRAIN}$	the decay-corrected average voxel intensity of the brain RR of a subject at the anterior view at 1 or 3-hours post-injection
$\bar{X}_{ROI}$	the decay-corrected average voxel intensity of a region of interest

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INTRODUCTION

Description

This Statistical Analysis Plan (SAP) is consistent with Amendment 4 of the study protocol (dated 2 February 2021) and includes the latest details of efficacy and safety summaries to be included in the clinical study report (CSR).

The preparation of this SAP was done in accordance with STATKING Clinical Services SOP SCI 02-54, Statistical Analysis Plans.

1.0 Synopsis of Study Design/Procedures

This study is a prospective, open-label, multicenter, evaluation of the reliability and sensitivity of Tilmanocept Uptake Value (TUV) assessments based on planar imaging localization of intravenously (IV) injected Tc 99m tilmanocept to skeletal joints in subjects with and without active rheumatoid arthritis (RA).

The study has three arms. Arm 1 consists of Healthy Control (HC) subjects. Arm 2 consists of RA patients on stable therapy. Arm 3 consists of RA patients who are candidates for initiation of, or change to a new anti-tumor necrosis factor α (TNFα) biological disease-modifying antirheumatic drug (bDMARD) treatment.

The objectives of the study are:

Primary Objectives:

- To assess the longitudinal precision of TUV_{joint} and TUV_{global} on planar imaging in subjects with clinically diagnosed active RA on stable anti-rheumatic therapy.

- To evaluate camera-specific precision of TUV_{joint} and TUV_{global} on planar imaging in HCs and in subjects with clinically diagnosed active RA using centralized and standardized imaging parameters.

- To assess the correlation of TUV and changes in TUV with changes in clinical assessments at multiple time points after initiation of a new anti-anti-TNFα bDMARD therapy.

Secondary Objectives:

- To assess the temporal post-injection stability of TUV_{joint} and TUV_{global} at a dose of 150mcg tilmanocept radiolabeled with 10 mCi of Tc 99m.

- To establish normal ranges for TUV_{joint} in HCs.

- To assess Tc 99m tilmanocept anatomic localization based on single photon emission computed tomography/ computed tomography (SPECT/CT) imaging of the synovial space in hands and wrists.

Safety Objective:

- To evaluate safety through the examination of adverse event (AE) incidence and changes over time in laboratory tests, vital signs, and physical examination findings.

1.1 Design and Treatment

Subjects will receive the administration of Tc 99m tilmanocept through an IV route of administration. All subjects will receive a 150 μg mass dose of tilmanocept labeled with 10 mCi of Tc 99m in a 3 ml volume. Following injection a 10 ml sterile normal saline flush will be administered. The preferred site of IV placement will be between the elbow and wrist.

Arm 1 HC subjects receive a single administration of 10 mCi of Tc 99m in a 150 μg mass dose of tilmanocept. Arm 2 RA subjects receive two (2) IV administrations of 10 mCi Tc 99m in a 150 μg mass dose of tilmanocept. Arm 3 RA subjects receive up to four (4) administrations of 10 mCi Tc 99m in a 150 μg mass dose of tilmanocept.

Table 1 Study arms

Arm	Subjects	Evaluations
1	HC subjects clinically free of any inflammatory disease and/or joint pain.	Image, Re-image
2	Subjects with clinically diagnosed RA who have been on stable anti-rheumatic therapy.	Image, Re-image Test, Re-test
3	Subjects with clinically diagnosed RA who are candidates for initiation of, or change to, a new anti-TNFα bDMARD treatment.	Positive Predictive Value, Negative Predictive Value, Clinical Concordance

1.2 Study Procedures

Subjects will visit the study site for screening procedures up to 30 days (Day -30 to Day -1) before enrollment into the study. Screening procedures (demographics, vital signs, medical history, blood and urine samples for clinical

labs, RA specific labs, urine pregnancy testing for subjects of childbearing potential, and physical exam) will be completed along with RA evaluations using the 2010 ACR/EULAR score. The DAS28 score instrument will be used in Arms 2 and 3.

Subjects arriving for Study Day 0 will be considered enrolled in the study. On Day 0 subjects will receive Tc 99m injection and imaging procedures. Pre-injection procedures include the following: a urine pregnancy test will be administered to all subjects with childbearing potential. Up to 30 minutes prior to drug administration an ECG will be performed, followed by assessment of vital signs and AEs. After pre-injection procedures are completed subjects will receive a single IV dose with 150 μg of tilmanocept radiolabeled with 10 mCi of Tc 99m. Within 30 minutes of injection, subjects will receive an ECG followed by vital sign and AE check. Whole body planar imaging will be conducted on the subject at the time points specified for the arm into which he/she was enrolled (see Section 1.0). For subjects in Arms 1 and 2, planar images of the whole body and bilateral hands and wrists will be taken at 60 (± 15) minutes and at 180 (± 15) minutes after injection. Blood will be drawn for clinical laboratory evaluations after all image acquisitions have been completed.

On Study Day 5 (± 3 days) a safety follow-up telephone call will include a review of concomitant medications and assessment of adverse events. Arm 1 HC subjects have completed the study at this point.

On Study Day 8 (± 1 day) RA subjects in Arm 2 will receive repeat Tc 99m tilmanocept imaging. Pre-injection procedures include the following: a urine pregnancy test will be administered to all subjects with childbearing potential. Up to 30 minutes prior to drug administration an ECG will be performed, followed by assessment of vital signs and AEs. After pre-injection procedures are completed subjects will receive a single IV dose with 150 μg of tilmanocept radiolabeled with 10 mCi of Tc 99m. Within 30 minutes of injection, subjects will receive an ECG followed by vital signs and AE assessment. Planar images of the whole body and bilateral hands and wrists will be taken at 60 (± 15) minutes and 180 (± 15) minutes after injection. Following the 180 minute planar imaging, subjects will have SPECT/CT images of the bilateral hands and wrists taken. Blood will be drawn for clinical laboratory evaluations after all image acquisitions have been completed.

From 1 to 3 days of the second imaging day (i.e., Study Day 9 to 11 if imaging is done on Study Day 8), a safety follow-up telephone call will be made to review concomitant medications and AE check. Arm 2 RA subjects have completed the study at this point.

For RA subjects in Arm 3, Study Day 0 is modified to include planar whole body and planar images of the hands and wrists once only at 60 minutes post-injection. All other procedures remain the same on Study Day 0. The new therapy (anti-

TNFα bDMARD) will be initiated following the Day 0 imaging. A safety follow-up telephone call will be conducted on Study Day 5 (± 3 days). Follow-up images of the hands and wrists and whole body will be made at 5 weeks (± 1 week) after initiation of the new anti-TNFα bDMARD therapy using the same procedures as in Arm 2 Day 8, except that no images will be taken at 180 minutes in Arm 3 and the post imaging clinical laboratory assessments will include an RA panel. CDAI, DAS28, HAQ-DI, WPI, and an AE check will also occur at this visit. A safety follow-up telephone call will be conducted 1 to 3 days later. At weeks 12 (± 1 week) and 24 (± 1 week) after initiation of the new anti-TNFα bDMARD therapy, Arm 3 subjects will have a return visit for imaging and assessment of their RA status. These visits will include clinical laboratory assessments and RA-specific labs (post imaging), tilmanocept injection and image acquisition 60 (± 15) minutes following injection, CDAI, DAS28, HAQ-DI, WPI , and AE check at both of these time points. ACR Response Criteria will be assessed at weeks 5, 12 and 24. After the week 24 visit, Arm 3 RA subjects have completed the study.

The centralized core image laboratory contracted by Navidea Biopharmaceuticals completed a quantitative read of the images to determine the amount of radiotracer uptake in the joints (TUV_{joint}) and in the brain (TUV_{brain}) for Interim Analysis 2. The core image laboratory will also evaluate localization of Tc 99m tilmanocept in the 180 minute planar and SPECT/CT images of Arm 2 RA patients. Navidea internal work instructions and imaging charter will be followed for all other quantitative and qualitative reads for all other imaging data.

1.3 Sample Size

Up to 105 subjects from up to 10 study centers will be enrolled into Arms 1, 2, and 3 as allocated below, and imaged. Arm 1 will have N = 38 evaluable subjects, Arm 2 will have N = 38 evaluable subjects, and Arm 3 will have N = 29 evaluable subjects. A subject is considered evaluable if he/she meets the criteria for the analysis population and has the data necessary for computing the primary endpoint.

The sample size for Arm 1 was determined to assess temporal stability of the 150 μg mass dose/10mCi radiolabeling dose. The sample size for Arm 2 was determined to power a hypothesis test at 0.80:

$$H_0: \pi \leq 0.80$$
$$vs$$
$$H_a: \pi > 0.80,$$

where π represent the fraction of unsigned differences less than 7.5% The sample size for Arm 3 was determined to provide a lower 97.5% confidence limit for the rank correlation of at most 0.15 when ρ = 0.70, using Fisher's Z-transformation methods.

2.0 Data Analysis Considerations

2.1 Types of Analyses

Data analyses described in this SAP will consist of analyzing efficacy and safety data.

2.2 Analysis Populations

The following analysis populations will be used in the study:

Safety Population – The safety population includes all patients that have been enrolled in the study and injected with at least one dose of Tc 99m tilmanocept.

Intent-to-Diagnose (ITD) Population – The ITD population includes all patients that have been enrolled in the study, injected with Tc 99m tilmanocept, and received all imaging and evaluations necessary for the primary endpoint(s) appropriate to their respective arm.

Per Protocol (PP) Population: The PP population will include all ITD subjects without major protocol violations. All protocol deviations will be classified as major or minor prior to database lock.

All efficacy analyses will be carried out on the ITD and PP populations with the ITD population being the primary analysis set. All analyses of safety data and baseline subject characteristics will be carried out on the safety population. A data listing displaying the patients excluded from each population will be created, as shown in Appendix B.

2.3 Missing Data Conventions

No missing value imputation will be used in this analysis. All analyses will be based on the observed data.

2.4 Interim Analyses

After the injection, imaging, and quantitation of a total of 4 subjects in Arms 1 and 2 combined, an interim analysis (Interim Analysis 1) was held for the review of quantitative TUV results and assessment of imaging parameters and logistics. A second interim analysis was held after a total of 30 subjects (and at least 15 RA subjects) in Arms 1 and 2 were injected, imaged, and quantified for the review of inter- and intra-subject TUV variation to contribute to the power analysis of a future Phase 3 study and/or to terminate the study on grounds of data sufficiency.

After 15 subjects in Arm 3 completed Visit 4, an interim analysis (Interim Analysis 3) was performed to estimate the distribution of treatment effects on TUV and to optimize the TUV metric based on the interim data from all three arms.

Interim analysis plans (IAPs) were written and approved for the second interim analysis of Arms 1 and 2 and for the third interim analysis of all three study arms.

2.5 Calculation of TUV

All calculations are done on a reader-specific basis. That is, there is no statistical aggregation of the reader results.

Calculating Joint TUV
For an individual joint, TUV_{joint} is defined as the average pixel intensity of the joint divided by the average pixel intensity of the hand, right or left and anterior or posterior, (includes the region from one wrist region of interest (ROI) diameter above the wrist ROI down to the fingertips).

