Statistical Analysis Plan (SAP)

Evaluation of Tc 99m Tilmanocept Imaging for the Early Prediction of Anti-TNFα Therapy Response in Patients with Moderate to Severe Active Rheumatoid Arthritis (RA)

Study No: NAV3-33

Version 4.0

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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 3.0 to 4.0

- Updated signature page to reflect changes in staff and contacts
- Removed non-bucketing algorithms, so that all subjects with $TUV_{global[b]} < 5$ will be predicted non-responders
- Clarified secondary objective in section 1.0 for qualitative assessment of Tc 99m tilmanocept imaging by removing language pertaining to change from baseline
- Added description of tipping point analyses for mean imputation of clinical status at week 24 and TUV prediction to section 2.3
- Modified section 4.1.4 to indicate that the secondary efficacy variables will be based on bucketing algorithms
- Removed table and listing shells for non-bucketing algorithms
- Removed columns, footnotes, and annotations in TLF shells for non-bucketing algorithms
- Added figures to summarize tipping point analyses using 95% confidence intervals to TLF shells

Version 2.0 to 3.0

- Added description of analysis of qualitative assessments to section 4.2.3
- Added description of analysis of the additive effect of either quantitative or qualitative assessment of Tc 99m tilmanocept imaging to section 4.2.3
- Modified description of concordance of improvement classification of each algorithm with clinical improvement criteria to indicate that p-values for sensitivity and specificity will be included
- Added tables for concordance of qualitative assessment of Tc 99m tilmanocept imaging with clinical improvement criteria
- Added tables for concordance of qualitative plus quantitative assessment of Tc 99m tilmanocept imaging with clinical improvement criteria
- Added tables for summary of generalized linear mixed model to asses the additive effect of either quantitative or qualitative assessment of Tc 99m tilmanocept imaging on patient response status
- Added p-values for all clinical assessments in addition to those for ACR50 to tables 15-22
- Added data listing for qualitative imaging assessments
- Added data listing for qualitative plus quantitative assessments which differ from original quantitative assessment
- Updated TLF table of contents to remove redundant tables
- Added new tables and listings to TLF table of contents
- Renumbered TLFs to include new additions

Version 1.0 to 2.0

- Changed intent-to-diagnose population in section 2.2 to include all subjects who were injected with Tc 99m tilmanocept at visit 2 and received planar imaging of the hands at visit 2, regardless of if they received any other assessments.
- Changed wording in section 1.3 to specify that at least the same two of three readers must reject both null hypotheses for the two co-primary endpoints to be achieved.
- Added detail in section 2.3 regarding imputation strategies, and proposed secondary imputation strategy for some missing data scenarios if primary imputation strategy does not work.
- Added detail in section 4.1.1.1 regarding the possibility for a patient's TUV prediction from bucketing vs. non-bucketing to differ, and how these findings will be summarized.
- Added tables 27-28 to summarize the number of patients who TUV predictions from bucketing vs. non-bucketing differ.
- Added data listing 28 to provide detail on patients who TUV predictions from bucketing vs. non-bucketing differ.

Table of Contents

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
CT	X-ray computed tomography
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	metacarpophalangeal
MedDRA	Medical Dictionary for Regulatory Activities
MI	macrophage-involved contribution
NPV	Negative Predictive Value
OA	Overall Accuracy
PIP	proximal interphalangeal
PP	per protocol
PPV	Positive Predictive Value
PR	the time from the onset of the P wave to the start of the QRS complex
QRS	time from the start of the Q wave to the end of the S wave, representing ventricular depolarization
QT	time from the start of the Q wave to the end of the T wave
QTcF	QT interval with Fridericia's correction formula
RA	rheumatoid arthritis
ROI	region of interest
SAE	serious adverse event

Term	Definition
SAP	statistical analysis plan
SJC	swollen joint count
SOC	system organ class
SPECT	single photon emission computed tomography
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)
TJC	tender joint count
TUV	Tilmanocept uptake value
US	United States
WPI	Widespread Pain Index

INTRODUCTION

Description

This statistical analysis plan (SAP) is consistent with Amendment #3 of the study protocol (dated 29 September 2023) and includes details of efficacy and safety summaries for use in support of the planned trial, as outlined in ICH E3 (Structure and Content of Clinical Study Reports) and ICH E9 (Statistical Principles for Clinical Trials). Considerations were also given to the FDA Guidance for industry on Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies (June 2004), FDA Guidance for Industry on Clinical Trial Imaging Endpoint Process Standards (April 2018) and Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests - Guidance for Industry and FDA Staff (March 2007). The study design and analysis plans align with recommendations received from the US FDA at the End of Phase 2 meeting on 01 September 2021 (IND 132943).

1.0 Synopsis of Study Design/Procedures

This is a prospective, multicenter, open-label study designed to evaluate the early predictive capacity of quantitative Tc 99m tilmanocept planar imaging for downstream clinical response(s) in individuals with moderate to severe rheumatoid arthritis (RA) who are candidates for change in anti-TNFα therapy. Temporal changes (from baseline to 5-weeks) in quantitative imaging will be correlated with longitudinal changes (from baseline to 12 weeks and baseline to 24 weeks) in RA clinical assessments, with the intent of evaluating the clinical utility of Tc 99m tilmanocept for the expedited evaluation of antirheumatic treatment efficacy when compared with longitudinal assessments in clinical practice.

The study objectives are as follows:

Primary:

- To demonstrate that global tilmanocept uptake values (TUV_{global}) obtained before initiation of anti-TNFa therapy ($TUV_{global[b]}$) and at 5 weeks ± 1 week following change in therapy ($TUV_{global[5w]}$) has a specificity of greater than 80% to correctly specify a clinical non-response to therapy at 24 weeks.
- To demonstrate that TUV_{global} obtained before initiation of anti-TNFα therapy and at 5 weeks ± 1 week following change in therapy has a sensitivity of greater than 65% to correctly classify a positive clinical response to therapy at 24 weeks.

Key Secondary

- To evaluate the negative predictive value (NPV) of TUV_{global} obtained before initiation of anti-TNFα therapy ($TUV_{global[b]}$) relative to a clinical non-response to therapy at 24 weeks.

Secondary

- To evaluate the sensitivity and specificity of TUV_{global} obtained before initiation of anti-TNFα therapy and at 5 weeks ± 1 week following change in therapy relative to a positive clinical response or a non-response to therapy at 12 weeks.
- To evaluate the NPV of $TUV_{global[b]}$ relative to a clinical non-response to therapy at 12 weeks.
- To evaluate the positive predictive value (PPV), NPV, and overall accuracy (OA) of TUV_{global} obtained before initiation of anti-TNFα therapy and at 5 weeks ± 1 week ($\Delta TUVglobal_{[5w]}$) following change in therapy relative to a positive clinical response or a non-response to therapy at 12 and/or 24 weeks.
- To evaluate the qualitative assessment of Tc 99m tilmanocept imaging to predict clinical response or non-response following a change in anti-TNFα therapy.
- To evaluate the additive effect of either quantitative or qualitative assessment of Tc 99m tilmanocept imaging to the other at baseline and change from baseline to 5 weeks ± 1 week to predict clinical response or non-response following a change in anti-TNFα therapy.
- To evaluate the correlation of changes in TUV_{global} obtained before initiation of anti-TNFα therapy and at 5 weeks ± 1 week following a change in therapy with changes in composite clinical assessments and their constituent parameters at 12 and/or 24 weeks.
- To evaluate the correlation of changes in TUV_{global} obtained before initiation of anti-TNFα therapy and at 5 weeks ± 1 week following a change in therapy with changes in clinical assessments at 12 and/or 24 weeks for specific anti-TNFα bDMARD agents.
- To evaluate the ability of changes in TUV_{global} obtained before initiation of anti-TNFα therapy and at 12 weeks ± 1 week following change in therapy to accurately predict a clinical response or non-response at 24 weeks.
- To evaluate the correlation of changes with TUV_{global} and changes in clinical RA assessments as a means to monitor therapy.
- To evaluate sensitivity and specificity in patient subgroups.

- To evaluate the safety of IV-administered tilmanocept radiolabeled with Tc 99m.

The statistical endpoints that address these objectives are defined in Section 4 (efficacy) and Section 5 (safety). Refer to Section 2.2.1 for subgroup definitions and considerations.

1.1 Design and Treatment

This is a prospective, open-label, multicenter study designed to evaluate the early predictive capacity of quantitative Tc 99m tilmanocept planar imaging for downstream clinical response(s) in individuals with moderate to severe RA who are candidates for change in anti-TNFα therapy.

All patients will receive an IV dose of 150 mcg tilmanocept radiolabeled with 10 mCi of Tc 99m prior to imaging.

1.2 Study Procedures

Prior to the initiation of a new anti-TNFα therapy, patients will undergo baseline rheumatological evaluations of ACR/EULAR 2010, Clinical Disease Activity Index (CDAI), DAS28, and Health Assessment Questionnaire Disability Index (HAQ-DI) for the characterization of disease activity. After these evaluations, patients will receive an IV dose of 150 mcg tilmanocept radiolabeled with 10 mCi of Tc 99m and undergo baseline planar imaging of the bilateral hands and wrists. Upon completion of baseline imaging procedures, patients will commence a new anti-TNFα bDMARD treatment regimen and return to the clinic 5 +/- 1 weeks, 12 +/- 1 weeks, and 24 +/- 1 weeks later for a series of rheumatological evaluations (including CDAI, DAS28, ACR Response Criteria, and HAQ-DI), drug administration, and bilateral hand/wrist imaging.

Images will undergo centralized quantification for the derivation of joint-specific and global TUV. At the joint level, TUV is defined as the intrapatient ratio of the average pixel intensity of a joint to the average pixel intensity of the reference region. TUV_{global} is a per patient summary of TUV_{joint} values greater than the normative database representing RA-specific inflammation.

All images will be read by three nuclear medicine specialists trained in the reading of these images. Each reader will work independently of the other readers. Each reader will provide both a qualitative read and map regions of interest for calculation of TUV.

Temporal differences in TUV_{global} from baseline to 5 +/- 1 weeks of therapy ($\Delta TUV_{global[5w]}$) will be compared with longitudinal clinical outcomes at 12 +/- 1

and 24 +/- 1 weeks of therapy defined by changes in CDAI ($\Delta CDAI_{[12/24w]}$), changes in ACR Response Criteria ($\Delta ACR_{[12/24w]}$), and changes in DAS28 ($\Delta DAS28_{[12/24w]}$) to evaluate the efficacy of TUV_{global} for the accelerated prediction of clinical response to antirheumatic drugs.

Refer to the clinical study protocol for further details on the study procedures and for the schedule of events table.

1.3 Sample Size

NAV3-33 is sized with respect to achieving specified goals in the co-primary endpoints of sensitivity and specificity of $\Delta TUV_{global[5w]}$ with bucketing. Sensitivity and specificity require knowledge of the patient's clinical status at Week 24, and so hypothesis testing will be performed after classification. The value of $\Delta TUV_{global[5w]}$ necessary to predict response vs. non-response and the value of $TUV_{global[b]}$ at baseline necessary to predict non-response will be determined in advance. The classification procedure occurs in two stages, following the baseline image acquisition and (possibly) following the 5 week image acquisition and calculation of $\Delta TUV_{global[5w]}$. After the baseline imaging, patients whose $TUV_{global[b]}$ is < 5 are predicted to be non-responders. After $\Delta TUV_{global[5w]}$ is available, patients whose $TUV_{global[b]}$ is ≥ 5 and D% is ≤ -10% are predicted to be responders. All other patients are predicted to be non-responders. The Week 24 ACR50 will be used as the primary determination of clinical response for the reference standard

The hypotheses for the co-primary endpoints to be tested are:

$$H_{O1}: \pi_{\mathrm{Sp}} \leq 0.8$$
$$H_{A1}: \pi_{\mathrm{Sp}} > 0.8;$$

And

$$H_{O2}: \pi_{\mathrm{Se}} \leq 0.65$$
$$H_{A2}: \pi_{\mathrm{Se}} > 0.65.$$

In the above π_{Sp} represents the true specificity of the classification procedure and π_{Se} represents the true sensitivity of the classification procedure when used to predict the outcome of the anti-TNFα bDMARD inhibitor therapy at 24 weeks. An overall two-tailed Type I error rate of 0.05 (one-tailed 0.025) was used without adjusting for multiple endpoints, as both co-primary endpoints must be achieved in order to have a successful study. If the actual specificity is 0.92 and the actual sensitivity is 0.8, and if an exact binomial test is used to test the above hypotheses, a total of 98 clinical non-responders and 100 clinical responders are

needed for 90% power of the individual tests. That is, a minimum of 198 total patients is needed. This applies to a single reader.

To evaluate the power characteristics of this process with 3 correlated readers where at least the same two of the three readers must reject both null hypotheses above, a simulation study was performed. Correlated binomial random variables were generated using a copula. The hypotheses were tested for each simulated reader using an exact binomial test, and the number of iterations where at least the same two of the three readers rejected both hypotheses was counted. Under the conditions above this procedure has power 0.93 when $\rho = 0.7$ and 0.89 when $\rho = 0.9$.

In Arm 3 of the NAV3-31 study a ratio of 5 non-responders to 1 responder was observed. If this ratio is maintained in NAV3-33 for the $\Delta TUV_{global[5w]}$ with bucketing predictions, a total of 600 patients is needed to achieve the desired power. That is, a total of 500 clinical non-responder patients is expected to be enrolled before reaching the required 100 clinical responders.

Taking into account a 10% dropout rate, the anticipated total sample size for the study is approximately 672 patients (560 clinical non-responders and 112 clinical responders). That is:

- Clinical Non-Responders: 90% completion rate relative to 560 enrolled patients will result in 500 completed patients
- Clinical Responders: 90% completion rate relative to 112 enrolled patients will result in 100 completed patients

Because there is uncertainty about how responding and non-responding patients will enroll, enrollment may continue until at least 560 clinical non-responders and 112 clinical responders are participating in the study. The cumulative enrollment of clinical non-responders and responders will be tracked throughout the study in order to stop enrollment once the required number has been reached for each clinical category. This tracking of clinical response and non-response status will be performed by individuals without knowledge of the TUV data. At the Sponsor's discretion, the week 12 clinical response outcomes may be used to help track enrollment.

If the two co-primary endpoints are achieved (i.e., both null hypotheses are rejected for at least the same 2 out of 3 readers), then the following hypotheses will be tested at one-tailed 0.025 for the key secondary endpoint of NPV of $TUV_{global[b]}$ with respect to ACR50 at week 24:

$$H_{O3}: \pi_{\text{NPV}} \leq 0.7$$
$$H_{A3}: \pi_{\text{NPV}} > 0.7;$$

If the actual NPV is 0.85, and if an exact binomial test is used to test the above hypotheses, a total of 89 predicted non-responders using $TUV_{global[b]}$ are needed for 90% power and a total of 71 non-responders using $TUV_{global[b]}$ are needed for 80% power. Enrollment of predicted non-responders at baseline will be tracked in order to ensure enough subjects are enrolled to achieve at least 80% power for this endpoint.

All enrollment tracking will be done in aggregate by individuals without knowledge of the subject-level data. Enrollment tracking will include the total number of predicted non-responders at baseline, the total number of clinical responders at or beyond week 12, and the total number of clinical non-responders at or beyond week 12.

2.0 Data Analysis Considerations

2.1 Types of Analyses

Efficacy, safety, and descriptive analyses will be performed on the data collected in this trial.

2.2 Analysis Populations

The following analysis populations will be defined.

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 – Patients in the safety population meeting the following criteria are members of the ITD population:

- were injected with Tc 99m tilmanocept at Visit 2 (Day 0)
- received planar imaging of the hands at Visit 2 (Day 0)

This population will include all patients for whom a prediction might be made, although some patients may be excluded from analysis under this definition if a prediction cannot be made due to missing imaging or clinical data.

Per-protocol (PP) population – The PP population will include all ITD patients 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 patient 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.

2.2.1 Subgroup Definitions and Considerations

Summaries of the agreement between the primary TUV prediction algorithm and all clinical outcomes will be performed in the following subgroups:

- Age (< 60 years, 60 years and older)
- Sex
- Race (white, non-white)
- Time from RA diagnosis (< 5 years, 5 years and longer)
- Disease severity at baseline (moderate, severe)
- Previous use of biologics (yes, no)
- Previous and current use of DMARDs (background methotrexate only, other conventional DMARDs only, combination of methotrexate and other conventional DMARDs)
- Specific anti-TNFα therapy taken during trial
- Prednisone use on-study (on a stable dose, no prednisone use)
- ACPA level at baseline (high/low: 85 and above / < 85)

The study will make every effort to enroll enough patients in each of these subgroups so that half-widths of the 95% confidence intervals of sensitivity and specificity are less than 20%. P-values on parameter estimates will not be included.

2.3 Missing Data Conventions

In the statistical analysis of the primary efficacy endpoints of the study, missing data will be handled according to the following table of missing data scenarios:

Variable	Scenario	Primary Imputation Rule	Secondary Imputation Rule
Clinical Status at Week 24	Patient discontinued anti-TNFα therapy prior to Week 24 due to non-response to therapy	Patient classified as a clinical non-responder	N/A

Clinical Status at Week 24	Patient discontinued study for reasons not attributable to non-response to therapy	Clinical status set to missing	Impute mean clinical response*
TUV Prediction	Patient has $TUV_{global[b]}$ that is ≥ 5 but is missing week 5 imaging data	Impute mean prediction**	Prediction is Y (patient has improved)
TUV Prediction	Patient is missing $TUV_{global[b]}$	Prediction set to missing	N/A

*Mean clinical response will be calculated as follows: calculate the proportion of unique patients whose clinical status is Y (patient is a clinical responder), randomly allocate this proportion of "Y" to the missing clinical status at week 24 values. Assign all other missing clinical status values "N" (patient is clinical non-responder).