Calculating Global TUV
For each independent blind reader, determine the average TUV_{joint} and 95% prediction interval of both the anterior and posterior views of the wrists, MCPs, and PIPs in healthy individuals (NAV3-31 Arm 1). For all following calculations, reader specific average TUV_{joint} and 95% prediction intervals will be used.

For each RA subject do the following.

Step 1: Calculate TUV_{joint} for each of the 22 DAS 28 joints for which data are collected.

Step 2: Identify all imaged joints with TUV_{joint} > upper limit of normal for the anatomically similar joint and view. These will be referred to as inflamed joints (IJ). Each joint has an anterior and posterior view: a joint is considered an IJ if either view has a TUV_{joint} higher than the upper bound from the normative data set.

Step 3: Calculate the macrophage-involved contribution (MI) to Tc 99m tilmanocept localization for each IJ. This is done by expressing the TUV for the IJ as a fractional change from the mean TUV for the anatomically equivalent joint and view. That is, if TUV_{joint} and $\overline{H}_{joint}$ represent the joint and view specific TUV and the mean TUV for the anatomically equivalent joint and view from the normative data set respectively, the macrophage contribution to TUV is MI_{joint}:

$$MI_{joint} = \frac{TUV_{joint} - \overline{H}_{joint}}{\overline{H}_{joint}}.$$

Step 4: TUV_{global} is the total of the macrophage-involved contributions for the IJs. (Note that MI_k is effectively 0 if TUV_{joint} is less than or equal to the upper limit of normal from the normative data set.) That is,

$$\mathrm{TUV}_{\mathrm{global}} = \sum_{\text{All IJs}} \mathrm{MI}_{\mathrm{IJ}},$$

$$\mathrm{TUV}_{\mathrm{global}} = \sum_{k=1}^{22} \mathrm{MI}_k.$$

The change in TUV_{global} ($\Delta TUV_{global[5w]}$) is the Δ% from baseline ($TUV_{global[b]}$):

$$\Delta\mathrm{TUV}_{\mathrm{global[5w]}} = 100 \cdot \frac{\mathrm{TUV}_{\mathrm{global[5w]}} - \mathrm{TUV}_{\mathrm{global[b]}}}{\mathrm{TUV}_{\mathrm{global[b]}}}.$$

Arms 1 and 2:

Precision endpoints for both arms will be assessed estimating the mean, standard deviation, n, minimum, median, and maximum of the signed differences (change from baseline) of TUV for each evaluated DAS28 joint. The RMSD will be calculated using the following equation:

$$RMSD = \sqrt{\frac{1}{n-1}\sum_{k=1}^{n}(y_k - w_k)^2}$$

where y_k and w_k are the measurements at the two timepoints (for example, the two scans at 60 minutes, the two scans at 180 minutes, or the first 60-minute scan and the first 180-minute scan) and *k* represents the subject number. A 95% confidence interval for the RMSD based on Normal theory will be provided, as will a 95% bootstrap confidence interval based on N = 5000 bootstrap samples. Box-and-whisker plots of TUV will be provided by arm at each timepoint for each joint, pooling small joints (MCPs and PIPs) and all joints bilaterally. Joints will not be pooled by type or bilaterally in IA 3.

ΔTUV will be summarized with descriptive statistics as the signed difference. If T_1 represents the observed TUV at the first time point and T_2 the observed TUV at the second time point, then

$$\Delta TUV = T_2 - T_1.$$

Arm 1 Only:

The distribution of TUV_{joint} in healthy controls will be summarized by time point for global TUV and each evaluated DAS28 joint with the number of joints, mean, standard deviation, 80^{th} and 90^{th} percentiles, the median, and 95% prediction limits for a future observation of that type at that time point. Joints will not be pooled. Box-and-whisker plots of the data will be presented by joint and time point. A scatter plot matrix for the three readers will be provided on a joint-specific basis showing the relationship between the reader TUV for the A and B scans.

Arm 2 Only:

The longitudinal precision of TUV_{joint} will be analyzed for each evaluated DAS28 joint. The signed differences will be analyzed with descriptive statistics and the RMSD will be calculated as defined for Arms 1 and 2 above. A 95% confidence interval for the RMSD based on Normal theory will be provided, as will a 95% bootstrap confidence interval based on N = 5000 bootstrap samples. Joints will not be pooled by type or bilaterally. A scatter plot matrix for the three readers will be provided on a joint-specific basis showing the relationship between the reader TUV for the A and B scans.

Arm 3 Only:

The Kendall rank correlation between $\Delta TUV_{global[5w]}$ with $\Delta CDAI_{12w}$ will be computed and a 95% confidence interval for its value will be computed using Fisher's Z-transformation. Similarly, the Kendall rank correlation between $\Delta TUV_{global[5w]}$ with changes from baseline in each of the ACR Response Criteria components at 12 weeks (tender joint count (TJC), swollen joint count (SJC), patient assessment of global disease activity, rheumatologist assessment of global disease activity, patient assessment of pain, patient assessment of physical function, and acute-phase reactant value) will be computed and a 95% confidence interval for its value will be computed using Fisher's Z-transformation.

2.6 Study Center Considerations in the Data Analysis

A study center is defined as a treatment administration site or group of treatment administration sites under the control and supervision of the same Principal Investigator (PI). There will be no selective pooling of study centers.

2.7 Documentation and Other Considerations

The data analyses described in this SAP will be conducted using SAS© Software, version 9.4 or later.

3.0 Analysis of Baseline Patient Characteristics

Baseline and demographic characteristics of the safety population will be summarized by subject arm and overall. Continuous variables (age, height, weight, and time from diagnosis of RA) will be summarized via mean, standard deviation, minimum, maximum, and number of non-missing responses. Categorical variables (gender, race, and ethnicity) will be summarized via counts and percentages.

A detailed listing of baseline data for each patient in the safety population will also be provided, as shown in Appendix B.

4.0 Analysis of Efficacy

4.1 Description of Efficacy Variables

The efficacy variables for this study are as follows:

- Quantitative determination of TUV_{joint} and TUV_{global} at Day 0, Day 8, Week 5, Week 12, and Week 24 as appropriate to the subject's study arm.
- Qualitative determination of tilmanocept localization in planar images and SPECT/CT images of the bilateral hands and wrists.
- Subject RA status evaluations in Arm 3 as summarized in the CDAI overall score and its subscores.
- Subject RA status evaluation in Arm 3 as summarized by the ACR Response Criteria.
- Change in TUV.

The presence of radiotracer uptake for a joint indicates the presumed presence of activated macrophages. The use of the term "localization" in this SAP is synonymous with the presence of radiotracer uptake.

TUV is defined as:

$$\mathrm{TUV}_{\mathrm{joint}} = \frac{\bar{X}_{joint}}{\bar{X}_{\mathrm{RR}}};$$

where

- $\bar{X}_{\mathrm{joint}}$ is the average voxel intensity of a particular joint of a subject at the anterior or posterior views at 1 or 3-hours post-injection;

- $\bar{X}_{RR}$ is the average voxel intensity of the reference region (RR) of a subject at the anterior or posterior views at 1 or 3-hours post-injection.

4.1.1 Primary efficacy variables

The primary efficacy variables for this study are:

- Quantitative measurement of TUV_{joint} (all arms) and TUV_{global} (Arms 2 and 3 only)
- CDAI scores at baseline, 12 (± 1) weeks and 24 (± 1) weeks (Arm 3 only)
- DAS28 scores at baseline, 12 (± 1) weeks and 24 (± 1) weeks (Arm 3 only)
- ACR Response Criteria at 12 (± 1) weeks and 24 (± 1) weeks (Arm 3 only).

The primary efficacy variables of this study in Arms 1 and 2 are:

- The camera-specific precision of TUV_{joint} and TUV_{global} in subjects with active RA and healthy controls, which is defined as the Root Mean Square Difference (RMSD) between the consecutive 15-minute planar images.
- The stability of the mean/variance relationship, which is assessed by comparing the Coefficient of Variation (CV) of TUV_{joint} and TUV_{global} in subjects with active RA and healthy controls.

An added primary variable in Arm 2 only is:

- The longitudinal (8-day) precision of TUV_{joint} and TUV_{global} in subjects with active RA, which is defined as the RMSD of the TUV between the baseline and 8 day image at the same time point.

The primary endpoints in Arm 3 are:

- The Kendall rank correlation of $\Delta TUV_{global[5w]}$ with the response to new anti-TNFα bDMARD therapy defined as $\Delta CDAI_{12w}$ and $\Delta CDAI_{24w}$ (overall scores only) in study arm 3.
- The Kendall rank correlation of $\Delta TUV_{global[5w]}$ with the response to new anti-TNFα bDMARD therapy defined as the changes from baseline in DAS28 and in each of the ACR Response Criteria components at 12 (± 1) weeks and at 24 (± 1) weeks in study arm 3.

4.1.2 Secondary efficacy variables

- Qualitative evaluations of SPECT/CT image detecting localization of Tc 99m tilmanocept in the synovial spaces of the bilateral hands and wrists. (Arm 2 only).

- CDAI score at baseline ($CDAI_{0w}$), 12 ($CDAI_{12w}$) and 24 weeks ($CDAI_{24w}$) (Arm 3 only).

- ACR Response Criteria at 12 and 24 weeks (Arm 3 only).

- Constituent scores of the ACR Response Criteria at baseline, 12 weeks, and 24 weeks, including:
    - TJC
    - SJC
    - Patient assessment of global disease activity
    - Rheumatologist assessment of global disease activity
    - Patient assessment of pain
    - Patient assessment of physical function
    - Acute-phase reactant value.

- Constituent scores of the CDAI score
    - TJC
    - SJC
    - Patient Global Assessment
    - Physician Global Assessment.

The secondary efficacy endpoints for this study are:

ARMS 1-2

- The temporal stability of TUV_{joint} and TUV_{global} using a 150 mcg tilmanocept mass dose/10 mCi radiolabeling dose, which is defined as the squared difference between the 1-hour and 3-hour planar images. (This endpoint was analyzed to the sponsor's satisfaction in IA-3.)

ARM 1

- The normal upper limit of TUV_{joint} in HC subjects, which is defined the upper limit of a 95% prediction interval at 60 ±15 minutes:
    - TUV_{joint} of evaluated joints (i.e., wrists, MCPs, PIPs, knees, elbows, shoulders in Arms 1 and 2, and wrists, MCPs, and PIPs in Arm 3).

ARM 2

- The qualitative evaluations of SPECT/CT in detecting localization within synovial spaces of the bilateral hands and wrists.

ARM 3

- $TUV_{global[0w]}$ and response to new anti-TNFα bDMARD therapy defined by the change from baseline (CFB) of CDAI to 12 ± 1 weeks and 24 ± 1 weeks ($\Delta CDAI_{12w}$ and $\Delta CDAI_{24w}$, respectively) and by the changes from baseline in each of the ACR Response Criteria components at 12 (± 1) weeks and at 24 (± 1) weeks.