**Mean prediction will be calculated as follows: using the patients for whom $TUV_{global[b]} \geq 5$, calculate the proportion whose TUV prediction is Y (patient has improved), randomly allocate this proportion of "Y" to the missing TUV predictions. Assign all other missing TUV predictions "N" (patient has not improved).

To assess the appropriateness of the missing data conventions for clinical status at week 24 and TUV prediction using mean imputation, tipping point analyses will be performed. Specifically, 95% confidence intervals for sensitivity and specificity will be plotted against increasing proportions of missing values imputed as "Y" to see at what point the conclusion of the study is reversed.

2.4 Interim Analyses

There are no interim analyses planned for this study.

2.5 Calculation of TUV

TUV_{joint} is defined to be the mean pixel intensity of the region of interest (ROI) defined by the reader divided by the mean pixel intensity of the hand reference region. Each of the three blinded readers will have determined the TUV distribution for both anterior and posterior views of the wrists and hands (wrists, MCPs, and PIPs) for the healthy patient normative data set. For all of the following calculations, the reader-specific TUV_{joint} limits will be used. The upper

limit of normal is defined to be the upper limit of the 95% prediction interval of the joint-and-view-specific TUV in the normative data set.

For each RA patient do the following.

Step 1: Calculate TUV_{joint} for each of the 22 DAS28 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}:

$$\mathrm{MI}_{\mathrm{joint}} = \frac{\mathrm{TUV}_{\mathrm{joint}} - \overline{\mathrm{H}}_{\mathrm{joint}}}{\overline{\mathrm{H}}_{\mathrm{joint}}}.$$

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:

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

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 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 (i.e., those injected with tilmanocept) will be summarized for all patients in the safety population. Continuous variables will be displayed via summary statistics (mean, median, sample size, standard deviation, minimum and maximum). Categorical variables will be summarized via counts and percentages.

Detailed listings of all baseline and demographic data for each patient will also be provided as shown in Section 7 below.

4.0 Analysis of Efficacy

4.1 Description of Efficacy Variables

4.1.1 Definition of Responder/Non-Responder Status

4.1.1.1 Prediction Algorithms

The following two prediction algorithms will be defined for use in evaluating primary and secondary efficacy. Each algorithm will be used to predict a clinical response, and the subsequent prediction will be compared to the actual observed clinical response as described in Sections 4.1.2 and 4.1.3. In addition to these two prediction algorithms, the use of $TUV_{global[b]}$ alone for the prediction of non-response will be analyzed as the key secondary efficacy variable. If $TUV_{global[b]}$ is < 5 then the prediction is N (no improvement), otherwise, prediction is Y (improvement).

The $\Delta TUV_{global[5w]}$ values will be used to predict improvement at 12 and 24 weeks according to algorithm 1. The $\Delta TUV_{global[12w]}$ values will be used to predict improvement at 24 weeks according to algorithm 2. Both algorithms 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 $TUV_{global[b]}$ represents the global TUV at baseline:

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

$$\Delta TUV_{global[5w]} = \frac{TUV_{global[5w]} - TUV_{global[b]}}{TUV_{global[b]}} \leq -0.10$$

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

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

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

$$\Delta TUV_{global[12w]} = \frac{TUV_{global[12w]} - TUV_{global[b]}}{TUV_{global[b]}} \leq -0.10$$

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.

Tables which display the concordance between the predictions from each algorithm vs. clinical assessment will be provided. A listing showing which algorithms provide a prediction of improvement vs. no improvement, by patient, will also be provided.

4.1.1.2 Clinical Assessments

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 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 and 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 and 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 and swollen joint counts as well as 70% improvement in at least 3 of the other 5 criteria.

Each patient 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 patient is a yes for ACR70 at a given time point, then the patient is also a yes for ACR50 and ACR20 for that same time point.

A patient 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 patient 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 patient is not improved.
- If the baseline value is less than 10, a decrease of more than 1 will be classified as improved. Otherwise the patient is not improved.

A patient 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 patient is not improved on the HAQ-DI.

4.1.2 Description of Primary Efficacy Variables

The primary efficacy variables for determining clinical response are the response/non-response status at 24 weeks to new or changed anti-TNFα bDMARD therapy for rheumatoid arthritis based on the ACR50 criterion. The primary efficacy variables for determining the predicted response and non-response are $\Delta TUV_{global[5w]}$ bucketing.

The co-primary efficacy endpoints of the study are:

- Specificity of $\Delta TUV_{global[5w]}$ bucketing with respect to ACR50 at week 24.
- Sensitivity of $\Delta TUV_{global[5w]}$ bucketing with respect to ACR50 at week 24.

4.1.3 Description of Key Secondary Efficacy Variables

The key secondary efficacy endpoint is:

- NPV of $TUV_{global[b]}$ with respect to ACR50 at week 24.

4.1.4 Description of Secondary Efficacy Variables

The secondary efficacy predictor variables are the findings based on prediction algorithms 1 and 2, as described in Section 4.1.1.

The secondary efficacy response variables are:

- CDAI score at baseline ($CDAI_b$), 12 ($CDAI_{12w}$) and 24 weeks ($CDAI_{24w}$)
- ACR Response Criteria (ACR20, ACR50, ACR70) at 12 and 24 weeks
- DAS28 Score at baseline, 12 weeks, and 24 weeks
- 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 at baseline, 12 weeks, and 24 weeks, including:
  - TJC
  - SJC
  - Patient Global Assessment
  - Physician Global Assessment

The secondary efficacy endpoints are as follows:

- Sensitivity and specificity of $\Delta TUV_{global[5w]}$ bucketing with respect to ACR50 at week 12.
- NPV, PPV, and OA of $\Delta TUV_{global[5w]}$ bucketing with respect to ACR50 at weeks 12 and 24.
- NPV of $TUV_{global[b]}$ with respect to ACR50 at week 12
- $TUV_{global[b]}$ 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), by the CFB of DAS28 to 12 ± 1 weeks and 24 ± 1 weeks ($\Delta DAS28_{12w}$ and $\Delta DAS28_{24w}$,

respectively) and by the CFB in each of the ACR Response Criteria components at 12 ± 1 weeks and at 24 ± 1 weeks.

- $\Delta TUV_{global[5w]}$ bucketing 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).
- Concordance of $\Delta TUV_{global[5w]}$ bucketing with clinical criteria, including ACR Response Criteria, CDAI, DAS28, and HAQ-DI©. Concordance between the predicted response or non-response status and the clinical criteria will be evaluated using NPV, PPV, sensitivity, specificity, and OA.
- Concordance of $\Delta TUV_{global[12w]}$ bucketing with clinical criteria, including ACR Response Criteria, CDAI, DAS28, and HAQ-DI©. Concordance between the improvement classifications and the clinical criteria will be evaluated using NPV, PPV, sensitivity, specificity, and OA.
- 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 $\Delta TUV_{global[5w]}$ bucketing 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

Efficacy analyses will be conducted on the ITD and PP populations, with the ITD population serving as the primary analysis population.

4.2.1 Analysis of Primary Efficacy Variables

The co-primary efficacy variables will be summarized by reader in a 2 by 2 contingency table displaying the cell frequencies and marginal totals at 24 weeks. The specificity of $\Delta TUV_{global[5w]}$ bucketing and the sensitivity of $\Delta TUV_{global[5w]}$ bucketing will be calculated for each reader. The 95% exact (Clopper-Pearson) confidence intervals will be provided for each of these parameters. Observed significance levels (p-values) for the exact binomial tests of specificity of $\Delta TUV_{global[5w]}$ bucketing greater than 0.8 and sensitivity of

$\Delta TUV_{global[5w]}$ bucketing greater than 0.65 (see hypotheses specified in Section 1.3 above) will be provided.

Sensitivity and specificity are defined according to the following cross-tabulation:

	Clinical Response		
Predicted Response	Responder	Non-Responder	Total
Responder	A	B	T_1
Non-Responder	C	D	T_2
Total	T_3	T_4	N

$$\text{Sensitivity} = A/T_3.$$
$$\text{Specificity} = D/T_4.$$

The above 2 by 2 contingency table will also be used to calculate the secondary efficacy endpoints of NPV, PPV, and OA as follows:

$$NPV = D/T_2.$$
$$PPV = A/T_1.$$
$$OA = (A + D)/N.$$

4.2.2 Analysis of Key Secondary Efficacy Variables

NPV of $TUV_{global[b]}$ will be calculated for each reader. The 95% exact (Clopper-Pearson) confidence intervals will be provided. Observed significance levels (p-values) for the exact binomial tests of NPV of $TUV_{global[b]}$ greater than 0.7 will be provided.