- $\Delta TUV_{global[5w]}$ and response to new anti-TNFα bDMARD therapy defined by the CFB of CDAI to 12 ± 1 weeks and 24 ± 1 weeks ($\Delta CDAI_{12w}$ and $\Delta CDAI_{24w}$, respectively).

- $\Delta TUV_{global[12w]}$ and $\Delta TUV_{global[24w]}$.

- Concordance of improvement classification using $\Delta TUV_{global[5w]}$ and $\Delta TUV_{global[5w]}$ with anti-citrullinated protein/peptide antibody (ACPA) bucketing improvement classification using clinical criteria, including ACR Response Criteria, CDAI, DAS28, and HAQ-DI. See section 4.2.2 below for the definitions of improvement on these clinical criteria.

- Concordance of improvement classification using $\Delta TUV_{global[12w]}$ and $\Delta TUV_{global[12w]}$ with ACPA bucketing improvement classification using clinical criteria, including ACR Response Criteria, CDAI, DAS28, and HAQ-DI.

- Response to new anti-TNFα bDMARD therapy defined by the CFB of CDAI to 12 ± 1 weeks and 24 ± 1 weeks ($\Delta CDAI_{12w}$ and $\Delta CDAI_{24w}$, respectively).

- The correlation of $\Delta TUV_{global[5w]}$ and response to new anti-TNFα bDMARD therapy from baseline to 24 ± 1 weeks defined by the changes from baseline in each of the ACR Response Criteria components.

- Constituent parameters of $CDAI_{12w}$, $CDAI_{24w}$, $\Delta CDAI_{12w}$, $\Delta CDAI_{24w}$, ACR Response Criteria at 12 and 24 weeks, including:
    - TJC
    - SJC
    - Patient assessment of global disease activity
    - Rheumatologist assessment of global disease activity
    - Patient assessment of pain
    - Patient assessment of physical function
    - Acute-phase reactant value.

4.2 Analysis of Efficacy Variables

4.2.1 Primary Efficacy Variables

Primary Endpoints for Arms 1 and 2

All TUV data will be analyzed with summary statistics (mean, standard deviation, n, minimum, median, maximum) by study arm and joint.

Precision endpoints will be assessed estimating the mean, standard deviation, n, minimum, median, and maximum of the signed differences (CFB). The RMSD will be calculated

$$RMSD = \frac{1}{n-1}\sum_{k=1}^{n}(y_k - w_k)^2$$

where y_k and w_k are the measurements at the two timepoints and k represents the subject number. A 95% confidence interval for the RMSD based on Normal theory will provided, as will a 95% bootstrap confidence interval based on N = 5000 bootstrap samples. Timepoints analyzed in this way will include the 60 minute A and B scans, the 180 minute A and B scans, and the difference between the 60 and 180 minute A scans. These will be done for all joints assessed and for TUV_{global}. (These analyses were completed to the sponsor's satisfaction in IA-3.)

Primary Endpoint for Arm 2 Only

The longitudinal (8-day) variation of TUV will be analyzed for each DAS28 joint and globally. The signed differences will be analyzed with descriptive statistics and the RMSD will be calculated as defined for Arm 2 above. A 95% confidence interval for the RMSD based on Normal theory will provided, as will a 95% bootstrap confidence interval based on N = 5000 bootstrap samples will be computed, and 95% confidence limits for its value will be provided. This will be done for TUV_{joint} for all evaluated joints and TUV_{global} in the 60 minute images using the "A" image at baseline. The fraction of unsigned ΔTUV_{global} values less than 7.5% will be summarized in a frequency table and an exact binomial test of the hypotheses described in Section 1.3 will be included for each timepoint.

Primary Endpoints for Arm 3 Only

The Kendall rank correlation between $\Delta TUV_{global[5w]}$ with $\Delta CDAI_{12w}$ and $\Delta CDAI_{24w}$ will be computed and a 95% confidence interval for its value will be computed using Fisher's Z-transformation. Similarly, the Kendall rank correlation between $\Delta TUV_{global[5w]}$ with changes from baseline in DAS28 and in each of the ACR Response Criteria components at weeks 12 and 24 will be computed and a 95% confidence interval for its value will be computed using Fisher's Z-transformation. The marginal distributions of the variables will be characterized with the mean, standard deviation, and the number of data pairs.

4.2.2 Secondary Efficacy Variables

Secondary Endpoints for Arm 1 only

The normal ranges of TUV_{joint} will be estimated from data collected from healthy subjects (study arm 1) at 60 minutes post-injection. The mean, standard deviation, n (number of joints), and quantile regression estimates of the 5 and 95 percentiles will be provided for shoulder, elbow, wrist, MCP, PIP, and knee. All joints will be summarized individually.

Secondary Endpoints for Arms 1 and 2

The temporal quantitative stability of the images will be assessed by computing the fraction of observations for which $|\Delta TUV_{global}| \leq 0.075$ for the difference between the 60 and 180 minute images. The hypotheses

$$H_0: \pi \leq 0.80$$
$$vs$$
$$H_a: \pi > 0.80,$$

where π represent the fraction of unsigned differences less than 7.5% will be tested with an exact test and a Clopper-Pearson (exact) 95% confidence interval for p will be provided. The RMSD will be analyzed by joint, providing 95% confidence intervals for the RMSD using both Normal theory methods and a bootstrap estimate with 5000 bootstrap replications.

The 80th and 90th percentiles of the distribution of unsigned differences will be estimated using quantal regression methods. (These analyses were completed to the sponsor's satisfaction in IA-3.)

Secondary Endpoint for Arm 2 only

Qualitative evaluations of SPECT/CT imaging in localizing tilmanocept uptake will be estimated from the active RA subjects (Arm 2 only) on the joints of the hands and wrists. A frequency table of counts and percent of subjects will be provided.

Secondary Endpoints for Arm 3 only

All RA quantitative assessment variables (CDAI, ACR Response Criteria component scores, DAS28 score, and HAQ-DI) will be summarized by arm, computing the mean, standard deviation, number of observations, minimum, median, and maximum for the observed values at each time point and for the change from baseline for values collected after Day 0. The ACR Response Criteria will be summarized with a frequency table of the highest ACR Response level (None, ACR20, ACR50, ACR70) attained by that subject at that time point. That is, a subject who satisfies ACR50 also satisfies ACR20 but will not appear in the frequency count for ACR20.

The Kendall rank correlation between ΔTUV_{global} at 5 weeks, ΔTUV_{global} at 12 and 24 weeks with the component parameters of $\Delta CDAI_{12w}$ and $\Delta CDAI_{24w}$ will be computed and 95% confidence intervals for the values provided using Fisher's Z-transformation. This analysis will be repeated for the correlation between ΔTUV_{global} at 12 and 24 weeks with change in DAS28 and with ACR Response Criteria components at 12 weeks and 24 weeks (Note: the Kendall rank correlation analysis with DAS28 and ACR Response Criteria components at 5 weeks is a primary endpoint, as described above in Section 4.2.1). The marginal distributions of the variables will be characterized with the mean, standard deviation, and the number of data pairs.

Concordance of improvement classification for: 1) $\Delta TUV_{global[5w]}$ bucketing; 2) $\Delta TUV_{global[5w]}$; 3) $\Delta TUV_{global[5w]}$ bucketing with ACPA bucketing; 4) $\Delta TUV_{global[12w]}$ bucketing; 5) $\Delta TUV_{global[12w]}$; 6) $\Delta TUV_{global[12w]}$ bucketing with ACPA bucketing; and 7) ACPA bucketing alone with clinical criteria (ACR Response, CDAI, DAS28, and HAQ-DI) will be analyzed as follows.

ACR Response is derived through a combination of reductions from baseline in swollen or tender joint counts as well as improvement from baseline in at least at least 3 of the other parameters (patient assessment, physician assessment, pain scale, disability/functionality questionnaire, and acute phase reactant [ESR]). This study will evaluate the following three levels of ACR Response:

- ACR20: An ACR20 indicates that 20% improvement is observed in tender or swollen joint counts as well as 20% improvement in at least 3 of the other 5 criteria.
- ACR50: An ACR50 indicates that 50% improvement is observed in tender or swollen joint counts as well as 50% improvement in at least 3 of the other 5 criteria.
- ACR70: An ACR70 indicates that 70% improvement is observed in tender or swollen joint counts as well as 70% improvement in at least 3 of the other 5 criteria.

Each subject will be classified as a yes or a no for whether they meet each of the above ACR Response Criteria at each of the applicable post-baseline time points. Note that the above criteria are nested, such that if a subject is a yes for ACR70 at a given time point, then the subject is also a yes for ACR50 and ACR20 for that same time point.

A subject will be classified as improved on the CDAI depending on the baseline score as follows:

- If the baseline value is greater than 22, a reduction of more than 12 will be classified as improved. Otherwise, the subject is not improved.

- If the baseline value is between 10 and 22 (inclusive) a decrease of more than 6 will classified as improved. Otherwise, the subject is not improved.
- If the baseline value is less than 10, a decrease of more than 1 will be classified as improved. Otherwise the subject is not improved.

A subject will be classified as improved on the DAS28 with a score change of greater than 1.2.

A decrease of at least 0.22 in the HAQ-DI will be classified as improved. Otherwise, the subject is not improved on the HAQ-DI.

The $\Delta TUV_{global[5w]}$ values will be used to predict improvement at 12 and 24 weeks according to algorithms 1-3. The $\Delta TUV_{global[12w]}$ values will be used to predict improvement at 24 weeks according to algorithms 4-6. A seventh algorithm based on ACPA bucketing alone with also be applied to predict improvement at 12 and 24 weeks. Algorithms 1-6 will be applied after the change in TUV calculations have been rounded to the nearest integer percentage (i.e., nearest hundredths place for a proportion).

1. $\Delta TUV_{global[5w]}$ bucketing

   In the below, TUV_{global} represents the global TUV at the current time point and $TUV_{global[Day\ 0]}$ represents the global TUV at baseline:
   - If $TUV_{global[Day\ 0]}$ is < 5 then the prediction is N (No improvement)
   - Else if
     $$\Delta TUV_{global[5w]} = \frac{TUV_{global[5w]} - TUV_{global[Day0]}}{TUV_{global[Day0]}} \leq -0.10$$
     the prediction is Y (patient has improved). That is, a patient will be predicted as improved if TUV_{global} goes down by greater than or equal to 10%.
   - Otherwise, the prediction is N.

2. $\Delta TUV_{global[5w]}$

   The TUV_{global} prediction of improvement will also be computed according to the following algorithm:

   - If TUV_{global} goes down by greater than or equal to 10%, then predict response
   - If TUV_{global} does not go down by 10% or more, then predict no response

3. $\Delta TUV_{global[5w]}$ bucketing with ACPA bucketing

The TUV_{global} prediction of improvement will also be evaluated by combination of the above two algorithms such that:

For patients with TUV_{global} of below 5.0 at baseline:

- ACPA Levels before initiation (at baseline) of the new anti-TNF therapy:
  - ACPA levels ≤85 predicts treatment failure (non-response)
  - ACPA level >85 predicts treatment success (significant clinical improvement)

For patients with TUV_{global} at or above 5.0 at baseline:

- If TUV_{global} goes down by greater than or equal to 10%, then predict response (no need to refer to ACPA)
- If TUV_{global} does not go down by 10% or more, then refer to baseline ACPA for prediction:
  - ACPA levels ≤85 predicts treatment failure (non-response)
  - ACPA level >85 predicts treatment success (significant clinical improvement)

4. $\Delta TUV_{global[12w]}$ bucketing

In the below, TUV_{global} represents the global TUV at the current time point and $TUV_{global[Day\ 0]}$ represents the global TUV at baseline:

- If $TUV_{global[Day\ 0]}$ is < 5 then the prediction is N (No improvement)
- Else if

$$\Delta \mathrm{TUV}_{\mathrm{global[12w]}} = \frac{\mathrm{TUV}_{\mathrm{global[12w]}} - \mathrm{TUV}_{\mathrm{global[Day0]}}}{\mathrm{TUV}_{\mathrm{global[Day0]}}} \leq -0.10$$

  the prediction is Y (patient has improved). That is, a patient will be predicted as improved if TUV_{global} goes down by greater than or equal to 10%.
- Otherwise, the prediction is N.

5. $\Delta TUV_{global[12w]}$

The TUV_{global} prediction of improvement will also be computed according to the following algorithm:

- If TUV_{global} goes down by greater than or equal to 10%, then predict response
- If TUV_{global} does not go down by 10% or more, then predict no response

6. $\Delta TUV_{global[12w]}$ bucketing with ACPA bucketing

The TUV_{global} prediction of improvement will also be evaluated by combination of the above two algorithms such that:

For patients with TUV_{global} of below 5.0 at baseline:

- ACPA Levels before initiation (at baseline) of the new anti-TNF therapy:
  - ACPA levels ≤85 predicts treatment failure (non-response)
  - ACPA level >85 predicts treatment success (significant clinical improvement)

For patients with TUV_{global} at or above 5.0 at baseline:

- If TUV_{global} goes down by greater than or equal to 10%, then predict response (no need to refer to ACPA)
- If TUV_{global} does not go down by 10% or more, then refer to baseline ACPA for prediction:
  - ACPA levels ≤85 predicts treatment failure (non-response)
  - ACPA level >85 predicts treatment success (significant clinical improvement)

7. ACPA bucketing alone

The following will be used to predict improvement solely on the basis of ACPA:

- ACPA baseline level ≤85 predicts treatment failure (non-response)
- ACPA baseline level >85 predicts treatment success (significant clinical improvement)

For each of the RA improvement criteria, a cross-classification table will be provided. The Uncertainty coefficient for the clinical criterion given the $\Delta TUV_{global[5w]}$ of $\Delta TUV_{global[12w]}$ classification and its standard error will be calculated. The positive predictive value (PPV), negative predictive value (NPV), and overall accuracy (OA) will be calculated and 95% exact (Clopper-Pearson) confidence intervals will be provided.

PPV and NPV will be calculated as follows, where $\Delta TUV_{global[XXw]}$ is either $\Delta TUV_{global[5w]}$ or $\Delta TUV_{global[12w]}$, as appropriate:

	Clinical Criterion Classification		
$\Delta TUV_{global[XXw]}$ and/or ACPA Classification	Improved	Not Improved	Total
Improved	A	B	A+B
Not Improved	C	D	C+D
Total	A+C	B+D	A+B+C+D

PPV = A/(A+B)
NPV = D/(C+D)
OA = (A+D)/(A+B+C+D).

A separate table will be provided to summarize the baseline ACPA levels on a continuous scale and the number and percentage of subjects in each ACPA category (≤70, >70).

Figures displaying the ΔTUV_{global} by time point (5, 12, and 24 weeks) will be created to display the relationship between ΔTUV_{global} over time with the corresponding clinical response assessment (ACR20/50/70, DAS28, and CDAI) at the given time point.

5.0 Analysis of Safety

5.1 Description of Safety Variables

The safety analysis variables are defined as follows:

- Adverse Events (AEs)
- Clinical Laboratory Tests (hematology, serum chemistry, urinalysis, RA panel)
- ECG Parameters
- Vital Signs

5.2 Description of Safety Analysis

The following describes the safety analyses to be performed for the study. All safety analyses will be performed on the safety population. Follow up timing will vary by arm as noted above.

Adverse Events
Adverse events will be observed for each subject from signing of informed consent until termination from the study. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). A treatment-emergent AE (TEAE) is defined as an AE whose start date is on or after the initial procedure date. Based on the coded terms, frequencies of each TEAE will be summarized

by MedDRA® preferred term within system organ class (SOC), by severity grade, and by relationship to Tc 99m Tilmanocept for each arm and overall.

A summary of TEAEs will be constructed showing the following by arm and overall:

- Number of subjects with at least one TEAE
- TEAEs by arm and severity grade
- TEAE by arm and relationship to Tc 99m tilmanocept
- TEAEs by arm and relationship of TEAE to study procedure
- Number of subjects with at least one treatment emergent serious adverse event

Treatment-emergent serious adverse events (TESAEs) will be tabulated by MedDRA® preferred term within SOC by arm and overall.

A by-patient AE data listing of all AEs including verbatim term, coded term, grade, and relation to study drug will be provided.

Clinical Laboratory Tests

Clinical laboratory tests will be performed at screening (baseline) and after the final image acquisition on each imaging day. Only abnormal laboratory values and RA lab values will be assessed for clinical significance as applicable. For each quantitative laboratory test, summary statistics (mean, standard deviation, median, range, n) on the raw as well as their changes from baseline will be presented by timepoint by arm and overall. A shift table will also be produced to show the changes in lab values over time relative to the normal ranges.

If multiple labs were performed at a given visit, then the latest results will be summarized in the analysis tables. All collected lab data will be listed.

ECG Parameters

ECGs will be performed just prior and just after injection. For each ECG parameter (heart rate, QRS, QT, PR, and QTcF), summary statistics (mean, standard deviation, median, range, n) on the raw as well as their changes from baseline will be presented by timepoint, by arm, and overall. A shift table will be provided to show changes in the qualitative assessment (abnormal or normal) from baseline (pre-injection) to post-injection. The baseline value for each of the post-injection ECG parameters will be the corresponding pre-injection time point. All ECG data will be listed.

Vital Signs

Vital signs will be performed at screening, just prior to and just after injection. Height and weight will be measured only at screening and will be summarized as part of the baseline and demographic information. For each vital sign (respiration

rate, systolic blood pressure, diastolic blood pressure, heart rate and temperature), summary statistics (mean, standard deviation, minimum, maximum, n) on the raw as well as their changes from baseline will be presented by timepoint, by dose, and overall. The baseline value for each of the post-injection vital sign parameters will be the corresponding pre-injection time point. If there are multiple vital signs taken at any time point, then the latest set of vital signs will be used for the analysis. All vital sign data will be listed.

6.0 Other Relevant Data Analyses/Summaries

6.1 Patient Completion

A table will be constructed with counts of screen failures and enrolled subjects. Of those enrolled, counts and percentages of patients withdrawing from the study before study completion and the number completing the study will be displayed. For those subjects that withdraw before completion of the study, counts and percentages of the reasons for withdrawal will be tabulated. The table will include summary counts and percentages by study arm and overall. A data listing of all subject completion and withdrawal data will also be constructed.

6.2 Physical Exam

Physical exams will be performed at screening. All physical exam data will be listed.

6.3 Study Drug Administration

The volume, the calculated mass dose, and radioactivity of Tc 99m Tilmanocept injected will be summarized by arm and overall. All study drug administration data will be listed.

6.4 RA Evaluation and Screening Physical Exam

Each RA subject will undergo a DAS28 evaluation during screening. Arm 3 subjects will also undergo a DAS28 evaluation at weeks 5, 12, and 24. The swollen and tender joints will be identified and documented during the physical examination. Results of all DAS28 evaluations will be listed.

6.5 Concomitant Medications

All prior and concomitant medications will be listed, as shown in Appendix B. A separate data listing will be created to show only those medications that were taken for RA within the 6 months prior to Day 0 injection. In addition to the summarization of prior RA-specific treatments, recent or concomitant treatments

taken for RA in the last 6 months must be collected in accordance with the following time windows:

- Traditional DMARDs: On therapy at least 90 days and at a stable dose at least 30 days prior to the first imaging visit (Day 0)
- bDMARDs: More than 180 days prior to the first imaging visit (Day 0)
- JAK inhibitors: More than 180 days prior to the first imaging visit (Day 0)
- NSAIDs/Corticosteroids: At least 28 days prior to the first imaging visit (Day 0)

7.0 List of Analysis Tables, Figures and Listings

Table No.	Table Title	Included in Final Tables	Shown in Appendix B
1	Subject Disposition by Study Arm	X	X
2	Demographics and Baseline Data Summary Statistics by Arm - Continuous Variables (Safety Population)	X	X
3	Demographics and Baseline Data Summary Statistics by Arm – Categorical Variables (Safety Population)	X	X
4	Summary of Study Drug Administration by Arm (Safety Population)	X	X
5	Summary of TUV by Arm, Study Day, and DAS28 Joint (ITD population)	X	X
6	Summary of TUV by Arm, Study Day, and DAS28 Joint (PP Population)	X	
7	Summary for Eight-Day Longitudinal Stability of TUV (Arm 2 Only) (ITD Population)	X	X
8	Summary for Eight-Day Longitudinal Stability of TUV (Arm 2 Only) (PP Population)	X	
9	Analysis of Eight-Day Longitudinal Stability of ΔTUV_{global} (ITD population)	X	X
10	Analysis of Eight-Day Longitudinal Stability of ΔTUV_{global} (PP population)	X	X
11	Summary for Day 0 vs Day 8 RA Images (ITD Population)	X	X
12	Summary for Day 0 vs Day 8 RA Images (PP Population)	X	
13	Assessment of Mean/Variance Relationship by Time Point (ITD Population)	X	X
14	Assessment of Mean/Variance Relationship by Time Point (PP Population)	X	
15	Normal Range of TUV in Healthy Control Subjects (ITD Population)	X	X
16	Normal Range of TUV in Healthy Control Subjects (PP Population)	X	
17	RA Status Summaries (ITD Population)	X	X
18	RA Status Summaries (PP Population)	X	
19	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 5 weeks in Arm 3 (ITD Population)	X	X
20	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 5 weeks in Arm 3 (PP Population)	X	
21	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 12 weeks in Arm 3 (ITD Population)	X	X
22	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 12 weeks in Arm 3 (PP Population)	X	