4.2.3 Analysis of Secondary Efficacy Variables

All RA quantitative assessment variables (CDAI, ACR Response Criteria component scores, DAS28 score, and HAQ-DI) will be summarized by 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 patient at that time point. That is, a patient who satisfies ACR50 also satisfies ACR20 but will not appear in the frequency count for ACR20.

The qualitative assessments will be summarized in a 2 by 2 contingency table displaying the cell frequencies and marginal totals by reader as shown in section

4.2.1 above. The PPV and NPV of the predicted response will be calculated for each reader, as will the OA. In addition, 95% exact confidence intervals will be provided for each of these parameters. Observed significance levels (p-values) for the exact binomial (Clopper-Pearson) tests of PPV and NPV (see sections 1.3 and 4.2.1 above) will be provided for each reader. These tests will be based on PPV of the predicted response greater than 0.65, and NPV of the predicted response greater than 0.7.

Concordance of improvement classification for: 1) $\Delta TUV_{global[5w]}$ bucketing and 2) $\Delta TUV_{global[12w]}$ bucketing with clinical criteria (ACR Response, CDAI, DAS28, and HAQ-DI) will be analyzed as follows. Note that the concordance of $\Delta TUV_{global[5w]}$ bucketing with ACR50 at 24 weeks is evaluated as co-primaries (sensitivity and specificity). For each of the RA improvement criteria, a cross-classification table will be provided. The PPV, NPV, sensitivity, specificity, and OA will be calculated and 95% exact (Clopper-Pearson) confidence intervals will be provided. Observed significance levels (p-values) for the exact binomial (Clopper-Pearson) tests for sensitivity and specificity will be provided for each reader.

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.

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.

The additive effect of either quantitative or qualitative assessment of Tc 99m tilmanocept imaging will be assessed with a generalized linear mixed model with the logit link function. The patient's response status will be used as the response variable. Fixed model terms for the quantitative and qualitative plus quantitative assessments will be used. The quantitative assessment will be based on $\Delta TUV_{global[5w]}$ bucketing. Random terms will be fit for the subject and reader within subject using the variance component model. A table displaying the partial hypothesis tests (Type 3 test) for the fixed effects will be displayed.

5.0 Analysis of Safety

All safety analyses will be performed on the Safety Population.

The safety analysis variables are defined as follows:

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

Adverse Events
Adverse events will be observed for each patient 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.

A summary of TEAEs will be constructed showing the following:

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

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

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 image acquisition on each imaging day (Visits 2, 4, 6, and 8). Only RA panel lab values and abnormal clinical laboratory 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. 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 within 30-minutes before and 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. 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 and within 30-minutes before and 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. 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 patients. 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 patients that withdraw before completion of the study, counts and percentages of the reasons for withdrawal will be tabulated. A data listing of all patient 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. All study drug administration data will be listed.

6.4 RA Evaluation and Screening Physical Exam

Each RA patient will undergo a DAS28 evaluation during screening and 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.

7.0 List of Analysis Tables, Figures and Listings

Table No.	Table Title	Included in Final Tables	Shown in Appendix B
1	Patient Disposition	X	X
2	Demographics and Baseline Data Summary Statistics - Continuous Variables (Safety Population)	X	X
3	Demographics and Baseline Data Summary Statistics– Categorical Variables (Safety Population)	X	X
4	Summary of Study Drug Administration (Safety Population)	X	X
5	Summary of TUV by Study Day and DAS28 Joint (ITD population)	X	X
6	Summary of TUV by Study Day and DAS28 Joint (PP Population)	X	
7	RA Status Summaries (ITD Population)	X	X
8	RA Status Summaries (PP Population)	X	
9	ACR Response Classification by Time Point (ITD Population)	X	X
10	ACR Response Classification by Time Point (PP Population)	X	
11	Concordance of $TUV_{global[b]}$ Alone and of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria (ITD Population)	X	X
12	Concordance of $TUV_{global[b]}$ Alone and of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria (PP Population)	X	
13	Concordance of $TUV_{global[b]}$ Alone and of $\Delta TUV_{global[5w]}$ Bucketing and Week 24 Clinical Improvement Criteria (ITD Population)	X	
14	Concordance of $TUV_{global[b]}$ Alone and of $\Delta TUV_{global[5w]}$ Bucketing and Week 24 Clinical Improvement Criteria (PP Population)	X	
15	Concordance of $\Delta TUV_{global[12w]}$ Bucketing and Week 24 Clinical Improvement Criteria (ITD Population)	X	X
16	Concordance of $\Delta TUV_{global[12w]}$ Bucketing and Week 24 Clinical Improvement Criteria (PP Population)	X	
17	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria in Subgroups (ITD Population)	X	X
18	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria in Subgroups (PP Population)	X	
19	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 24 Clinical Improvement Criteria in Subgroups (ITD Population)	X	
20	Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 24 Clinical Improvement Criteria in Subgroups (PP Population)	X	
21	Concordance of Qualitative Assessment of Tc 99m Tilmanocept Imaging and Week 12 Clinical Improvement Criteria (ITD Population)	X	X

Table No.	Table Title	Included in Final Tables	Shown in Appendix B
22	Concordance of Qualitative Assessment of Tc 99m Tilmanocept Imaging and Week 12 Clinical Improvement Criteria (PP Population)	X	
23	Concordance of Qualitative Assessment of Tc 99m Tilmanocept Imaging and Week 24 Clinical Improvement Criteria (ITD Population)	X	
24	Concordance of Qualitative Assessment of Tc 99m Tilmanocept Imaging and Week 24 Clinical Improvement Criteria (PP Population)	X	
25	Concordance of Qualitative plus Quantitative Assessment of Tc 99m Tilmanocept Imaging and Week 12 Clinical Improvement Criteria (ITD Population)	X	
26	Concordance of Qualitative plus Quantitative Assessment of Tc 99m Tilmanocept Imaging and Week 12 Clinical Improvement Criteria (PP Population)	X	
27	Concordance of Qualitative plus Quantitative Assessment of Tc 99m Tilmanocept Imaging and Week 24 Clinical Improvement Criteria (ITD Population)	X	
28	Concordance of Qualitative plus Quantitative Assessment of Tc 99m Tilmanocept Imaging and Week 24 Clinical Improvement Criteria (PP Population)	X	
29	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 5 weeks (ITD Population)	X	X
30	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 5 weeks (PP Population)	X	
31	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 12 weeks (ITD Population)	X	X
32	Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 12 weeks (PP Population)	X	
33	Kendall Rank Correlation of ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 24 weeks (ITD Population)	X	X
34	Kendall Rank Correlation of ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 24 weeks (PP Population)	X	
35	Summary of Generalized Linear Mixed Model to Asses the Additive Effect of either Quantitative or Qualitative assessment of Tc 99m Tilmanocept Imaging on Patient Response Status at Week 12 (ITD Population)	X	X
36	Summary of Generalized Linear Mixed Model to Asses the Additive Effect of either Quantitative or Qualitative assessment of Tc 99m Tilmanocept Imaging on Patient Response Status at Week 12 (PP Population)	X	
37	Summary of Generalized Linear Mixed Model to Asses the Additive Effect of either Quantitative or Qualitative assessment	X	

Table No.	Table Title	Included in Final Tables	Shown in Appendix B
	of Tc 99m Tilmanocept Imaging on Patient Response Status at Week 24 (ITD Population)		
38	Summary of Generalized Linear Mixed Model to Asses the Additive Effect of either Quantitative or Qualitative assessment of Tc 99m Tilmanocept Imaging on Patient Response Status at Week 24 (PP Population)	X	
39	Number and Percentage of Patients with TEAEs (Safety Population)	X	X
40	Summary of TEAEs (Safety Population)	X	X
41	Number and Percentage of Patients with TESAEs (Safety Population)	X	X
42	Number and Percentage of Patients with TEAEs by Severity Grade (Safety Population)	X	X
43	Number and Percentage of Patients with TEAEs by Level of Relationship to Tc 99m Tilmanocept (Safety Population)	X	X
44	Serum Chemistry Clinical Laboratory Parameters Summary Statistics (Safety Population)	X	X
45	Hematology Clinical Laboratory Parameters Summary Statistics (Safety Population)	X	
46	Urinalysis Clinical Laboratory Parameters Summary Statistics (Safety Population)	X	
47	Serum Chemistry Clinical Laboratory Parameters Shift Table (Safety Population)	X	X
48	Hematology Clinical Laboratory Parameters Shift Table (Safety Population)	X	
49	Urinalysis Clinical Laboratory Parameters Shift Table (Safety Population)	X	
50	ECG Parameters Summary Statistics (Safety Population)	X	X
51	ECG Shift Table (Safety Population)	X	X
52	Vital Signs Summary Statistics (Safety Population)	X	X

Figure No.	Figure Title	Included in Final Figures	Shown in Appendix B
Fig1	Plot of ΔTUV_{global} by Imaging Time Point and ACR20 (ITD Population)	X	X
Fig2	Plot of ΔTUV_{global} by Imaging Time Point and ACR50 (ITD Population)	X	
Fig3	Plot of ΔTUV_{global} by Imaging Time Point and ACR70 (ITD Population)	X	
Fig4	Plot of ΔTUV_{global} by Imaging Time Point and CDAI (ITD Population)	X	
Fig5	Plot of ΔTUV_{global} by Imaging Time Point and DAS28 (ITD Population)	X	
Fig6	Sensitivity Analysis #1 – Tipping Point Analysis to Assess the Appropriateness of Imputation of Clinical Status at Week 24 (ITD Population)	X	X

Figure No.	Figure Title	Included in Final Figures	Shown in Appendix B
Fig7	Sensitivity Analysis #2 – Tipping Point Analysis to Assess the Appropriateness of Imputation of TUV Prediction (ITD Population)	X	

Listing No.	Data Listing Title	Included in Final Listings	Shown in Appendix B
DL1	Patient 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	Patients Excluded from ITD Population Data Listing	X	X
DL6	Patients Excluded from PP Population Data Listing	X	X
DL7	Patients 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	Patient Laboratory Profiles – Hematology Data Listing	X	X
DL13	Patient Laboratory Profiles – Serum Chemistry Data Listing	X	
DL14	Patient Laboratory Profiles – Urinalysis Data Listing	X	
DL15	Patient 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	DAS28 by Joint Data Listing	X	X
DL21	DAS28 by Patient 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	Qualitative Assessment Data Listing	X	X
DL29	Qualitative plus Quantitative Assessments which differ from Original Quantitative Assessment	X	X
DL30	ACR Response Criteria Data Listing	X	X

8.0 References

N/A

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 (Date)” 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 (i.e., for a missing day value, the value displayed is in yyyy-mm format).

Appendix B – Table, Figure, and Listing Shells

Page x of y

Table 1. Patient Disposition
Navidea Biopharmaceuticals - Study No. NAV3-33

		Overall (N = xx)
Screen Failures		xx
Enrolled		xx
Completed		xx (xxx%)
Withdrawn		xx (xxx%)
Withdrawal Reason	Adverse Event	xx (xxx%)
	Protocol Violation	
	Lost to Follow Up	xx (xxx%)
	Withdrawal of Consent	xx (xxx%)
	Sponsor Discretion	xx (xxx%)
	Investigator Discretion	xx (xxx%)
	Death	xx (xxx%)
	Other	xx (xxx%)

The denominator for all percentages in the table is the number of enrolled patients.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 2. Demographics and Baseline Data Summary Statistics – Continuous Variables
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

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

[a] Calculated as the difference between date of enrollment and date of RA diagnosis.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 3. Demographics and Baseline Data Summary Statistics – Categorical Variables
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Variable	Category	Overall (N=xxx)
Gender	Male	xxx (xxx%)
	Female	xxx (xxx%)
Race	American Indian or Alaska Native	xxx (xxx%)
	Asian	xxx (xxx%)
	Black or African American	xxx (xxx%)
	Native Hawaiian or Other Pacific Islander	xxx (xxx%)
	White	xxx (xxx%)
	Other	
Ethnicity	Hispanic or Latino	xxx (xxx%)
	Not Hispanic or Latino	xxx (xxx%)
Severity of Disease	Mild	xxx (xxx%)
	Moderate	xxx (xxx%)
	Severe	xxx (xxx%)
Age Group	< 60 Years	xxx (xxx%)
	60 Years and Older	xxx (xxx%)
Previous Use of Biologics	Yes	xxx (xxx%)
	No	xxx (xxx%)
Baseline ACPA Level	Low (< 85)	xxx (xxx%)
	High (85 and Above)	xxx (xxx%)

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

Table 4. Summary of Study Drug Administration
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

	Mean	Std Dev	n	Min	Max	Median
Tc 99m Dose (mCi)	xxxx	xxxx	xx	xxxx	xxxx	xxxx
Mass Dose (µg)	xxxx	xxxx	xx	xxxx	xxxx	xxxx
Total Volume of Tc 99m Tilmanocept Injected (mL)	xxxx	xxxx	xx	xxxx	xxxx	xxxx

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

Page x of y

Table 5. Summary of TUV by Study Day and DAS28 Joint
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

DAS28 Joint	Study Day	View	Number of Patients	Mean	Std Dev	n	Min	Max	Median	%CV
xxxxxxxxxxxxxxx	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
		xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
		xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
xxxxxxxxxxxxxxxx	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
		xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
		xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
xxxxxxxxxxxxxxxx	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
		xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
	xxxx	xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x
		xxxxxxxxx	xx	xxxx.x	xxxx.x	xxx	xxxx.x	xxxx.x	xxxx.x	xxxx.x

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

Table format is repeated for the PP population (table 6).

Page x of y

Table 7. RA Status Summaries
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

RA Status Measure	Study Visit	Data Type	Mean	Standard Deviation	n	Min	Max	Median
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

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

Table format is repeated for the PP population (table 8).

Table 9. ACR Response Classification by Time Point
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

	Assessment			
Time Point	None	ACR20	ACR50	ACR70
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%)

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

Table Format Repeats for PP Population (table 10).

Page x of y

Table 11. Concordance of $TUV_{global[b]}$ Alone and of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

Part 1 of 6: ACR20

TUV Prediction Algorithm	Reader	Algorithm Classification	Clinical Assessment: Improved	Clinical Assessment: Not Improved	Total	Measure	Value[a]
$TUV_{global[b]}$ Alone	x	Not Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	NPV	xxxx
						Confidence Limits	(xxxx, xxxx)
						p-value	x.xxxx
$\Delta TUV_{global[5w]}$ Bucketing	x	Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Sensitivity	xxxx
						Confidence Limits	(xxxx, xxxx)
						p-value	x.xxxx
		Not Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)		
						Specificity	xxxx
		Total	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Confidence Limits	(xxxx, xxxx)
						p-value	x.xxxx
						NPV	xxxx
						Confidence Limits	(xxxx, xxxx)
						PPV	xxxx
						Confidence Limits	(xxxx, xxxx)
						OA	xxxx
						Confidence Limits	(xxxx, xxxx)

[a] p-values of TUV Alone for NPV testing Ho: $\pi = 0.7$ and of TUV Bucketing for sensitivity testing Ho: $\pi = 0.65$ and specificity testing Ho: $\pi = 0.8$.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Within each part, the above two TUV prediction algorithm results will be displayed for each reader and sorting will be done by reader then prediction algorithm. For TUV Alone, the only reported outcome measure is NPV. For TUV Bucketing, outcome measures will include sensitivity, specificity, PPV, NPV, and OA, as shown above.

This format repeats for Part 2 (ACR50), Part 3 (ACR70), Part 4 (CDAI), Part 5 (DAS28), and Part 6 (HAQ-DI).
Full table format repeats for PP population (table 12) and for tables 13 – 14.

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Table 15. Concordance of $\Delta TUV_{global[12w]}$ Bucketing and Week 24 Clinical Improvement Criteria
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

Part 1 of 6: ACR20

		Clinical Assessment				
Reader	$\Delta TUV_{global[12w]}$ Bucketing Classification	Improved	Not Improved	Total	Measure	Value
x	Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	PPV	xxxx
					Confidence Limits	(xxxx, xxxx)
	Not Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)		
					NPV	xxxx
	Total	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Confidence Limits	(xxxx, xxxx)
					Sensitivity	xxxx
					Confidence Limits	(xxxx, xxxx)
					Specificity	xxxx
					Confidence Limits	(xxxx, xxxx)
					OA	xxxx
					Confidence Limits	(xxxx, xxxx)

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

Within each part, the above will be displayed for each reader. This format repeats for Part 2 (ACR50), Part 3 (ACR70), Part 4 (CDAI), Part 5 (DAS28), and Part 6 (HAQ-DI). Full table format repeats for PP population (table 16).