Table No.	Table Title	Included in Final Tables	Shown in Appendix B
23	Kendall Rank Correlation of ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 24 weeks in Arm 3 (ITD Population)	X	X
24	Kendall Rank Correlation of ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 24 weeks in Arm 3 (PP Population)	X	
25	Frequency Counts of Localization in SPECT/CT Imaging in RA-2 Subjects (ITD Population)	X	X
26	Frequency Counts of Localization in SPECT/CT Imaging in RA-2 Subjects (PP Population)	X	
27	Number and Percentage of Subjects with TEAEs (Safety Population)	X	X
28	Summary of TEAEs (Safety Population)	X	X
29	Number and Percentage of Subjects with TESAEs (Safety Population)	X	X
30	Number and Percentage of Subjects With TEAEs by Severity Grade (Safety Population)	X	X
31	Number and Percentage of Subjects With TEAEs by Level of Relationship to Tc 99m Tilmanocept (Safety Population)	X	
32	Number and Percentage of Subjects With TEAEs by Level of Relationship to Procedure (Safety Population)	X	X
33	Serum Chemistry Clinical Laboratory Parameters Summary Statistics by Arm (Safety Population)	X	X
34	Hematology Clinical Laboratory Parameters Summary Statistics by Arm (Safety Population)	X	
35	Urinalysis Clinical Laboratory Parameters Summary Statistics by Arm (Safety Population)	X	
36	Serum Chemistry Clinical Laboratory Parameters Shift Table by Arm (Safety Population)	X	X
37	Hematology Clinical Laboratory Parameters Shift Table by Arm (Safety Population)	X	
38	Urinalysis Clinical Laboratory Parameters Shift Table by Arm (Safety Population)	X	
39	ECG Parameters Summary Statistics by Arm (Safety Population)	X	X
40	ECG Shift Table by Arm (Safety Population)	X	X
41	Vital Signs Summary Statistics by Arm (Safety Population)	X	X
42	ACR Response Classification by Time Point (ITD Population)	X	X
43	ACR Response Classification by Time Point (PP Population)	X	
44	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria (ITD Population)	X	X
45	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria (PP Population)	X	
46	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 24 Clinical Improvement Criteria (ITD Population)	X	
47	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 24 Clinical Improvement Criteria (PP Population)	X	
48	Concordance of $\Delta TUV_{global[5w]}$ and Week 12 Clinical Improvement Criteria (ITD Population)	X	

Table No.	Table Title	Included in Final Tables	Shown in Appendix B
49	Concordance of $\Delta TUV_{global[5w]}$ and Week 12 Clinical Improvement Criteria (PP Population)	X	
50	Concordance of $\Delta TUV_{global[5w]}$ and Week 24 Clinical Improvement Criteria (ITD Population)	X	
51	Concordance of $\Delta TUV_{global[5w]}$ and Week 24 Clinical Improvement Criteria (PP Population)	X	
52	Concordance of $\Delta TUV_{global[5w]}$ Bucketing with ACPA Bucketing and Week 12 Clinical Improvement Criteria (ITD Population)	X	
53	Concordance of $\Delta TUV_{global[5w]}$ Bucketing with ACPA Bucketing and Week 12 Clinical Improvement Criteria (PP Population)	X	
54	Concordance of $\Delta TUV_{global[5w]}$ Bucketing with ACPA Bucketing and Week 24 Clinical Improvement Criteria (ITD Population)	X	
55	Concordance of $\Delta TUV_{global[5w]}$ Bucketing with ACPA Bucketing and Week 24 Clinical Improvement Criteria (PP Population)	X	
56	Concordance of $\Delta TUV_{global[12w]}$ Bucketing and Week 24 Clinical Improvement Criteria (ITD Population)	X	
57	Concordance of $\Delta TUV_{global[12w]}$ Bucketing and Week 24 Clinical Improvement Criteria (PP Population)	X	
58	Concordance of $\Delta TUV_{global[12w]}$ and Week 24 Clinical Improvement Criteria (ITD Population)	X	
59	Concordance of $\Delta TUV_{global[12w]}$ and Week 24 Clinical Improvement Criteria (PP Population)	X	
60	Concordance of $\Delta TUV_{global[12w]}$ Bucketing with ACPA Bucketing and Week 24 Clinical Improvement Criteria (ITD Population)	X	
61	Concordance of $\Delta TUV_{global[12w]}$ Bucketing with ACPA Bucketing and Week 24 Clinical Improvement Criteria (PP Population)	X	
62	Concordance of ACPA Bucketing Alone and Week 12 Clinical Improvement Criteria (ITD Population)	X	
63	Concordance of ACPA Bucketing Alone and Week 12 Clinical Improvement Criteria (PP Population)	X	
64	Concordance of ACPA Bucketing Alone and Week 24 Clinical Improvement Criteria (ITD Population)	X	
65	Concordance of ACPA Bucketing Alone and Week 24 Clinical Improvement Criteria (PP Population)	X	
66	ACPA Summary Statistics in Arm 3 (ITD Population)	X	X
67	ACPA Summary Statistics in Arm 3 (PP Population)	X	

Figure No.	Figure Title	Included in Final Figures	Shown in Appendix B
Fig1	Plot of ΔTUV_{global} by Imaging Time Point and ACR-20 for Arm 3 (ITD Population)	X	X
Fig2	Plot of ΔTUV_{global} by Imaging Time Point and ACR-50 for Arm 3 (ITD Population)	X	
Fig3	Plot of ΔTUV_{global} by Imaging Time Point and ACR-70 for Arm 3 (ITD Population)	X	

Figure No.	Figure Title	Included in Final Figures	Shown in Appendix B
Fig4	Plot of ΔTUV_{global} by Imaging Time Point and CDAI for Arm 3 (ITD Population)	X	
Fig5	Plot of ΔTUV_{global} by Imaging Time Point and DAS28 for Arm 3 (ITD Population)	X	

Listing No.	Data Listing Title	Included in Final Listings	Shown in Appendix B
DL1	Subject Disposition Data Listing	X	X
DL2	Inclusion/Exclusion Data Listing	X	X
DL3	Protocol Deviations Data Listing	X	X
DL4	Demographics Data Listing	X	X
DL5	Subjects Excluded from ITD Population Data Listing	X	X
DL6	Subjects Excluded from PP Population Data Listing	X	X
DL7	Subjects Excluded from Safety Population Data Listing	X	X
DL8	Medical History Data Listing	X	X
DL9	Prior and Concomitant Medications Data Listing	X	X
DL10	Prior and Concomitant RA Medications Data Listing	X	X
DL11	Adverse Events Data Listing	X	X
DL12	Subject Laboratory Profiles – Hematology Data Listing	X	X
DL13	Subject Laboratory Profiles – Serum Chemistry Data Listing	X	
DL14	Subject Laboratory Profiles – Urinalysis Data Listing	X	
DL15	Subject Laboratory Profiles – Rheumatology Panel Data Listing	X	
DL16	Physical Exam Data Listing	X	X
DL17	ACR/EULAR 2010 Classification Data Listing	X	X
DL18	ACR Data Listing	X	X
DL19	CDAI, DAS28, HAQ-DI, and WPI Scores Data Listing	X	X
DL20	DAS-28 by Joint Data Listing	X	X
DL21	DAS-28 by Subject Data Listing	X	X
DL22	Vital Signs Data Listing	X	X
DL23	ECG Parameters Data Listing	X	X
DL24	Study Drug Administration Data Listing	X	X
DL25	Post-Injection Imaging Data Listing	X	X
DL26	SPECT/CT Reader Results Data Listing – Hands and Wrists	X	X
DL27	TUV Data Listing	X	X
DL28	ACR Response Criteria Data Listing	X	X

9.0 References

Food & Drug Administration Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research (September 1998). Guidance for Industry: ICH E9 Statistical Principles for Clinical Trials.

Forkman, J. (2009) Estimator and Tests for Common Coefficients of Variation in Normal Distributions. *Communications in Statistics: Theory and Methods*. **38**:2, pp233- 251.

Appendix A – Tables, Figures and Listing Specifications

Orientation

Tables and figures will be displayed in landscape.

Margins

Margins will be 1 inch on all sides. Table and listing boundaries will not extend into the margins.

Font

Courier New, 8 point.

Headers

The table number will be on the first line of the title. The title area will contain the Sponsor name, the study number, and the name of the table. The title area will contain the page number (Page x of y) on the far right, 1 line above the name of the table.

Footers

- The first line will be a solid line.
- Next will be any footnotes regarding information displayed in the table.
- Below these footnotes will be displayed “STATKING Clinical Services (DD-MMM-YYYY)” on the far left.
- The last line will display the name of the SAS program that generated the table and (if applicable) the source data reference.

Table Disclaimer

The format of the mock tables shown in the appendix of this SAP will be the format of the deliverable tables to the extent that Word document constructed tables can match production tables produced by SAS. This formatting includes the content and format of the header and footer areas of the tables. The Sponsor agrees to the format of the tables as shown in the appendix.

Further programming charges will be applicable for changes in the format of tables (including title statements, notes, data dependent footnotes, etc.) made after the approval of the SAP.

Missing Values

All missing values will be displayed on the output tables/listings as blanks.

Display of Study Dates

The date format to be used is dd-mmm-yyyy. Missing parts of dates are not shown (ie, for a missing day value, the value displayed is in yyyy-mm format).

Appendix B – Table Shells

Table 1. Subject Disposition by Study Arm
Navidea Biopharmaceuticals - Study No. NAV3-31

		Arm[a]			
		HC (N = xx)	RA-2 (N = xx)	RA-3 (N = xx)	Overall (N = xx)
Screen Failures					xx
Enrolled		xx	xx	xx	xx
Completed		xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
Withdrawn		xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
Withdrawal Reason	Adverse Event	xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
	Protocol Violation				
	Lost to Follow Up	xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
	Withdrawal of Consent	xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
	Sponsor Discretion	xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
	Investigator Discretion	xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
	Death	xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)
	Other	xx (xxx%)	xx (xxx%)	xx (xxx%)	xx (xxx%)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
The denominator for all percentages in the table is the number of enrolled subjects in the respective arm and overall.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Page x of y

Table 2. Demographics and Baseline Data Summary Statistics by Arm – Continuous Variables
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Variable	Arm[a]	Mean	Std Dev	n	Min	Max	Median
Age (years)	HC	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	xxx	xxx	xxx	xxx	xxx	xxx
Height (inches)	HC	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	xxx	xxx	xxx	xxx	xxx	xxx
Weight (pounds)	HC	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	xxx	xxx	xxx	xxx	xxx	xxx
Time from Diagnosis of RA (months)[b]	RA-2	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	xxx	xxx	xxx	xxx	xxx	xxx

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
[b] Calculated as the difference between date of enrollment and date of RA diagnosis.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Table 3. Demographics and Baseline Data Summary Statistics by Arm – Categorical Variables
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

		Arm[a]		
Variable	Category	HC (N=xxx)	RA-2 (N=xxx)	RA-3 (N=xxx)
Gender	Male	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	Female	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Race	American Indian or Alaska Native	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	Asian	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	Black or African American	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	Native Hawaiian or Other Pacific Islander	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	White	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	Other			
Ethnicity	Hispanic or Latino	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	Not Hispanic or Latino	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Table 4. Summary of Study Drug Administration by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

	Arm[a]	Mean	Std Dev	n	Min	Max	Median
Tc 99m Dose (mCi)	HC	xxxx	xxxx	xx	xxxx	xxxx	xxxx
	RA-2	xxxx	xxxx	xx	xxxx	xxxx	xxxx
	RA-3	xxxx	xxxx	xx	xxxx	xxxx	xxxx
Mass Dose (µg)	HC	xxxx	xxxx	xx	xxxx	xxxx	xxxx
	RA-2	xxxx	xxxx	xx	xxxx	xxxx	xxxx
	RA-3	xxxx	xxxx	xx	xxxx	xxxx	xxxx
Total Volume of Tc 99m Tilmanocept Injected (mL)	HC	xxxx	xxxx	xx	xxxx	xxxx	xxxx
	RA-2	xxxx	xxxx	xx	xxxx	xxxx	xxxx
	RA-3	xxxx	xxxx	xx	xxxx	xxxx	xxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Table 5. Summary of TUV by Arm, Study Day and DAS28 Joint
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Arm[a]	DAS28 Joint	Study Day	View	Number of Subjects	Mean	Std Dev	n	Min	Max	Median
xxxx	xxxxxxxxxxxxxx	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
			xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
		xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
			xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
	xxxxxxxxxxxxxxx	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
			xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
		xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
			xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
	xxxxxxxxxxxxxxx	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
			xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
		xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x
			xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints for all groups (HC, RA-2, RA-3), all imaging days (for RA-2 and RA-3 only). Table format is repeated for the PP population.