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Table 17. Concordance of $\Delta TUV_{global[5w]}$ Bucketing and Week 12 Clinical Improvement Criteria in Subgroups
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

Part 1 of 6: ACR20

Subgroup	Reader	$\Delta TUV_{global[5w]}$ Bucketing Classification	Clinical Assessment: Improved	Clinical Assessment: Not Improved	Clinical Assessment: Total	Measure	Value
Female (N=xx)	x	Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	PPV	xxxx
						Confidence Limits	(xxxx, xxxx)
		Not Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	NPV	xxxx
						Confidence Limits	(xxxx, xxxx)
		Total	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Sensitivity	xxxx
						Confidence Limits	(xxxx, xxxx)
						Specificity	xxxx
						Confidence Limits	(xxxx, xxxx)
						OA	xxxx
						Confidence Limits	(xxxx, xxxx)
xxxxxxxxxx (N=xx)	x	Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	PPV	xxxx
						Confidence Limits	(xxxx, xxxx)
		Not Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	NPV	xxxx
						Confidence Limits	(xxxx, xxxx)
		Total	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Sensitivity	xxxx
						Confidence Limits	(xxxx, xxxx)
						Specificity	xxxx
						Confidence Limits	(xxxx, xxxx)
						OA	xxxx
						Confidence Limits	(xxxx, xxxx)

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

Within each part, the above will be displayed for each reader and subgroup, sorted by reader then subgroup. This format repeats for Part 2 (ACR50), Part 3 (ACR70), Part 4 (CDAI), Part 5 (DAS28), and Part 6 (HAQ-DI). Full table format repeats for PP population (table 18) and for tables 19 - 20.

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Table 21. Concordance of Qualitative Assessment of Tc 99m Tilmanocept Imaging and Week 12 Clinical Improvement Criteria
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

Part 1 of 6: ACR20

Reader	Qualitative Assessment	Clinical Assessment: Improved	Clinical Assessment: Not Improved	Total	Measure	Value[a]
x	Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	PPV	xxxx
					Confidence Limits	(xxxx, xxxx)
					p-value	x.xxxx
	Not Improved	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)		
					NPV	xxxx
	Total	xxx (xxx%)	xxx (xxx%)	xxx (xxx%)	Confidence Limits	(xxxx, xxxx)
					p-value	x.xxxx
					OA	xxxx
					Confidence Limits	(xxxx, xxxx)

[a] p-values for PPV testing Ho: $\pi = 0.65$ and for NPV testing Ho: $\pi = 0.7$.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Within each part, the above will be displayed for each reader. This format repeats for Part 2 (ACR50), Part 3 (ACR70), Part 4 (CDAI), Part 5 (DAS28), and Part 6 (HAQ-DI). Full table format repeats for PP population (table 22) and for tables 23 – 28.

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Table 29. Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 5 Weeks
Navidea Biopharmaceuticals - Study No. NAV3-33
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.
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 30).

Table 31. Kendall Rank Correlation of ΔTUV, ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 12 Weeks
Navidea Biopharmaceuticals - Study No. NAV3-33
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.
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 32).

Table 33. Kendall Rank Correlation of ΔCDAI, ΔACR Response Criteria Components, and ΔDAS28 with ΔTUV at 24 Weeks
Navidea Biopharmaceuticals - Study No. NAV3-33
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.
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 34).

Table 35. Summary of Generalized Linear Mixed Model to Asses the Additive Effect of either Quantitative or Qualitative Assessment of Tc 99m Tilmanocept Imaging on Patient Response Status at Week 12
Navidea Biopharmaceuticals - Study No. NAV3-33
ITD Population (N=xxx)

Model Term[a]	Parameter Estimate[b]	Standard Error	95% Confidence Limits	p-value[c]
Quantitative Imaging Assessment	xxx.xxx	xxx.xxx	(xxx.xxx, xxx.xxx)	x.xxxx
Qualitative plus Quantitative Imaging Assessment	xxx.xxx	xxx.xxx	(xxx.xxx, xxx.xxx)	x.xxxx

[a] Indicator variable for prediction of "Improved" compared to the reference category of "Not Improved."
[b] Estimate calculated from a generalized linear mixed model with the logit link function with patient response status as the response variable, fixed terms for quantitative and qualitative plus quantitative imaging assessment, and random terms for subject and reader within subject using a variance component model.
[c] Based on a two-sided t-test.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table is repeated for the PP population (table 36) and for tables 37 – 38.

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Table 39. Number and Percentage of Patients with TEAEs
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Adverse Event Category[a]:	Overall (N=xxx)
Total Number of TEAEs	xxx
Patients with at Least One TEAE	xxx (xxx%)
System Organ Class 1	xxx (xxx%)
Preferred Term 1	xxx (xxx%)
Preferred Term 2	xxx (xxx%)
System Organ Class 2	xxx (xxx%)
Preferred Term 1	xxx (xxx%)
Preferred Term 2	xxx (xxx%)

[a] Adverse events coded with MedDRA Coding Dictionary Version XXX.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 40. Summary of TEAEs
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

	Overall (N=xxx)
Patients With at Least One TEAE	xxx
Maximum TEAE Severity Grade	
Mild	xxx (xxx%)
Moderate	xxx (xxx%)
Severe	xxx (xxx%)
Highest Relationship of TEAE to Tc 99m tilmanocept	
Definitely Not [n(%)]	xxx (xxx%)
Probably Not [n(%)]	xxx (xxx%)
Possibly [n(%)]	xxx (xxx%)
Probably [n(%)]	xxx (xxx%)
Definitely [n(%)]	xxx (xxx%)
Highest Relationship of TEAE to Study Procedure	
Definitely Not [n(%)]	xxx (xxx%)
Probably Not [n(%)]	xxx (xxx%)
Possibly [n(%)]	xxx (xxx%)
Probably [n(%)]	xxx (xxx%)
Definitely [n(%)]	xxx (xxx%)
Patients with at Least One TESAE	xxx (xxx%)

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

Table 41. Number and Percentage of Patients with TESAEs
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Adverse Event Category[a]:	Overall (N=xxx)
Total Number of TESAEs	xxx
Patients with at Least One TESAE	xxx (xxx%)
System Organ Class 1	xxx (xxx%)
Preferred Term 1	xxx (xxx%)
Preferred Term 2	xxx (xxx%)
System Organ Class 2	xxx (xxx%)
Preferred Term 1	xxx (xxx%)
Preferred Term 2	xxx (xxx%)

[a] Adverse events coded with MedDRA Coding Dictionary Version XXX.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 42. Number and Percentage of Patients with TEAEs by Severity Grade
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

	Severity Grade		
Adverse Event Category[a]:	Mild	Moderate	Severe
Total Number of TEAEs	xxx	xxx	xxx
Patients 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] Adverse events coded with MedDRA Coding Dictionary Version XXX.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 43. Number and Percentage of Patients with TEAEs by Level of Relationship
to Tc 99m Tilmanocept
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

	Level of Relationship				
Adverse Event Category[a]:	Definitely Not	Probably Not	Possibly Related	Probably Related	Definitely Related
Total Number of TEAEs	xxx	xxx	xxx	xxx	xxx
Patients 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] Adverse events coded with MedDRA Coding Dictionary Version XXX.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Table 44. Serum Chemistry Clinical Laboratory Parameters Summary Statistics
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Parameter(units)	Visit	Data Type[a]	Mean	Std Dev	n	Min	Max	Median
xxxxxxxx(xxx)	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
	Day 8	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		CFB	xxx	xxx	xxx	xxx	xxx	xxx
xxxxxxxx(xxx)	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
	Day 8	RAW	xxx	xxx	xxx	xxx	xxx	xxx
		CFB	xxx	xxx	xxx	xxx	xxx	xxx

[a] 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 45 and 46.

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Table 47. Serum Chemistry Clinical Laboratory Parameters Shift Table
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Part 1 of 4: 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%)

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

Table format is repeated for Tables 48 (Hematology) and 49 (Urinalysis)

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Table 47. Serum Chemistry Clinical Laboratory Parameters Shift Table
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Part 2 of 4: 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%)

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

Table format is repeated for Tables 48 (Hematology) and 49 (Urinalysis)

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Table 47. Serum Chemistry Clinical Laboratory Parameters Shift Table
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Part 3 of 4: 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%)

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

Table format is repeated for Tables 48 (Hematology) and 49 (Urinalysis)

Table 47. Serum Chemistry Clinical Laboratory Parameters Shift Table
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Part 4 of 4: 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%)

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

Table format is repeated for Tables 48 (Hematology) and 49 (Urinalysis)

Table 50. ECG Parameters Summary Statistics
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

ECG Parameter(units)	Visit	Data Type[a]	Mean	Std Dev	n	Min	Max	Median
xxxxxxxxx (xxx)	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
	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
	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
	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] 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 51. ECG Shift Table
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

	Baseline Result/ Post-Injection Result			
Visit	Abnormal/ Abnormal	Abnormal/ Normal	Normal/ Abnormal	Normal/ Normal
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%)
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%)
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%)