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Table 7. Summary for Eight-Day Longitudinal Stability of TUV (Arm 2 Only)
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 1 of 4

Global TUV or DAS28 Joint TUV	View	Reader	Number of Subjects	Mean Difference	Std Dev	Coefficient of Variation	n	Min	Max	Median
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xxx	xx.xxx	xx.xx

STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population.

Table 7. Summary for Eight-Day Longitudinal Stability of TUV (Arm 2 Only)
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 2 of 4

Global TUV or DAS28 Joint TUV	View	Reader	Number of Subjects	Mean Absolute Difference	80th Percentile of Absolute Differences	90th Percentile of Absolute Differences
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xx	xx.xx

STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population.

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Table 7. Summary for Eight-Day Longitudinal Stability of TUV (Arm 2 Only)
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 3 of 4

Global TUV or DAS28 Joint TUV	View	Reader	Percent |ΔTUV| < 7.5%	95% Exact Confidence Limits
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)

STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population.

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Table 7. Summary for Eight-Day Longitudinal Stability of TUV (Arm 2 Only)
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 4 of 4

Global TUV or DAS28 Joint TUV	View	Reader	RMSD	95% Confidence Limits	95% Bootstrap Confidence Limits
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)

STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population.

Table 9. Analysis of Eight-Day Longitudinal Stability of ΔTUV_{global}
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Reader	$\lvert\Delta TUV_{global}\rvert \leq 7.5\%$	Frequency	Fraction	95% Exact Confidence Limits	P-value[1]
xxx	True	xx	x.xxx	(x.xxx, x.xxx)	x.xxxx
	False	xx	x.xxx		
xxx	True	xx	x.xxx	(x.xxx, x.xxx)	x.xxxx
	False	xx	x.xxx		
xxx	True	xx	x.xxx	(x.xxx, x.xxx)	x.xxxx
	False	xx	x.xxx		

[1] Exact binomial test of the hypotheses $H_0: \pi \leq 0.80$ vs $H_1: \pi > 0.80$.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for the PP population.

Table 11. Summary of Day 0 vs Day 8 RA Images
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 1 of 2

Global TUV or DAS28 Joint TUV	View	Reader	Number of Joints	Mean Difference	Standard Deviation of Difference	Minimum Difference	Median Difference	Maximum Difference
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
xxxxxxxxxxxxxxxx	xx	xx	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx

If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population.

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Table 11. Summary of Day 0 vs Day 8 RA Images
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 2 of 2

DAS28 Joint	Reader	View	$\|\Delta TUV_{global}\| \leq 7.5\%$	95% Confidence Limits	80 %tile	90 %tile
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx
xxxxxxxxxxxxxxxx	xx	xx	xx.xxx	(xx.xxx, xx.xxx)	xx.xxx	xx.xxx

If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population.

Table 13. Assessment of Mean/Variance Relationship by Time Point
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 1 of 2

Global TUV or DAS28 Joint TUV	View	Reader	Arm[a]	Number of Joints	Mean	Std Dev	Minimum	Maximum	Median
xxxxxxxxxxxxxxx	xx	xx	HC	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
			RA-2	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
		xx	HC	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
			RA-2	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
		xx	HC	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
			RA-2	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
	xx	xx	HC	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
			RA-2	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
		xx	HC	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
			RA-2	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
		xx	HC	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx
			RA-2	xx	xx.xxx	xx.xxx	xx.xx	xx.xx	xx.xx

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen).
If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population, .

Table 13. Assessment of Mean/Variance Relationship by Time Point
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 2 of 2

Global TUV or DAS28 Joint TUV	View	Reader	Arm[a]	Coefficient of Variation	95% Confidence Limits	Bootstrap Confidence Interval
xxxxxxxxxxxxxxx	xx	xx	HC	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
			RA-2	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
		xx	HC	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
			RA-2	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
		xx	HC	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)
			RA-2	xx.xxx	(xx.xxx, xx.xxx)	(xx.xxx, xx.xxx)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen).
If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

All evaluated DAS28 joints will be included in this table. Table format is repeated for the PP population.

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Table 15. Normal Range of TUV in Healthy Control Subjects
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Joint	View	Reader	Number of Joints	Mean	Standard Deviation	Estimated 5 %tile	Estimated 95 %tile
xxxxxxxxxxxxx	xx	xx	xxx	xxx.xx	xx.xxx	xx.xxx	xx.xxx
		xx	xxx	xxx.xx	xx.xxx	xx.xxx	xx.xxx
		xx	xxx	xxx.xx	xx.xxx	xx.xxx	xx.xxx
	xx	xx	xxx	xxx.xx	xx.xxx	xx.xxx	xx.xxx
		xx	xxx	xxx.xx	xx.xxx	xx.xxx	xx.xxx
		xx	xxx	xxx.xx	xx.xxx	xx.xxx	xx.xxx

If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

DAS28 joints will not be pooled in this table. Table format is repeated for the PP population.

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Table 17. RA Status Summaries
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Arm[a]	RA Status Measure	Study Visit	Data Type	Mean	Standard Deviation	n	Min	Max	Median
xxxx	xxxxxxxxxxx	xxx	Baseline	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
		xxx	RAW	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
			CFB	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
	xxxxxxxxxxx	xxx	Baseline	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
		xxx	RAW	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
			CFB	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
	xxxxxxxxxxx	xxx	Baseline	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
		xxx	RAW	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x
			CFB	xxxx.x	xxx.xx	xxx	xxxx.x	xxxx.x	xxxx.x

[a] RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for the PP population. RAW and CFB lines will exist only for ARM RA-3.

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Table 19. Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 5 Weeks in Arm 3
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 1 of 3: Reader x

Measure[a]	Component Parameter	Time Point	Kendall Correlation[b]	95% Confidence Limits[c]	n	Mean	Standard Deviation
ΔTUV		5 Weeks	--	--	xxx	xxxxxx	xxxxxx
ΔTUV		12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔCDAI	Overall	5 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔCDAI	xxxxxxxx	5 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔACR	xxxxxxxx	5 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔDAS28		5 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx

[a] Change in ACR will be evaluated through the following components of the ACR Response Criteria: swollen joint count, tender joint count, patient assessment, physician assessment, pain scale, disability/functionality questionnaire, and acute phase reactant (ESR).
[b] Kendall rank correlation between ΔTUV at 5 weeks and the indicated measurement and time point.
[c] Confidence limits calculated using Fisher's Z-transformation.
If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for each reader. Entire table (all parts) is repeated for the PP population.

Table 21. Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 12 Weeks in Arm 3
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 1 of 3: Reader x

Measure[a]	Component Parameter	Time Point	Kendall Correlation[b]	95% Confidence Limits[c]	n	Mean	Standard Deviation
ΔTUV		12 Weeks	--	--	xxx	xxxxxx	xxxxxx
ΔTUV		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔCDAI	Overall	12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔCDAI	xxxxxxxx	12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔACR	xxxxxxxx	12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔDAS28		12 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx

[a] Change in ACR will be evaluated through the following components of the ACR Response Criteria: swollen joint count, tender joint count, patient assessment, physician assessment, pain scale, disability/functionality questionnaire, and acute phase reactant (ESR).
[b] Kendall rank correlation between ΔTUV at 12 weeks and the indicated measurement and time point.
[c] Confidence limits calculated using Fisher's Z-transformation.
If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for each reader. Entire table (all parts) is repeated for the PP population.

Table 23. Kendall Rank Correlation of ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 24 Weeks in Arm 3
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Part 1 of 3: Reader x

Measure[a]	Component Parameter	Time Point	Kendall Correlation[b]	95% Confidence Limits[c]	n	Mean	Standard Deviation
ΔTUV		24 Weeks	--	--	xxx	xxxxxx	xxxxxx
ΔCDAI	Overall	24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔCDAI	xxxxxxxx	24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔACR	xxxxxxxx	24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx
ΔDAS28		24 Weeks	x.xxx	(x.xxx, x.xxx)	xxx	xxxxxx	xxxxxx

[a] Change in ACR will be evaluated through the following components of the ACR Response Criteria: swollen joint count, tender joint count, patient assessment, physician assessment, pain scale, disability/functionality questionnaire, and acute phase reactant (ESR).
[b] Kendall rank correlation between ΔTUV at 24 weeks and the indicated measurement and time point.
[c] Confidence limits calculated using Fisher's Z-transformation.
If there are no major protocol deviations, then analysis tables for the ITD and PP populations will contain identical results.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for each reader. Entire table (all parts) is repeated for the PP population.

Table 25. Frequency Counts of Localization in SPECT/CT Imaging in RA-2 Subjects
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

	Localized on SPECT/CT		
Reader	No	Yes	Total
xx	xxx xx.x%	xxx xx.x%	xxx
xx	xxx xx.x%	xxx xx.x%	xxx
xx	xxx xx.x%	xxx xx.x%	xxx

STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for the PP population.

Table 27. Number and Percentage of Subjects with TEAEs
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

	Arm[b]			
Adverse Event Category[a]:	HC	RA-2	RA-3	Overall
Total Number of TEAEs	xxx	xxx	xxx	xxx
Subjects with at Least One TEAE	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] Adverse events coded with MedDRA Coding Dictionary Version XXX.
[b] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 28. Summary of TEAEs
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

	Arm[b]			
	HC	RA-2	RA-3	Overall
Subjects With at Least One TEAE	xxx	xxx	xxx	xxx
Maximum TEAE Severity Grade				
Mild	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Moderate	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Severe	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Highest Relationship of TEAE to Tc 99m tilmanocept				
Definitely Not [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Probably Not [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Possibly [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Probably [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Definitely [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Highest Relationship of TEAE to Study Procedure				
Definitely Not [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Probably Not [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Possibly [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Probably [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Definitely [n(%)]	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Subjects with at Least One TESAE	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] Adverse events coded with MedDRA Coding Dictionary Version XXX.
[b] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 29. Number and Percentage of Subjects with TESAEs
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

	Arm[b]			
Adverse Event Category[a]:	HC	RA-2	RA-3	Overall
Total Number of TESAEs	xxx	xxx	xxx	xxx
Subjects with at Least One TESAE	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] Adverse events coded with MedDRA Coding Dictionary Version XXX.
[b] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 30. Number and Percentage of Subjects With TEAEs by Severity Grade
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 1 of 4 – HC[a]

Adverse Event Category[b]:	Severity Grade		
	Mild	Moderate	Severe
Total Number of TEAEs	xxx	xxx	xxx
Subjects with at Least One TEAE	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Adverse events coded with MedDRA Coding Dictionary Version XXX.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format repeats for RA-2 and RA-3 (Parts 2 and 3) and overall (Part 4).