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

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Table 52. Vital Signs Summary Statistics
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Vital Sign Parameter (units)	Visit	Data Type[a]	Mean	Std Dev	n	Min	Max	Median
xxxxxxxxx (xxx)	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
	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
	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
	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] 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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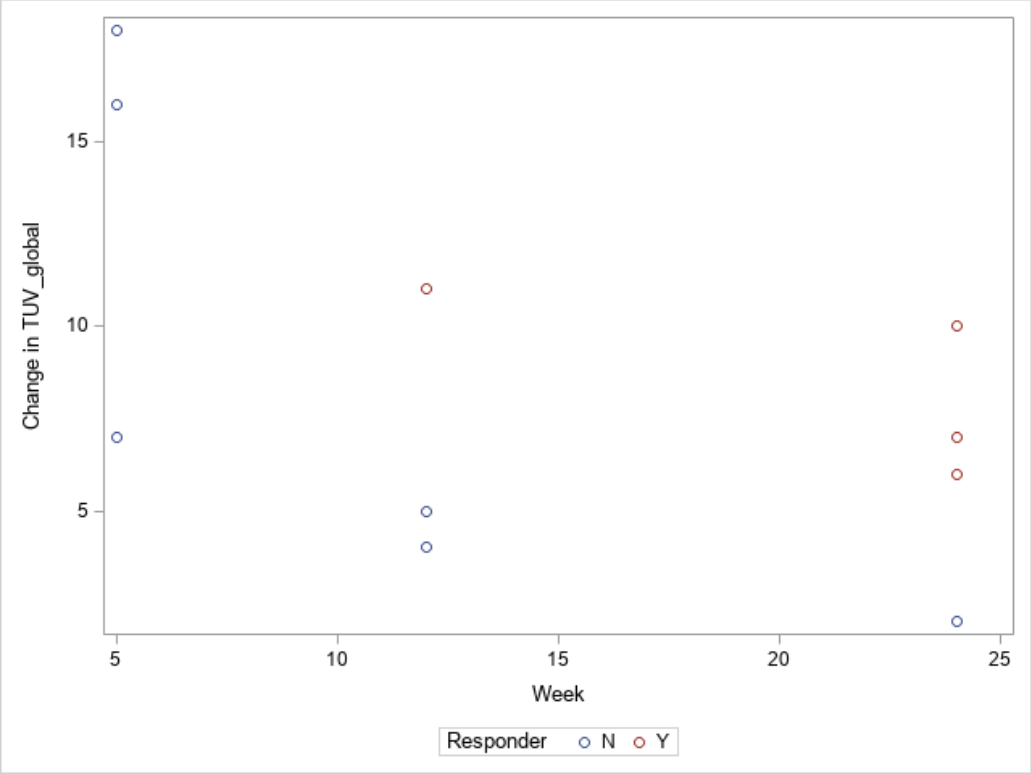
Figure 1. Plot of ΔTUV_{global} by Imaging Time Point and ACR20
Navidea Biopharmaceuticals – Study No. NAV3-33
ITD Population (N=xxx)

Part 1 of 3: Reader x



Responder status based on ACR20 at each week.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Figure format repeats for each part and for Figures 2-5. Footnote text will be updated in each figure to correspond to the clinical assessment noted in the title (ACR50, ACR70, CDAI, or DAS28).

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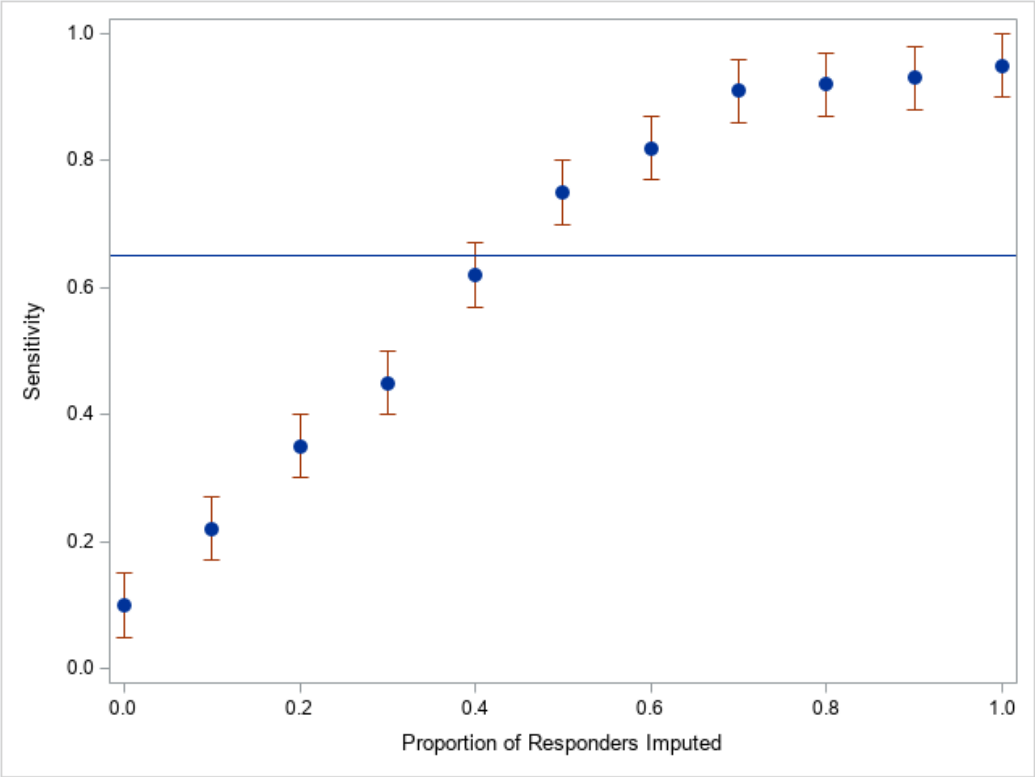
Figure 6. Sensitivity Analysis #1 – Tipping Point Analysis to Assess the Appropriateness of Imputation of Clinical Status at Week 24
Navidea Biopharmaceuticals – Study No. NAV3-33
ITD Population (N=xxx)

Part 1 or 2: Sensitivity



Remaining missing week 24 clinical status outcomes imputed as non-responders. Solid horizontal line represents 65% sensitivity.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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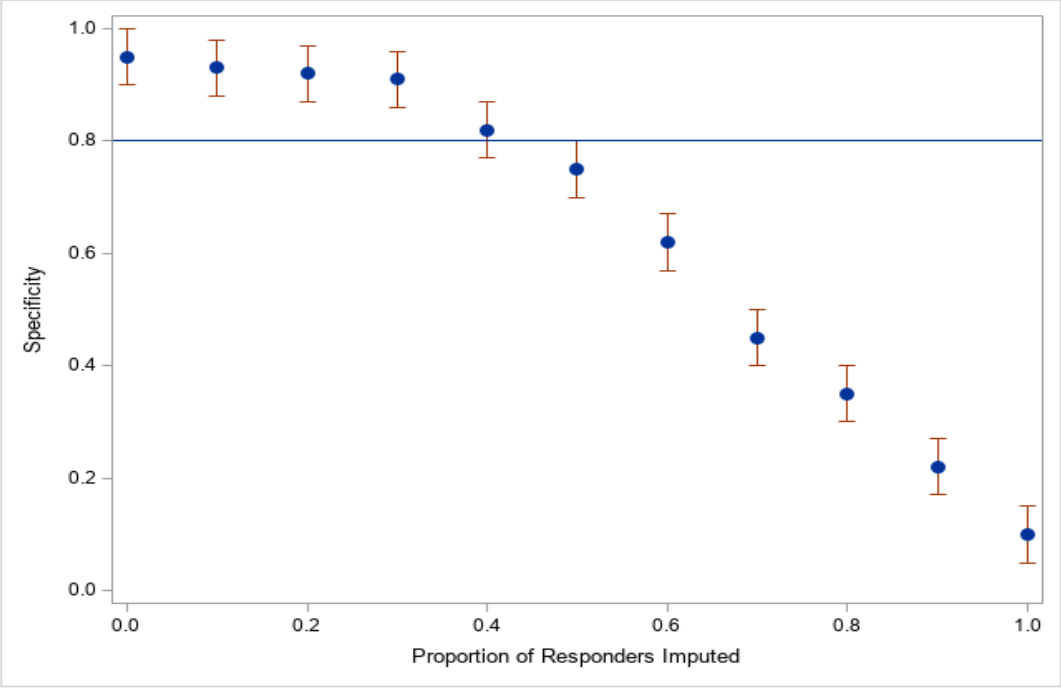
Figure 6. Sensitivity Analysis #1 – Tipping Point Analysis to Assess the Appropriateness of Imputation of Clinical Status at Week 24
Navidea Biopharmaceuticals – Study No. NAV3-33
ITD Population (N=xxx)

Part 2 of 2: Specificity



Remaining missing week 24 clinical status outcomes imputed as non-responders. Solid horizontal line represents 80% specificity.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Figure format repeats for Figure 7.

Data Listing 1. Patient Disposition Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33

Patient No.	Disposition Status	Date of Completion or Withdrawal	Withdrawal Reason
xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxx	xxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx

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

Data Listing 2. Inclusion/Exclusion Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33

Patient No.	Did Patient Meet All Eligibility Criteria?	Criterion Category	Criterion	Was a Waiver Granted?	Is Patient a Screen Failure?
Xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx
xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx
xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx
xxxx	xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx	xxxx	xxxx

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Source Program: xxxxxxx.sas

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Data Listing 3. Protocol Deviations Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33

Patient No.	Date of Deviation	Deviation Description	Deviation Category (Major/Minor)
xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx
xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx
xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx
xxxx	xxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxx

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

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Data Listing 4. Demographics Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	Informed Consent Date/Time	Time from Diagnosis of RA (months)[a]	Disease Severity	Date of Birth	Height (inches)	Weight (pounds)	Age (years)	Gender	Race	Ethnicity	Previous Use of Biologics (Y/N)	Baseline ACPA Level (Low/High)[b]
xxxx	xxxxxx	xxx	xxxxxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx	x	xxx
xxxx	xxxxxx	xxx	xxxxxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx	x	xxx
xxxx	xxxxxx	xxx	xxxxxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx	x	xxx
xxxx	xxxxxx	xxx	xxxxxx	xxxxxx	xxx	xxx	xxx	xxxxxx	xxxxxx	xxxxxx	x	xxx

[a] Calculated as the difference between date of enrollment and date of RA diagnosis.
[b] Low is < 85, and High is 85 and above.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 5. Patients Excluded from ITD Population Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
All Enrolled Patients (N=xxx)

Patient No.	Reason for Exclusion
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx

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

Data Listing 6. Patients Excluded from PP Population Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
All Enrolled Patients (N=xxx)

Patient No.	Reason for Exclusion
xxxx	xxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxx

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

Data Listing 7. Patients Excluded from Safety Population Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
All Enrolled Patients (N=xxx)

Patient No.	Reason for Exclusion
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx
xxxx	xxxxxxxxxxxxxxxxxxxxxxxxx

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

Data Listing 8. Medical History Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	MedDRA System Organ Class[a]/ MedDRA Preferred Term/ CRF Verbatim Term	Start Date	Resolution/Stop Date	Ongoing?
Xxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxx
	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxx
	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxx	xxxxxxx	xxx

[a] 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. NAV3-33
Safety Population (N=xxx)

Patient No.	Drug Preferred Term[a]/ Verbatim/ ATC Level 1 Text/ ATC Level 4 Text	Prior Medication?	Indication	Frequency	Start Date	Stop Date	Route	Ongoing?
Xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	x	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx
xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	x	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx

[a] Medications coded with WHO Coding Dictionary xxxxxxxxx
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 10. Prior and Concomitant RA Medications Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	Drug Preferred Term[a]/ Verbatim/ ATC Level 1 Text/ ATC Level 4 Text	Prior Medication?	Indication	Frequency	Start Date	Stop Date	Route	Ongoing?
Xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	x	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx
xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	x	xxxxxxx	xxxxxxx	xxxxxxx	xxxxxxx	xxxxx	xxxxx

[a] 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. NAV3-33
Safety Population (N=xxx)

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

[a] Adverse events coded with MedDRA Coding Dictionary Version xxx.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

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Data Listing 12. Patient Laboratory Profiles – Hematology Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	Visit	Sample Date and Time	Lab Parameter (Units)	Result	Normal Range		Clin. Sig?
					Lab Low	Lab High	
xxxx	xxxxxxxx	xxxxxxxx / xx:xx	xxxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
			xxxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
			xxxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
			xxxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
			xxxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx
			xxxxxxxxxxxxx (xxx)	xxx	xxx	xxx	xxx

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. NAV3-33
Safety Population (N=xxx)

Patient No.	Visit	Date Conducted	Body System	Result	Abnormality
xxxx	xxxxxxx	xxxxxxx	General Appearance	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Skin	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Eyes, Ears, Nose, Throat	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Head and Neck	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Lungs	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Heart	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Abdomen	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Lymph Nodes	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Musculoskeletal	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Nervous System	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			Other: XXXXXX	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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

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Data Listing 17. ACR/EULAR 2010 Classification Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

			ACR/EULAR 2010				
Patient No.	Visit	Date	Joint Involvement	Serology	Acute-Phase Reactants	Duration of Symptoms	Total Score
xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx
xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx

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Source Program: xxxxxxx.sas

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Data Listing 18. ACR Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

			ACR Components									
Patient 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	ACR20	ACR50	ACR70
xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

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

Data Listing 19. CDAI, DAS28, HAQ-DI, and WPI Scores Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

			CDAI Component									
Patient 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
xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	x	xx.x	x	xx.x	xx.x
xxxx	xxxxxxx	xxxxxxx	xxx	xxx	xxx	xxx	xxx	x	xx.x	x	xx.x	xx.x

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Source Program: xxxxxxx.sas

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Data Listing 20. DAS28 by Joint Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

				DAS28 Joint Classification	
Patient No.	Visit	Date	Joint	Result (Right Body)	Result (Left Body)
xxxx	xxxxxxx	xxxxxxx	xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx
xxxx	xxxxxxx	xxxxxxx	xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx
			xxxxxxxxx	xxx	xxx

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

Data Listing 21. DAS28 by Patient Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

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

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

Data Listing 22. Vital Signs Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	Visit	Date	Time	Temp. (°F)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (bpm)	Respirations per Minute
xxxx	xxxxxxx	xxxxxxx	xxxxx	xxx	xxx	xxx	xxx	xxx
			xxxxx	xxx	xxx	xxx	xxx	xxx
			xxxxx	xxx	xxx	xxx	xxx	xxx
xxxx	xxxxxxx	xxxxxxx	xxxxx	xxx	xxx	xxx	xxx	xxx
			xxxxx	xxx	xxx	xxx	xxx	xxx
			xxxxx	xxx	xxx	xxx	xxx	xxx

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

Data Listing 23. ECG Parameters Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

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

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

Data Listing 24. Study Drug Administration Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Patient 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
xxxx	xxxxxxxx/ xxxx	xxxxxxxx	xxx/ xxxx	xxx/ xxxx	xxx	xxx	xxx	xxx
xxxx	xxxxxxxx/ xxxx	xxxxxxxx	xxx/ xxxx	xxx/ xxxx	xxx	xxx	xxx	xxx
	xxxxxxxx/ xxxx	xxxxxxxx	xxx/ xxxx	xxx/ xxxx	xxx	xxx	xxx	xxx

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

Data Listing 25. Post-Injection Imaging Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	Visit	Date of Imaging	Start Time of Imaging	SPECT/CT Image Finding
xxxx	xxxxxxxx	xxxxxx	xx:xx	xxx
xxxx	xxxxxxxx	xxxxxx	xx:xx	xxx

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. NAV3-33
Safety Population (N=xxx)

Patient No.	Post-Injection Imaging Time Point	Joint	SPECT/CT Image Finding
xxxx	xxxxxxx	xxxxxxxxxxx xxxxxxxxxxx	xxxx
xxxx	xxxxxxx	xxxxxxxxxxx xxxxxxxxxxx	xxxx

Data Listing 27. TUV Data Listing
Navidea Biopharmaceuticals – Study No. NAV3-33
Safety Population (N=xxx)

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

[a] 1 = Change in Global TUV[5w] Bucketing, 2 = Change in Global TUV[12w] Bucketing
[b] Region of Interest is joint or Global.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 28. Qualitative Assessment Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	Reader No.	Qualitative Assessment[a]	Date/Time
xxxx	x	xxxxxxx	xxxxxxxx/ xxxx
xxxx	x	xxxxxxx	xxxxxxxx/ xxxx

[a] Qualitative Assessment is either "Improved" or "Not Improved."
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas

Data Listing 29. Qualitative plus Quantitative Assessments which differ from Original Quantitative Assessment
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

Patient No.	Reader No.	Qualitative plus Quantitative Assessment[a]	Date/Time of Qualitative plus Quantitative Assessment	Original Quantitative Assessment[a]	Date/Time of Original Quantitative Assessment
xxxx	x	xxxxxxx	xxxxxxxx/ xxxx	xxxxxx	xxxxxxxx/ xxxx
xxxx	x	xxxxxxx	xxxxxxxx/ xxxx	xxxxxx	xxxxxxxx/ xxxx

[a] Assessment is either "Improved" or "Not Improved."
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Source Program: xxxxxxx.sas

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Data Listing 30. ACR Response Criteria Data Listing
Navidea Biopharmaceuticals - Study No. NAV3-33
Safety Population (N=xxx)

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

[a] Options are None, ACR20, ACR50, or ACR70. Response assessment will be blank for baseline measurements.
STATKING Clinical Services (DD-MMM-YYYY)
Source Program: xxxxxxx.sas