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Table 31. Number and Percentage of Subjects With TEAEs by Level of Relationship
to Tc 99m Tilmanocept
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 1 of 4 – HC[a]

	Level of Relationship				
Adverse Event Category[b]:	Definitely Not	Probably Not	Possibly Related	Probably Related	Definitely Related
Total Number of TEAEs	xxx	xxx	xxx	xxx	xxx
Subjects with at Least One TEAE	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
System Organ Class 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 1	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Preferred Term 2	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Adverse events coded with MedDRA Coding Dictionary Version XXX.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format repeats for RA-2 and RA-3 (Parts 2 and 3) and overall (Part 4). Full Table (all parts) repeats for Table 32.

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Table 33. Serum Chemistry Clinical Laboratory Parameters Summary Statistics by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Parameter(units)	Arm[a]	Visit	Data Type[b]	Mean	Std Dev	n	Min	Max	Median
xxxxxxxx(xxx)	HC	Screening (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	Screening (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0	RAW						
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
		Day 8	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Screening (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
xxxxxxxx(xxx)	HC	Screening (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	Screening (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0	RAW						
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
		Day 8	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Screening (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		xxxxxxxxxx	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] RAW = data recorded in database; CFB = change from baseline= (parameter value at the current time point)-(Baseline parameter value).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format repeats for tables 34 and 35.

Table 36. Serum Chemistry Clinical Laboratory Parameters Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 1 of 7: Arm 1 HC[a] – Day 0

	Baseline Result/ Post-Injection Result								
Panel/Parameter (units)	Low/ Low	Low/ Normal	Low/ High	Normal/ Low	Normal/ Normal	Normal/ High	High/ Low	High/ Normal	High/ High
xxxxxxxx/ xxxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxxx/ xxxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxxx/ xxxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Tables 37 (Hematology) and 38 (Urinalysis)

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Table 36. Serum Chemistry Clinical Laboratory Parameters Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 2 of 7: Arm 2 RA-2[a] – Day 0

	Baseline Result/ Post-Injection Result								
Panel/Parameter (units)	Low/ Low	Low/ Normal	Low/ High	Normal/ Low	Normal/ Normal	Normal/ High	High/ Low	High/ Normal	High/ High
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Tables 37 (Hematology) and 38 (Urinalysis)

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Table 36. Clinical Laboratory Parameters Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 3 of 7: Arm 2 RA-2[a] – Day 8

	Baseline Result/ Post-Injection Result								
Panel/Parameter (Units)	Low/ Low	Low/ Normal	Low/ High	Normal/ Low	Normal/ Normal	Normal/ High	High/ Low	High/ Normal	High/ High
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Tables 37 (Hematology) and 38 (Urinalysis)

Table 36. Serum Chemistry Clinical Laboratory Parameters Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 4 of 7: Arm 3 RA-3[a] – Day 0

	Baseline Result/ Post-Injection Result								
Panel/Parameter (Units)	Low/ Low	Low/ Normal	Low/ High	Normal/ Low	Normal/ Normal	Normal/ High	High/ Low	High/ Normal	High/ High
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Tables 37 (Hematology) and 38 (Urinalysis)

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Table 36. Serum Chemistry Clinical Laboratory Parameters Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 5 of 7: Arm RA-3[a] – Week 5

	Baseline Result/ Post-Injection Result								
Panel/Parameter (Units)	Low/ Low	Low/ Normal	Low/ High	Normal/ Low	Normal/ Normal	Normal/ High	High/ Low	High/ Normal	High/ High
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Tables 37 (Hematology) and 38 (Urinalysis)

Table 36. Serum Chemistry Clinical Laboratory Parameters Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 6 of 7: Arm 3 RA-3[a] – Week 12

	Baseline Result/ Post-Injection Result								
Panel/Parameter (Units)	Low/ Low	Low/ Normal	Low/ High	Normal/ Low	Normal/ Normal	Normal/ High	High/ Low	High/ Normal	High/ High
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Tables 37 (Hematology) and 38 (Urinalysis)

Table 36. Serum Chemistry Clinical Laboratory Parameters Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Part 7 of 7: Arm 3 RA-3[a] – Week 24

	Baseline Result/ Post-Injection Result								
Panel/Parameter (Units)	Low/ Low	Low/ Normal	Low/ High	Normal/ Low	Normal/ Normal	Normal/ High	High/ Low	High/ Normal	High/ High
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxxxxx/ xxxxxxxx(xxx)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Tables 37 (Hematology) and 38 (Urinalysis)

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Table 39. ECG Parameters Summary Statistics by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

ECG Parameter(units)	Arm[a]	Visit	Data Type[b]	Mean	Std Dev	n	Min	Max	Median
xxxxxxxxx (xxx)	HC	Day 0 Pre-Injection (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	Day 0 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	Day 8 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 8 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Day 0 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Week 5 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Week 5 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Week 12 Pre-Injection (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Week 12 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Week 24 Pre-Injection (Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Week 24 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
[b] RAW = data recorded in database; CFB = change from baseline= (parameter value at the current time point)-(Baseline parameter value).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Table 40. ECG Shift Table by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

		Baseline Result/ Post-Injection Result			
Arm	Visit	Abnormal/ Abnormal	Abnormal/ Normal	Normal/ Abnormal	Normal/ Normal
xxxx	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxx	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
xxxx	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
	xxxxx	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Table 41. Vital Signs Summary Statistics by Arm
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Vital Sign Parameter (units)	Arm[a]	Visit	Data Type[b]	Mean	Std Dev	n	Min	Max	Median
xxxxxxxxx (xxx)	HC	Day 0 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	Day 0 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-2	Day 8 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 8 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Day 0 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Day 0 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Week 5 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Week 5 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Week 12 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Week 12 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx
	RA-3	Week 24 Pre-Injection(Baseline)	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		Week 24 Post-Injection	RAW	xxx	xxx	xxx	xxx	xxx	xxx
			CFB	xxx	xxx	xxx	xxx	xxx	xxx

[a] HC = healthy control, RA-2 = rheumatoid arthritis (stable treatment regimen), RA-3 = rheumatoid arthritis (candidate for changed treatment).
[b] RAW = data recorded in database; CFB = change from baseline= (parameter value at the current time point)-(Baseline parameter value).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 42. ACR Response Classification by Time Point
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Arm 3 – RA-3[a] Subjects Only

	Assessment			
Time Point	ACR-0	ACR-20	ACR-50	ACR-70
Week 5	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Week 12	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)
Week 24	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table Format Repeats for PP Population.

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Table 44. Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Arm 3 – RA-3[a] Subjects Only

Part 1 of 6: ACR-20

	Clinical Assessment				
$\Delta TUV_{global[5w]}$ Classification	Improved	Not Improved	Total	Measure	Value[b]
Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Uncertainty Coefficient (C|R)	xxxx (xxxxx)
Not Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Uncertainty Coefficient (Symmetric)	xxxx (xxxxx)
Total	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Positive Predictive Value	xxxx
				Confidence Limits	(xxxx, xxxx)
				Negative Predictive Value	xxxx
				Confidence Limits	(xxxx, xxxx)
				Overall Accuracy	xxxx
				Confidence Limits	(xxxx, xxxx)

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Values in parentheses are standard errors for the uncertainty coefficients, and p-values for positive predictive value and negative predictive value testing Ho: $\pi = 0.6$.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

This part repeats for Part 2 (ACR-50), Part 3 (ACR-70), Part 4 (CDAI), Part 5 (DAS28), and Part 6 (HAQ-DI)
Full table format repeats for PP population (table 45) and for tables 46 - 65.

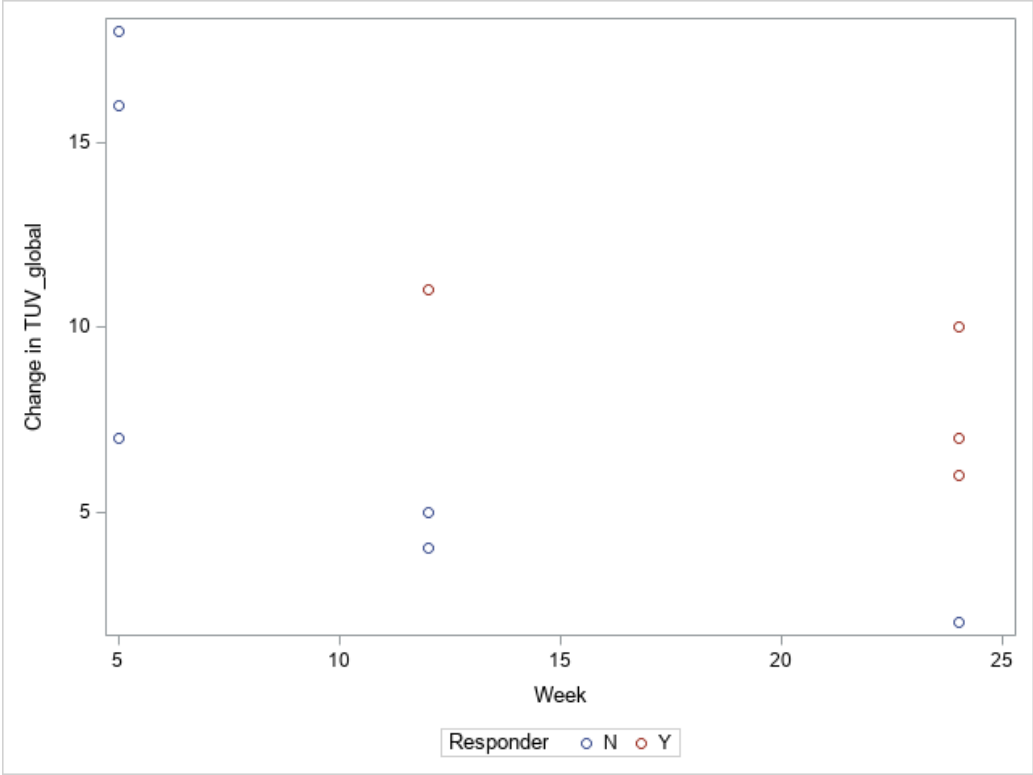
Table 66. ACPA Summary Statistics in Arm 3
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)

Visit	Variable or Category[a]	Statistic	ITD Population (N=xxx)
Screening (Baseline)	Quantitative ACPA Level	Mean (Std Dev)	xxx (xxxx)
		n	xxx
		Median	xxx
		(Min, Max)	(xxx, xxx)
	ACPA Level ≤ 70	n (%)	xxx (xxx%)
	ACPA Level > 70	n (%)	xxx (xxx%)

[a] Categories correspond to the ACPA bucketing levels used in the prediction of improvement algorithms.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format repeats for PP population

Figure 1. Plot of ΔTUV_{global} by Imaging Time Point and ACR-20 for Arm 3
Navidea Biopharmaceuticals - Study No. NAV3-31
ITD Population (N=xxx)



Responder status based on ACR-20 at each week.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Figure format repeats for Figures 2-5. Footnote text will be updated in each figure to correspond to the clinical assessment noted in the title (ACR-50, ACR-70, CDAI, or DAS28).

Data Listing 1. Subject Disposition Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31

Arm[a]	Subject No.	Disposition Status	Date of Completion or Withdrawal	Withdrawal Reason
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 2. Inclusion/Exclusion Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31

Arm[a]	Subject No.	Did Subject Meet All Eligibility Criteria?	Criterion Category	Criterion	Was a Waiver Granted?	Is Subject a Screen Failure?
xxxxxx	xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx
xxxxxx	xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx
xxxxxx	xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx
xxxxxx	xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 3. Protocol Deviations Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31

Arm[a]	Subject No.	Date of Deviation	Deviation Description	Deviation Category (Major/Minor)
xxxxxx	xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx
xxxxxx	xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx
xxxxxx	xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx
xxxxxx	xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 4. Demographics Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Informed Consent Date/Time	Time from Diagnosis of RA (months)[b]	Date of Birth	Height (inches)	Weight (pounds)	Age (years)	Gender	Race	Ethnicity
xxxxxx	xxxx	xxxxxx	xxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx
xxxxxx	xxxx	xxxxxx	xxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx
xxxxxx	xxxx	xxxxxx	xxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx
xxxxxx	xxxx	xxxxxx	xxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Calculated as the difference between date of enrollment and date of RA diagnosis.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 5. Subjects Excluded from ITD Population Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
All Enrolled Subjects (N=xxx)

Arm[a]	Subject No.	Reason for Exclusion
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 6. Subjects Excluded from PP Population Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
All Enrolled Subjects (N=xxx)

Arm[a]	Subject No.	Reason for Exclusion
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 7. Subjects Excluded from Safety Population Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
All Enrolled Subjects (N=xxx)

Arm[a]	Subject No.	Reason for Exclusion
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 8. Medical History Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	MedDRA System Organ Class[b]/ MedDRA Preferred Term/ CRF Verbatim Term	Start Date	Resolution/Stop Date	Ongoing?
xxxxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxx
		xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxx
		xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Medical history terms coded with MedDRA Coding Dictionary Version xxx.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 9. Prior and Concomitant Medications Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Drug Preferred Term[b]/ Verbatim/ ATC Level 1 Text/ ATC Level 4 Text	Indication	Frequency	Start Date	Stop Date	Route	Ongoing?
xxxxxx	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx
xxxxxx	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Medications coded with WHO Coding Dictionary xxxxxxxxx
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 10. Prior and Concomitant RA Medications Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Drug Preferred Term[b]/ Verbatim/ ATC Level 1 Text/ ATC Level 4 Text	Indication	Frequency	Start Date	Stop Date	Route	Ongoing?
xxxxxx	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx
xxxxxx	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Medications coded with WHO Coding Dictionary xxxxxxxxx
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 11. Adverse Events Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Start Date and Time/ End Date and Time	Start Date and Time of Nearest Previous tilmanocept Injection	Treatment Emergent?	MedDRA System Organ Class[b]/ MedDRA Preferred Term/ CRF Verbatim Term	Severity	Relation to Tc-99m tilmanocept/ Procedure	Serious?	Outcome
xxxxxx	xxxxxxxxx	xxxxxxx xxxxxxx/ xxxxxxx xxxxxxx	xxxxxxx xxxxxxx	xxx	xxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx	xxxxxxxx	xxxxxxxx/ xxxxxxxx	xxx	xxxxxxxx
xxxxxx	xxxxxxxxx	xxxxxxx xxxxxxx/ xxxxxxx xxxxxxx	xxxxxxx xxxxxxx	xxx	xxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxx	xxxxxxxx	xxxxxxxx/ xxxxxxxx	xxx	xxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Adverse events coded with MedDRA Coding Dictionary Version xxx.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 12. Subject Laboratory Profiles - Hematology Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

						Normal Range		
Arm[a]	Subject No.	Visit	Sample Date and Time	Lab Parameter (Units)	Result	Lab Low	Lab High	Clin. Sig?
xxxxxx	xxxx	xxxxxxxx	xxxxxxxx / xx:xx	xxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
				xxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
				xxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
				xxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
				xxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
				xxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table format is repeated for Serum Chemistry, Urinalysis, and Rheumatology Panel Listings (Listings 13, 14, 15).

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Data Listing 16. Physical Exam Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Visit	Date Conducted	Body System	Result	Abnormality
xxxxxx	xxxx	xxxxxxx	xxxxxxx	General Appearance	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Skin	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Eyes, Ears, Nose, Throat	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Head and Neck	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Lungs	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Heart	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Abdomen	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Lymph Nodes	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Musculoskeletal	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Nervous System	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
				Other: XXXXXX	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 17. ACR/EULAR 2010 Classification Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

				ACR/EULAR 2010				
Arm[a]	Subject No.	Visit	Date	Joint Involvement	Serology	Acute-Phase Reactants	Duration of Symptoms	Total Score
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 18. ACR Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

				ACR Components									
Arm[a]	Subject No.	Visit	Date	Tender Joint Count	Swollen Joint Count	Patient's Global Disease Activity	Physician's Global Disease Activity	Patient Assessment of Pain	Patient Assessment Physical Function	Acute Phase Reactant Value	ACR-20	ACR-50	ACR-70
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 19. CDAI, DAS28, HAQ-DI, and WPI Scores Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

				CDAI Component									
Arm[a]	Subject No.	Visit	Date	Tender Joint Score	Swollen Joint Score	Patient's Global Disease Activity	Physician's Global Disease Activity	CDAI Total Score	CDAI Improved	DAS28 Total Score	DAS28 Improved	HAQ-DI Total Score	WPI Total Score
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	x	xx.x	x	xx.x	xx.x
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	x	xx.x	x	xx.x	xx.x

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 20. DAS28 by Joint Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

					DAS28 Joint Classification	
Arm[a]	Subject No.	Visit	Date	Joint	Result (Right Body)	Result (Left Body)
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx
				xxxxxxxxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 21. DAS28 by Subject Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

				DAS28				
Arm[a]	Subject No.	Visit	Date	Tender Joint Count	Swollen Joint Count	Patient VAS Global (mm)	Erythrocyte Sedimentation Rate (ESR; mm/hr)	DAS28 Score
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 22. Vital Signs Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Visit	Date	Time	Temp. (°F)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)	Respirations per Minute
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxxxx	xxx	xxx	xxx	xxx	xxx
				xxxxx	xxx	xxx	xxx	xxx	xxx
				xxxxx	xxx	xxx	xxx	xxx	xxx
xxxxxx	xxxx	xxxxxxx	xxxxxxx	xxxxx	xxx	xxx	xxx	xxx	xxx
				xxxxx	xxx	xxx	xxx	xxx	xxx
				xxxxx	xxx	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 23. ECG Parameters Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Visit	Date	Time	Heart Rate (bpm)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTcF Interval (msec)	Overall Interpretation
xxxxxx	xxxx	xxxxxx	xxxxx	xxxxxx	xxxxxx	xxxxxxxx	xxxxxxx	xxxxxx	xxxx	xxxxxxxxxxxxxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 24. Study Drug Administration Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Date/ Time of Injection	Anatomic Location of Injection	Pre-Injection Radioactivity (mCi)/Time of Measurement	Post-Injection Radioactivity (mCi)/Time of Measurement	Calculated Amount of Administered Radioactivity (mCi)	Calculated Mass Dose (µg)	Volume Injected (mL)	Lot Number
xxxxxx	xxxx	xxxxxxxx/ xxxx	xxxxxxxx	xxx/ xxxx	xxx/ xxxx	xxx	xxx	xxx	xxx
xxxxxx	xxxx	xxxxxxxx/ xxxx	xxxxxxxx	xxx/ xxxx	xxx/ xxxx	xxx	xxx	xxx	xxx
		xxxxxxxx/ xxxx	xxxxxxxx	xxx/ xxxx	xxx/ xxxx	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 25. Post-Injection Imaging Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Visit	Date of Imaging	Start Time of Imaging	SPECT/CT Image Finding
xxxxxx	xxxx	xxxxxxxx	xxxxxx	xx:xx	xxx
xxxxxx	xxxx	xxxxxxxx	xxxxxx	xx:xx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] SPECT/CT imaging performed only in study arm RA-2.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 26. SPECT/CT Reader Results Data Listing – Hands and Wrists
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Post-Injection Imaging Time Point	Joint	SPECT/CT Image Finding
xxxxxx	xxxx	xxxxxxx	xxxxxxxxxxx xxxxxxxxxxx	xxxx
xxxxxx	xxxx	xxxxxxx	xxxxxxxxxxx xxxxxxxxxxx	xxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 27. TUV Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

		TUV Classification of Improvement						
Arm[a]	Subject No.	Algorithms Predicting Improvement[b]	Algorithms Predicting No Improvement[b]	Reader No.	Visit	Date/Time	Region of Interest[c]	TUV
xxxxxx	xxxx	x, x, x	x, x, x, x	xxx	xxxxxxx	xxxxxx	xxxxxx	xxxxx
				xxx	xxxxxxx	xxxxxx	xxxxxx	xxxxx
				xxx	xxxxxxx	xxxxxx	xxxxxx	xxxxx
				xxx	xxxxxxx	xxxxxx	xxxxxx	xxxxx
				xxx	xxxxxxx	xxxxxx	xxxxxx	xxxxx
xxxxxx	xxxx	x	x, x, x, x, x, x	xxx	xxxxxxx	xxxxxx	xxxxxx	xxxxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] 1 = Change in Global TUV(5w) Bucketing, 2 = Change in Global TUV(5w), 3 = Change in Global TUV(5w) Bucketing with ACPA Bucketing, 4 = Change in Global TUV(12w) Bucketing, 5 = Change in Global TUV(12w), 6 = Change in Global TUV(12w) Bucketing with ACPA Bucketing, 7 = ACPA Bucketing Alone.
[c] Region of Interest is joint for all arms, and joint or Global for the RA-2 and RA-3 arms.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 28. ACR Response Criteria Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-31
Safety Population (N=xxx)

Arm[a]	Subject No.	Visit	ACR Response Assessment[b]	Number of Tender Joints	Number of Swollen Joints	Patient Global Assessment	Physician Global Assessment	HAQ Total	VAS Pain Score	ESR
xxxxxx	xxxx	xxxxxxx	xxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xxxxxx	xxxx	xxxxxxx	xxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

[a] HC = Healthy Control, RA-2 = Rheumatoid Arthritis (stable treatment regimen), RA-3 = Rheumatoid Arthritis (candidate for changed treatment).
[b] Response assessment will be blank for baseline measurements.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas