Official Title: **PaTH Forward:** A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism

NCT Number: NCT04009291

Document Date: SAP Version 1.3: 28 October 2021

STATISTICAL ANALYSIS PLAN

Title:	**PaTH Forward:** A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism
Protocol:	TransCon PTH TCP-201
Investigational Product:	TransCon PTH
Phase:	2
Sponsor:	Ascendis Pharma Inc. 500 Emerson Street Palo Alto, CA 94301
IND and EudraCT Numbers:	133469; 2018-004815-33
Author:	[redacted]
Date/Version:	21 August 2019/ V 1.0 27 March 2020/ V 1.1 – Amendment 1 21 August 2020/ V 1.2 – Amendment 2 8 October 2021/ V 1.3 – Amendment 3
Original Protocol:	16 January 2019
Protocol Amendment:	Amendment 1 – 8 May 2019 Amendment 2 – 9 July 2020 Amendment 3 – 8 June 2021

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ABBREVIATIONS

Abbreviation	Description
AE	adverse events
AESIs	adverse events of special interest
BID	twice daily
BMD	bone mineral density
BMI	body mass index
CaSR	calcium-sensing receptor
CRO	contract research organization
CTx	c-telopeptide of type 1 collagen
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
EDC	electronic data capture
ER	emergency room
FECa	fractional excretion of calcium
HP	hypoparathyroidism
HPES	hypoparathyroid patient experience scale
ISR	injection site reaction
mPEG	methoxypolyethylene glycol
P1NP	procollagen type 1 amino-terminal propeptide
PD	pharmacodynamics
PK	pharmacokinetics
PTH	parathyroid hormone
PRO	patient-reported outcome
SAE	serious adverse events
SAP	statistical analysis plan
SC	subcutaneous
sCa	serum calcium
SoC	standard of care
SOC	system organ class
sP	serum phosphate
TBS	trabecular bone score
TSH	thyroid-stimulating hormone

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a more technical and detailed elaboration of the statistical analyses of efficacy, safety and pharmacokinetic (PK) data as outlined and/or specified in the trial protocol TransCon PTH TCP-201 (Amendment 3, 10 March 2021). If discrepancies exist between the text of this SAP and the planned analysis in the protocol, the final SAP will define the planned analysis of record.

2. TRIAL DESIGN

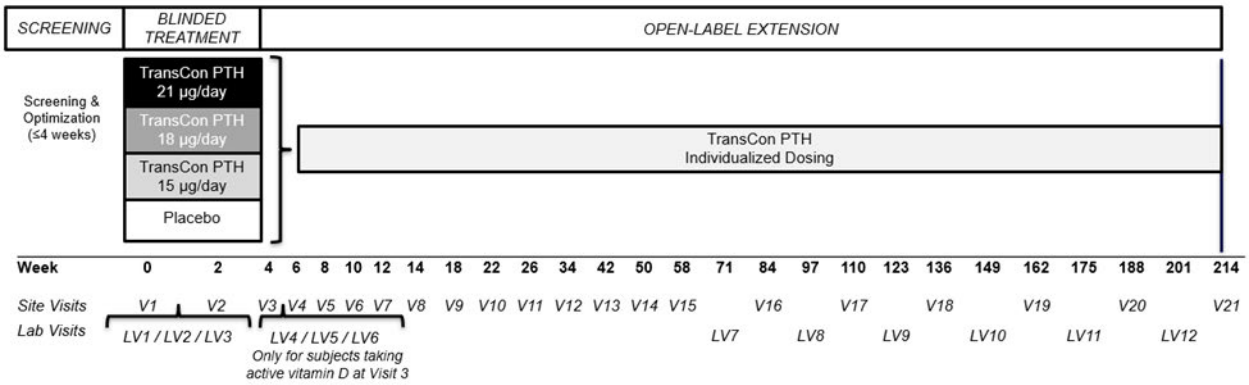
TransCon PTH TCP-201 is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group trial with an open-label extension, investigating the safety, tolerability and efficacy of TransCon PTH administered subcutaneously daily in adults with hypoparathyroidism (HP). HP is defined as either postsurgical HP or autoimmune, genetic, or idiopathic HP for at least 26 weeks, treated with a stable dose of ≥0.25 µg BID active vitamin D (or ≥1.0 µg/day alphacalcidol) and ≥400 mg BID calcium for at least 12 weeks prior to Screening. The total length of the trial will be 58 weeks with the double-blind portion lasting 4 weeks and the open-label extension lasting 54 weeks (approximately 1 year). Subjects meeting the inclusion criteria will be randomized into 4 treatment groups (1:1:1:1). The placebo group will be further sub-randomized into 3 groups (1:1:1) to mimic doses of 15, 18, and 21 µg/day and to preserve the blind.

- TransCon PTH 15 µg/day
- TransCon PTH 18 µg/day
- TransCon PTH 21 µg/day
- Placebo for TransCon PTH (excipient solution)
  - Mimicking dose of 15 µg/day
  - Mimicking dose of 18 µg/day
  - Mimicking dose of 21 µg/day

The trial design is presented in Figure 1.

- **Screening Period (supplement optimization):** Up to approximately 4 weeks
- **Blinded Treatment Period (study drug stable with standard of care (SOC) optimization):** 4 weeks
- Extension Period (open-label TransCon PTH treatment): 210 weeks, with up to an initial 14 weeks of TransCon PTH titration and SOC optimization, followed by approximately 196 weeks of individualized dosing

Figure 1: Trial Design



The schedule of evaluations is presented in Section 13.1, Table 4, Table 5, and Table 6 for blinded and extension periods respectively. The schedule of laboratory assessments is also presented under Section 13.1 in Table 6.

2.1. BLINDING AND RANDOMIZATION METHODS

Eligible subjects will be enrolled in the study and sequentially assigned an identification number. A randomization schedule will be developed by an independent contract research organization (CRO, Endpoint) to maintain blinding. Approximately 40 subjects (male and female) will be randomized into 4 treatment groups (1:1:1:1) and assigned to a treatment sequence group via an Interactive Web Randomization System (IWRS). The placebo group will be further sub-randomized into 3 groups (1:1:1) to mimic doses of 15, 18, and 21 µg/day and to preserve the blind. The treatment groups are as described above.

There are no stratification factors for randomization in this trial.

During the Blinded Treatment Period, subjects will be aware of the dose level they are assigned to; however, they will not be aware if they are on active TransCon PTH or placebo.

The Investigator and site personnel will remain blinded to the randomization code during the trial. Treatment assignment for an individual subject should be unblinded by the Investigator only in an emergency (eg, event concerning subject safety) and only if knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. The investigator is encouraged to notify the Medical Monitor/Medical Expert or clinical program manager before unblinding, when possible, but priority should be given to treatment of the subject.

The Investigator must record the date and reason for revealing the blinded treatment assignment for that subject within the IWRS. Treatment assignment may be unblinded by the Sponsor to satisfy expedited safety reporting requirements of regulatory authorities. The system to unblind an assignment will be maintained and executed through the IWRS, which will be available 24 hours a day, 7 days a week.

3. TRIAL OBJECTIVE(S)

3.1. PRIMARY OBJECTIVE

- To assess the effectiveness of daily TransCon PTH on serum and urine calcium levels (FECa) and active vitamin D and calcium doses at 4 weeks of treatment.

3.2. SECONDARY OBJECTIVE(S)

- To assess the safety and tolerability of daily TransCon PTH
- To assess the effectiveness of daily TransCon PTH on serum and urine calcium levels (FECa) and active vitamin D and calcium doses during the Extension Period
- To assess the treatment effect of daily TransCon PTH on daily pill burden (vitamin D and calcium)
- To assess the treatment effect of daily TransCon PTH on serum phosphate, serum magnesium, and calcium x phosphate product (sCa x sP product)
- To assess the treatment effect of daily TransCon PTH on hypocalcemia and hypercalcemia symptoms, emergency room (ER) visits, and hospitalizations
- To assess anti-PTH and anti-PEG antibody responses

3.3. EXPLORATORY OBJECTIVES

- To assess the treatment effect of daily TransCon PTH on:
  - Bone Mineral Density (BMD) and Trabecular Bone Score (TBS) by DXA
  - 24-hour urine calcium excretion
  - Patient-Reported Outcomes
  - Bone turnover markers (serum P1NP and CTx)
  - Vascular calcifications, nephrocalcinosis, and nephrolithiasis
- To assess the usability of the pre-filled injection pen

4. SAMPLE SIZE AND POWER CONSIDERATIONS

Based on clinical experience, the proportion of subjects on standard care meeting the primary endpoint will be rare and close to 0. According to the simulation data from the FDA (Briefing Document, BLA #125511, Khurana 2018), 66% of subjects with continuous infusion of PTH will have normal sCa. The phase 1 trial data predict that a large proportion of HP subjects (~ 90%) on TransCon PTH will have a normal FECa. Assuming that TransCon PTH has the same profile as PTH by continuous infusion, the proportion of subjects able to discontinue active vitamin D and require less than 1000 mg/day of supplemental calcium is estimated to be at least 70%. This translates to an estimate of the proportion of TransCon PTH-treated subjects meeting the primary endpoint at more than 40%. With 10 subjects per arm, the statistical power to detect a significant treatment difference is calculated in Table 1.

Table 1: Power Calculation for 10 Subjects Per Arm with Alpha Level at 0.05 and 0.10 (two-sided)

Proportion for TransCon PTH	Proportion for Placebo	Power	
		α=0.05 (2-sided)	α=0.10 (2-sided)
40%	1%	40.7%	53.2%
50%	1%	58.8%	70.4%
60%	1%	74.8%	83.8%
70%	1%	87.0%	92.5%
80%	1%	94.7%	97.3%

5. ANALYSIS

The full analysis of the Blinded Treatment Period will be conducted after treatment unblinding and database lock of the Blinded Treatment Period. No interim analysis prior to database lock of the Blinded Treatment Period is planned.

After Blinded Treatment Period completion, periodic analysis of the Extension Period data will be performed.

6. ANALYSIS ENDPOINTS

6.1. EFFICACY ENDPOINTS

6.1.1. Primary Efficacy Endpoint

At 4 weeks of treatment, the proportion of subjects with:

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

6.1.2. Secondary Efficacy Endpoints

6.1.2.1. Key Secondary Efficacy Endpoint

At 4 weeks of treatment, the proportion of subjects with:

- Albumin-adjusted or ionized sCa within the normal range **and**
- FECa within the normal range or a reduction by at least 50% from baseline **and**
- Not taking active vitamin D supplements **and**
- Taking ≤500 mg/day of calcium supplements

6.1.2.2. Other Secondary Efficacy Endpoints

- Primary and key secondary efficacy endpoints measured at predefined timepoints over the

Extension Period

At 4 weeks of treatment and at predefined timepoints over the Extension Period:

- Calcium and vitamin D doses
- Number of SOC supplements (pill burden)
- Spot AM FECa
- Serum phosphate
- Serum magnesium
- sCa x sP product, including proportion of subjects with sCa x sP product ≤55 mg^2/dL^2, ≤52 mg^2/dL^2, and ≤44 mg^2/dL^2
- Albumin-adjusted or ionized sCa

6.1.3. Exploratory Endpoints

At 4 weeks of treatment, assessment of the following:

- PRO measures
- Bone turnover markers (serum P1NP and CTx)
- Device usability questionnaire

Throughout the Extension Period, assessment at prespecified timepoints based on data collection and availability for each of the following:

- BMD and TBS by DXA
- 24-hour urine calcium excretion
- PRO measures
- Bone turnover markers (serum P1NP and CTx)

6.2. SAFETY & TOLERABILITY ENDPOINTS

The following safety endpoints will be assessed for both Blinded Treatment and Extension Periods:

- Serum chemistry, hematology, and spot urine parameters
- Incidence of AEs, serious adverse events (SAEs), adverse events of special interests (AESIs), TransCon PTH AESIs, and special situations
- Clinical events of hypo- or hypercalcemia (emergency/urgent care visits and hospitalizations) and progression of vascular calcifications, nephrocalcinosis, and nephrolithiasis
- Injection site tolerability (based on Local Tolerability Scale and AEs)
- Evaluation of anti-PTH and anti-PEG antibody response
- Physical examinations (AE-directed), including vital signs

6.3. PHARMACOKINETIC ANALYSIS

The primary PK (pharmacokinetic) analysis of interest is the plasma concentration of Free PTH [PTH (1-34) and PTH (1-33)] which showed the strongest correlation with PD (pharmacodynamic) in the Phase 1 trial.

7. DEFINITIONS AND COMPUTATIONS

7.1. TREATMENT

Blinded study drug is defined as TransCon PTH (15 µg/day, 18 µg/day, 21 µg/day) or Placebo.

Open-label study drug is defined as TransCon PTH (ranges from 6 µg/day to 60 µg/day).

7.2. BASELINE

Baseline in general is defined as the last non-missing measurement or assessment prior to the first dose of blinded study drug unless otherwise specified. For consistency of baseline definition across different PROs, baseline for all PROs is defined as the screening assessment.

7.3. STUDY DAY

Study day will be calculated in reference to the date of first dose of blinded study drug (day 1 for analysis purposes).

- If the visit or assessment is on or after the first dose date of study drug in the blinded period, then

  Study day= (visit/assessment date – date of the first dose of blinded study drug) + 1

- If the visit or assessment is before the first dose of study drug in the blinded period, then

  Study day = visit/assessment date – date of the first dose of double-blind study drug

7.4. DURATION OF EXPOSURE

Duration of blinded treatment exposure is defined as the duration of time from the date of the first dose of blinded study drug to the date of the last dose of blinded study drug. In days it is calculated as the last date of blinded study drug – first dose date of blinded study drug + 1 day.

Duration of open-label exposure is defined as the duration of time from the date of the first dose of open-label TransCon PTH to the date of the last dose of open-label TransCon PTH. In days it is calculated as the last date of TransCon PTH in the open-label period – first dose date of TransCon PTH in the open-label period + 1 day.

Overall PTH exposure is defined as the duration of time from first exposure to TransCon PTH to last exposure to TransCon PTH. In days it is calculated as the last date of TransCon PTH – first dose date of TransCon PTH + 1 day.

7.5. COMPLIANCE

Compliance is defined as total number of actual doses received in the specified period (Blinded Treatment or Extension) divided by the total number of days in the specified period multiplied by 100. Total number of doses is captured in subjects' diary data.

7.6. CONVENTIONS

Unless otherwise defined all conventions used are specified in the Biometrics standards document for conventions.

8. ANALYSIS POPULATIONS

8.1. RANDOMIZED POPULATION

The Randomized Population is defined as all subjects who were randomized (received a randomization identification number) to a treatment group in the trial.

8.2. FULL ANALYSIS POPULATION

The Full Analysis Population is defined as all subjects in the randomized population who received at least 1 dose of study drug. For the Blinded Period subjects are analyzed according to treatment assigned at randomization.

8.3. SAFETY ANALYSIS POPULATION

The Safety Analysis Population is defined as all subjects in the randomized population who received at least 1 dose of study drug. For the Blinded Period subjects are analyzed according to treatment received.

8.4. PHARMACOKINETIC POPULATION

Pharmacokinetic (PK) Population is defined as all subjects who received any amount of study drug and for whom the plasma concentration data are considered sufficient and interpretable.

8.5. PD-PK SUB-SET STUDY POPULATION

A PD-PK sub-set study population is defined as all subjects with a 24-hour admission in a research unit.

8.5.1. Subgroup Analysis Set

Subgroup analysis set of the PD-PK sub-set study population is defined as all subjects that had a pre-dose PK sample collected within 30 minutes prior to dosing.

9. DATA SCREENING AND ACCEPTANCE

9.1. GENERAL PRINCIPLES

Data will be reviewed periodically. Any questionable data will be reported to the clinical data manager promptly for query and resolution.

9.2. HANDLING OF MISSING AND INCOMPLETE DATA

Missing clinical outcome data can occur for multiple reasons, including missed subject visits and scales or measures with missing item scores. Missing and incomplete data will be identified through the data quality review plan for this trial. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the trial database lock or snapshot.

Unless specified otherwise, only the observed data will be presented in listings.

9.2.1. Missing Date of Birth

To impute missing birth date, the following rules will be applied:

If only day is missing, impute 15.

- If both day and month are missing, impute June 15.
- If year is missing, then no imputation will be done; the date will be missing.

9.2.2. Missing Hypoparathyroidism Disease History

If any of the hypoparathyroidism disease history related dates are partially missing, they will be imputed using the following rules:

If only day is missing, impute 15.

If both day and month are missing, impute June 15.

- If year is missing, then no imputation will be done; the date will be missing.

9.2.3. Missing Date Imputation for Adverse Events and Concomitant Medications

The following conventions will be used to impute missing portions of dates for adverse events (AE) and concomitant medications (CM). Note that the imputed values outlined here may not always provide the most conservative date.

Missing AE/CM Start Dates

- If only day is unknown, then:
  - If the month and year match the first dose of study drug start date month and year in this trial, then impute the day of the first dose date.
  - Otherwise, assign the first day of the month.
- If both day and month are unknown, then:
  - If the year matches the year of the first dose of study drug date in this trial, then impute the day and month of the first dose date in this trial.
  - Otherwise, assign ‘January 01’.
- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the imputed start date is later than the stop date (of the adverse event or concomitant medication), then the start date will be set as the same date as the end date.

Missing CM Stop Dates and not ongoing

- If only day is unknown, then assign the last day of the month.
- If both day and month is unknown, then assign ‘December 31’.

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
  - If the resulting stop date is after the date of trial completion/discontinuation/data snapshot date, set the imputed stop date as close to the date of trial completion/discontinuation/data snapshot date as possible without overwritten existing information.

9.2.4. Missing Causal Relationship to Investigational Product for Adverse Events

If the causal relationship to the investigational product is missing for an AE that started on or after the date of the first dose of double-blind investigational product, a causality of "related" will be assigned. The imputed values for causal relationship to investigational product will be used for the incidence summary; the values will be shown as missing in the data listings.

9.3. VISIT TIME WINDOWS

For laboratory parameters and other per visit assessments the following rules will be used:

Unscheduled visit (occurred after the date of initiation of the first dose) or end of study visit will be mapped to the closet scheduled dosing visit. If the unscheduled visit is in the middle of two scheduled dosing visits, map it to the later one.

After mapping, if there are more than one visits in the same window, the scheduled visit will be used if available; if there is no scheduled visit in the same window, the mapped visit closer to the target assessment day will be used. If more than one visits have the equal distance to the target day then the later one will be used, if more than one visits on the same day, use the time or the sequence number to select the later record. For listings all data points will be included.

Table 2 presents the visit window assigned for the scheduled assessments and the corresponding range of treatment days (window) during which an actual visit may occur. The window should be used for the data collected at regular trial visits. Pre-specified local laboratory visits during blinded and extension periods in the protocol will use nominal visit assigned in EDC. There will be no window defined and all data will be presented in listing as necessary.

Table 2: Analysis Visit Time Windows

Period	Visit (Week)	Scheduled Visit Target Day	Window
Blinded Treatment Period	Baseline (Week 0)	Day 1	Days ≤ 1 [prior to first dose of blinded study drug]
	Visit 1 (Week 0)	Day 1	Day 1
	Visit 2 (Week 2)	Day 14	Days [2-21]
	Visit 3 (Week 4)	Day 28	Days [22- subjects entering Extension Period and EOS for subjects that do not enter Extension Period]
Extension Period	Visit 4 (Week 6)	Day 42	Days [(first dose of open-label study drug + 1)-49]
	Visit 5 (Week 8)	Day 56	Days [50-63]
	Visit 6 (Week 10)	Day 70	Days [64-77]
	Visit 7 (Week 12)	Day 84	Days [78-91]
	Visit 8 (Week 14)	Day 98	Days [92-112]
	Visit 9 (Week 18)	– Day 126	Days [113-140]
	Visit 10 (Week 22)	Day 154	Days [141-168]
	Visit 11 (Week 26)	Day 182	Days [169-210]
	Visit 12 (Week 34)	Day 238	Days [211-266]
	Visit 13 (Week 42)	Day 294	Days [267-322]
	Visit 14 (Week 50)	Day 350	Days [323-378]
	Visit 15 (Week 58)	Day 406	Days [379-497]
	Visit 16 (Week 84)	Day 588	Days [498-679]
	Visit 17 (Week 110)	Day 770	Days [680-861]
	Visit 18 (Week 136)	Day 952	Days [862-1043]
	Visit 19 (Week 162)	Day 1134	Days [1044-1225]
	Visit 20 (Week 188)	Day 1316	Days [1226-1407]
	Visit 21 (Week 214)	Day 1498	Days >=1408

Note: Local lab visits LV1-3 and LV4-12 will only be presented in a listing and not summarized in table outputs per visit. For central lab visits the assessment date will be compared for the visit window.

For analysis of local tolerability assessment and exposure nominal visits will be used.

For PK and antibody data nominal visits will be used for the summaries per visit. Summaries may also be presented with reference to “weeks from dosing” of TransCon PTH. The weeks from dosing will be defined as follows:

- For subjects randomized to active treatment at time of trial enrollment the weeks from dosing will be in reference to first dose of active TransCon PTH, i.e. first blinded dose, **Visit 1, Week 0**.

- For subjects randomized to placebo treatment at time of trial enrollment the weeks from dosing will be in reference to first dose of active TransCon PTH, i.e. first open-label dose, **Visit 3, Week 0**.

Weeks from dosing will be derived using nominal visits. For local lab visits (LV1-12) weeks will be assigned as partial weeks, example LV1 – Week 0.4, LV2 – Week 0.9, LV3 – Week 1.3, etc.

For standard of care (SOC) parameters the following rules will be used, refer to Table 3.

Table 3: Analysis Visit Windows for SOC Supplements Collected via eDiary

Period	Visit (Week)	Analysis Day	Window
Blinded Treatment Period	Baseline (Week 0)	Visit 1 date - 1	Days < 1 [day prior to first dose date of blinded study drug]
	Visit 2 (Week 2)	Visit 2 date - 1	Days [1 to Visit 2 date – 1]
	Visit 3 (Week 4)	Visit 3 date - 1	Days [Visit 2 date to (Visit 3 date – 1)]
Extension Period	Visit 4 (Week 6)	Visit 4 date - 1	Days [Visit 3 date to (Visit 4 date – 1)]
	Visit 5 (Week 8)	Visit 5 date - 1	Days [Visit 4 date to (Visit 5 date – 1)]
	Visit 6 (Week 10)	Visit 6 date - 1	Days [Visit 5 date to (Visit 6 date – 1)]
	Visit 7 (Week 12)	Visit 7 date - 1	Days [Visit 6 date to (Visit 7 date – 1)]
	Visit 8 (Week 14)	Visit 8 date - 1	Days [Visit 7 date to (Visit 8 date – 1)]

Note: Subjects will not be collecting eDiary data past their Visit 8, when they should return the devices to the sites. If any records are outside of the specified window they will be presented as a listing and no analysis visit will be defined (Not Windowed). If the result of analysis day is missing and the subject has reached the visit, select the last non-missing record per analysis visit. If the actual visit is missing in the EDC the target date of the visit will be used for analyses.

For dose per visit summaries:

- For study drug, the dose taken on the day of Visit X will be considered as dose at Visit X. The actual visit X date is captured in EDC. If the actual visit is missing in the EDC the target date of the visit (Table 2) will be used for analyses.
- For SoC, the dose taken on the day prior to Visit X will be considered as dose at Visit X for each subject in summary tables (Table 3). If the actual visit is missing in the EDC the target date of the visit (Table 2) will be used for analyses.

9.4. TESTING/VALIDATION PLAN

Data will be reviewed by cross functional team periodically and issues will be addressed by clinical data management.

9.5. SOFTWARE

SAS® software version *9.4* or higher will be used to perform statistical analyses unless otherwise specified.

10. STATISTICAL METHODS OF ANALYSES

10.1. GENERAL PRINCIPLES

The efficacy analyses will be based on the Full Analysis Population by period. Safety analysis will be based on the Safety Analysis Population by period. PK analyses will be conducted using the PK population.

In general, continuous variables will be summarized by number of subjects, mean, SD/SE, median, minimum, and maximum values.

Categorical variables will be summarized by number and percentage of subjects.

All statistical tests will be two-sided and tested at significance level of 0.05. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

All tables, listings and figures will be presented for Blinded Treatment and Extension Periods separately. The Blinded Treatment Period summaries will include a summary for each dose level and a combined placebo. The Extension Period will present combined TransCon PTH group.

Select outputs may be presented as TransCon PTH Period defined as the period of exposure to TransCon PTH drug. TransCon PTH Period for subjects randomized to the active arm at trial enrollment will be the time from exposure to first dose of blinded active TransCon PTH until time of analysis in the Extension Period. TransCon PTH Period for subjects randomized to the placebo arm at trial enrollment will be the time from exposure to active TransCon PTH, i.e. time of open-label cross-over, to time of analysis in the Extension Period.

10.2. SUBGROUP ANALYSIS

To assess the robustness of the treatment effect across subgroups, subgroup analyses will be conducted for the demographic, primary and key secondary efficacy endpoints.

The following subgroups of interest will be considered provided that sufficient number of subjects falls in each category to perform appropriate statistical analysis:

- Age category (<30 vs >= 30; <65 vs >= 65)
- Prior treatment with PTH therapy (yes vs no)
- Gender (Female vs Male)
- Etiology of HP
  - Post-surgical vs. Other (Auto-immune, Idiopathic and genetic)
  - Post-surgical, Idiopathic and Auto-immune vs. Genetic
  - Post-surgical without CaSR (calcium-sensing receptor) mutation vs Post-surgical with CaSR mutation

10.3. SUBJECT ACCOUNTABILITY AND DISPOSITION

The number and percentage of subjects in each of the analysis populations (randomized, full analysis, safety, PK) will be summarized. Subjects excluded from the full analysis set will be presented in a listing.

The number and percentage of subjects who completed or discontinued study drug and/or the trial early during the Blinded Treatment Period will be presented for each treatment group for the Full Analysis Population. Similarly, subjects who completed or discontinued study drug and/or the trial early the Extension Period will be summarized for the Full Analysis Population. The reasons for discontinuation of treatment and trial are recorded on electronic case report forms (eCRFs).

Disposition summaries for the Extension Period will be presented at the time of Extension Period analysis.

10.4. PROTOCOL DEVIATIONS

Major protocol deviations will be summarized by deviation category and period. Both major and minor protocol deviations will be presented in a by-patient listing.

10.5. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic parameters (age; race; ethnicity; sex; weight; height, body mass index [BMI], geographic region) and other baseline characteristics (eg, menopausal status) will be summarized descriptively for the Full Analysis Population.

10.6. HP DISEASE CHARACTERISTICS AND HISTORY

Specific HP characteristics (cause of HP, prior PTH therapy, prior hospitalization and emergency visits for hypo- and hypercalcemia, selected diseases related to HP, including nephrolithiasis, ectopic calcifications, hypocalcemic seizures, etc.) as well as prior HP supplements (calcium, active vitamin D, vitamin D3, magnesium) will be summarized for the Full Analysis Population.

10.7. GENERAL MEDICAL HISTORY

Subjects medical history will be summarized by system organ class and preferred terms and will be presented for the Full Analysis Population.

10.8. PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as any medication started before the date of the first dose blinded study drug (medication start date prior to the first dose date).

Concomitant medication is defined as any medication taken on or after the date of the first dose of blinded study drug (medication end date on or after first dose date [or ongoing], and medication start date prior or on the last dose date). Any concomitant medications started after the date of the last dose of study drug will not be presented in the summary tables but will be included in the subject data listings by period.

If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject will be counted only once for the coded drug name or therapeutic class.

Summaries will be presented for prior and concomitant medications by WHO Drug Classification and by period for the Safety Analysis Population.

10.9. INVESTIGATIONAL PRODUCT ADMINISTRATION

10.9.1. Exposure

Exposure will be summarized using Safety Analysis Population and will be based on data collected in the eCRFs.

Duration of exposure to the blinded study drug for the Blinded Period will be presented for the following parameters:

- Duration of exposure to blinded treatment
- Total number of planned doses
- Total number of actual doses
- Average actual daily dosage (mcg)

Duration of exposure during the Extension Period will be summarized for the following parameters:

- Duration of exposure to open-label treatment
- Total number of planned doses
- Total number of actual doses
- Average actual daily dose (mcg)
- Final dose levels after titration.

Overall duration of exposure TransCon PTH will be summarized for the following parameters:

- Duration of exposure to TransCon PTH
- Total number of planned doses
- Total number of actual doses
- Average actual daily dosage (mcg)

10.9.2. Compliance

Descriptive statistics for study drug compliance and percent split out will be presented for the Safety Analysis Population per period.

10.9.3. Device Usability

The devise usability questionnaire will be summarized by assessment day.

10.10. EFFICACY ANALYSIS

10.10.1. General Analysis Methods

Blinded Treatment Period:

Fisher's exact test is considered the primary analysis for the primary and key secondary endpoints, and other categorical parameters.

The continuous efficacy endpoints, such as other secondary and exploratory endpoints, will be analyzed using ANCOVA model. In general, the continuous endpoint of interest or change from baseline will be included in the model as a response variable. Treatment assignment will be entered as a fixed effect and baseline value of the variable of interest will be entered as a covariate, unless otherwise specified.

Extension Period Analyses:

Endpoints will be reassessed at least at 6 months and 12 months of unblinded treatment (Extension Period) based on data availability. These endpoints will be summarized descriptively. Analysis may include significant change from baseline where appropriate.

10.10.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects that met the following criteria at 4 weeks of blinded treatment:

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

The primary analysis is the Fisher's exact test to compare the proportion of subjects meeting the listed criteria in the TransCon PTH vs pooled placebo groups. The analysis will be performed using Full Analysis Population. Subjects who do not have data on one or more of the criteria for the primary endpoint will be considered in the subgroup of not meeting the criteria and analyzed as non-responders.

A sensitivity analysis will be performed using the following criteria for determining a responder:

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

Another sensitivity analysis will be performed on a subset of subjects achieving albumin-adjusted sCa within 8.8-10 mg/dL range at Visit 3. Due to the FDA-mandated fixed dosing over the 4 weeks of blinded treatment period, subjects treated with TransCon PTH are more likely to have elevated calcium values at Visit 3 than are placebo-treated subjects (because all subjects started in the normal range, and 18 or 21 mcg/day could be too high a dose for some subjects). In Phase 3 or in the real world, patients will be able to titrate their dose to avoid hypercalcemia. Therefore, using this somewhat narrower normal range is expected to potentially show a more

accurate (more real world) response rate. The subjects in this subset will be evaluated to see if they meet the following criteria at Visit 3:

- Albumin adjusted serum calcium within the range of 8.8 to 10.0 mg/dL, **and**
- Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

10.10.3. Multiplicity Adjustment for Primary Efficacy Endpoint

To control the family wise error rate for comparisons of the 3 treatment dose levels of TransCon PTH with placebo for the primary efficacy endpoint, a multiplicity adjustment schema will be used. The details are presented in a 2-step approach. Fisher's exact test is the primary analysis to test the primary endpoint.

Step 1: Fisher's exact test is the primary analysis to compare pooled active treatment TransCon PTH vs pooled placebo. If the calculated p-value is <0.05, declare a statistical significance for overall TransCon PTH vs placebo and proceed to step 2. If the statistical significance cannot be declared, the formal hypothesis test for the individual dose levels of TransCon PTH will not be performed.

Step 2: Based on Fisher's exact test, compare each individual dose of TransCon PTH vs the pooled placebo using Hochberg procedure.

No adjustments are planned for multiple testing/comparisons in the key or other secondary and exploratory hypothesis tests.

10.10.4. Analysis of Secondary Efficacy Endpoint(s)

10.10.4.1. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the proportion of subjects that met the following criteria at 4 weeks of blinded treatment:

- Albumin-adjusted or ionized sCa within the normal range, **and**
- FECa within normal range or a reduction by at least 50% from baseline, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤500 mg/day of calcium supplements

The Fisher's exact test is the statistical method to compare the proportion of subjects meeting the listed criteria in the TransCon PTH (at each dose level individually) vs pooled placebo groups. Subjects who do not have data on one or more of the criteria for the primary endpoint will be considered in the subgroup of not meeting the criteria and analyzed as non-responders.

10.10.4.2. Other Secondary Efficacy Endpoints

At 4 weeks of blinded treatment the following other secondary endpoints will be considered:

- Calcium and vitamin D doses

- Number of SOC supplements (pill burden)
- Spot AM FECa
- Serum phosphate
- Serum magnesium
- sCa[1] x sP product, including proportion of subjects with sCa x sP product ≤55 mg2/dL2, ≤52 mg2/dL2, and ≤44 mg2/dL2
- Albumin-adjusted or ionized sCa

All the continuous endpoints will be analyzed using an ANCOVA model specified in Section 10.10.1.

Categorical variables, eg, the sCa x sP proportions at each level ≤55 mg2/dL2, ≤52 mg2/dL2, and ≤44 mg2/dL2 will be analyzed using Fisher's exact test.

10.10.5. Analyses of Efficacy Endpoint(s) in the Extension Period

During the Extension period at 6 months, 12 months and as needed, the efficacy analyses will be repeated using descriptive analyses for absolute and change from baseline.

10.10.5.1. Primary and Sensitivity Extension Period Endpoints

The primary efficacy endpoint in the Extension Period is the proportion of subjects that met the following criteria at the 6 months, 12 months, or as needed timepoints:

- Albumin-adjusted or ionized sCa within the normal range, **and**
- 24-Hour urine calcium within the normal range[2], **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

The primary analysis is descriptive and will present proportion of subjects meeting the predefined criteria at each Extension Period analysis timepoint. The analysis will be performed using Full Analysis Population. Subjects who do not have data on one or more of the criteria for the primary endpoint will be considered as missing response without data imputation.

The following sensitivity analysis will be performed using descriptive summaries for subjects considered as responders for each of the endpoints:

Extension Period Primary Endpoint Sensitivity 1

- Albumin-adjusted or ionized sCa within the normal range, **and**
- 24-Hour urine FECa within normal range (≤2%) or a reduction by at least 50% from baseline, **and**

[1] Albumin-adjusted serum calcium will be used for the purpose of calculating the sCa and sP product

[2] The normal range for 24-hour urine calcium is defined as <= 250 mg/day for female, <= 300 mg/day for male.

- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

Extension Period Primary Endpoint Sensitivity 2

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

Extension Period Primary Endpoint Sensitivity 3

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤1000 mg/day of calcium supplements

Extension Period Primary Endpoint Sensitivity 4

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤600 mg/day of calcium supplements

Extension Period Primary Endpoint Sensitivity 5

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Not taking active vitamin D supplements, **and**
- Taking 0 mg/day of calcium supplements

10.10.5.2. Key Secondary and Sensitivity Extension Period Endpoints

The key secondary efficacy endpoint in the Extension Period is the proportion of subjects that met the following criteria at the 6 months, 12 months, or as needed timepoints:

- Albumin-adjusted or ionized sCa within the normal range, **and**
- 24-Hour urine calcium within the normal range*[3], **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤500 mg/day of calcium supplements

The analysis is descriptive and will present proportion of subjects meeting the predefined criteria at each Extension Period analysis timepoint. The analysis will be performed using Full Analysis

[3] The normal range for 24-hour urine calcium is defined as <= 250 mg/day for female, <= 300 mg/day for male

Population. Subjects who do not have data on one or more of the criteria for the endpoint will be considered as missing response without data imputation.

The following sensitivity analysis will be performed using descriptive summaries for subjects considered as responders for each of the endpoints:

Extension Period Key Secondary Endpoint Sensitivity 1

- Albumin-adjusted or ionized sCa within the normal range, **and**
- 24-Hour urine FECa within normal range (≤2%) or a reduction by at least 50% from baseline, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤500 mg/day of calcium supplements

Extension Period Key Secondary Endpoint Sensitivity 2

- Albumin-adjusted or ionized sCa within the normal range, **and**
- Spot AM FECa within normal range (≤2%) or a reduction by at least 50% from baseline, **and**
- Not taking active vitamin D supplements, **and**
- Taking ≤500 mg/day of calcium supplements

10.10.5.3. Other Secondary Extension Period Endpoints

All other secondary endpoints described under Section 10.10.4.2 will be analyzed during the Extension Period at 6 months, 12 months and as needed. The analyses used will be descriptive and presented as change from baseline. Additionally, 24-hour urine parameters such as urine calcium, FECa, creatinine, sodium, magnesium, etc. will also be summarized.

10.10.6. Analysis of Exploratory Endpoint(s)

The Exploratory Endpoints are:

At 4 weeks of treatment, assessment of the following:

- Patient-Reported Outcome (PRO) measures
- Bone turnover markers (serum P1NP and CTx)
- Device usability questionnaire

Throughout the extension period, assessment of the following:

- BMD and TBS by DXA
- 24-hour urine calcium excretion
- PRO measures
- Bone turnover markers (serum P1NP and CTx)

10.10.6.1. PRO Measures

PRO measures for the trial consist of the following scales:

- Hypoparathyroidism Patient Experience Symptom Scale (HPES-Symptom)
  - Physical signs and symptoms domain
  - Cognitive signs and symptoms domain
  - Total HPES-Symptom Score
- Hypoparathyroidism Patient Experience Impact Scale (HPES-Impact)
  - Physical Functioning domain
  - Daily Life domain
  - Psychological Well-being domain
  - Social Life and Relationships domain
  - Total HPES-Impact Score
  - HP Interference in Life Questions
  - QOL
  - Physical functioning
  - Daily functioning
  - Social functioning
  - Emotional well-being
- Patient Global Impression of Severity (PGI-S)
  - Overall symptoms of HP
  - Physical symptoms due to HP
  - Cognitive symptoms due to HP.
- Clinician Global Impression of Severity (CGI-S) (filled by investigator)
  - Overall HP symptoms
  - HP physical symptoms
  - HP cognitive symptoms
- Cognitive Failures Questionnaire (CFQ)
- SF-36 Physical Health component v2 (SF-36)
  - 8 multiple-item scales: physical functioning, role limitations due to physical health problems, bodily pain, social functioning, general mental health, role limitations due to emotional problems, vitality, and general health perceptions
  - 2 summary scores: physical component (PCS) and mental component (MCS)

- Hospital Anxiety and Depression Scale (HADs)
  - Anxiety Subscale
  - Depression Subscale
- Endicott Work Productivity Scale (EWPS)

Scores for the PRO scales will be considered as continuous.

Descriptive statistics of observed values and changes from baseline for each treatment group and differences between each TransCon PTH group vs placebo at each time point will be presented for each of the scales and subscales.

The PRO analysis will be performed at 4 weeks of blinded treatment and an ANCOVA analysis for determining difference between treatment groups will be performed for change from baseline.

The PRO analysis will be repeated during the Extension Period at 6 months and 12 months and will be analyzed descriptively in terms of change from baseline, presenting data at each time point where it was collected and analyzed.

10.10.6.2. Bone Turnover Markers

Descriptive statistics of observed values, changes from baseline, and % change from baseline by period will be presented for each of the bone turnover markers, serum P1NP and CTx.

The bone turnover markers will also be analyzed as continuous endpoint using ANCOVA at 4 weeks of blinded treatment.

10.10.6.3. Devise Usability Questionnaire

Summary of each of the questions will be presented per timepoint per treatment group during the Blinded Treatment Period.

10.10.6.4. Bone Mineral Density and Trabecular Bone Score

BMD and TBS during Extension Period will be summarized by visit and in terms of change from baseline. The primary intent of this analysis is to assess for an increase in trabecular BMD.

10.10.6.5. 24-Hour Urine Calcium Excretion

Urine calcium excretion during Extension Period will be analyzed as change from baseline and summary statistics will be provided.

10.11. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Analysis Population per period. The safety parameters include adverse events (AEs), clinical laboratory, vital signs, electrocardiographic (ECG) parameters, local tolerability summary, and antibody parameters. For safety endpoints, all analyses will be based on the observed data (ie, with no imputation of missing data), unless otherwise stated.

10.11.1. Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version in accordance with the clinical data management plan.

An AE (classified by preferred term) will be considered a treatment emergent adverse event (TEAE) if it occurred on or after the first dose of study drug and up to 14 days after last dose of study drug and was not present prior to the first dose, or it was present at the first dose but increased in severity during the trial.

AEs of special interest (AESIs) are a subset of Events to Monitor (EtMs) of scientific and potential medical concern specific to the product and might require further investigation.

TransCon PTH AESIs include vasodilatory signs/symptoms, persistent severe hypocalcemia or hypercalcemia.

Special situations are non-standard medical conditions that provide valuable information about a medicinal product, even when they do not occur in association with an AE or medical condition.

TEAE occurring prior to first dose open-label treatment is defined as Blinded Period TEAE.

TEAE occurring after the first dose of open-label treatment is defined as Extension Period TEAE.

Subject incidence of TEAEs will be tabulated as the following by each period and overall TransCon PTH, where the summaries for Blinded Treatment Period will be presented by treatment group and for the Extension Period by total TransCon PTH:

- Summary of TEAEs
- TEAEs by SOC (system organ class) and PT (preferred term)
- Related TEAEs by SOC and PT
- TEAE by greatest relationship, SOC and PT
- Serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- TEAE by greatest severity, SOC and PT
- Deaths by SOC and PT
- TEAEs leading to discontinuation of trial by SOC and PT
- TEAEs leading to discontinuation of treatment by SOC and PT
- TEAEs by PT (sorted by descending frequency of PT)
- Related TEAEs by PT (sorted by descending frequency of PT)
- Serious TEAEs by PT (sorted by descending frequency of PT)
- AESIs
- TransCon PTH AESIs

- TEAEs special conditions
- TEAE related to hypocalcaemia/hypercalcemia leading to ER/urgent care visit and/or hospitalization by SOC and PT

Detailed listings for all TEAEs, serious TEAEs, TEAEs leading to the discontinuation of study, TEAEs leading to the discontinuation of treatment, and death will also be generated.

10.11.2. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in conventional and SI units) and changes from baseline values at each assessment time point will be presented by period for the following laboratory parameters:

Panel	**Tests/Analytes**				
Chemistry	Total Bilirubin Direct Bilirubin Indirect Bilirubin Alkaline Phosphatase ALT (SGPT) AST (SGOT)	GGT Urea Nitrogen Creatinine Uric Acid Calcium Phosphate	Total Protein Albumin Globulin CK Sodium Potassium	Bicarbonate Chloride Magnesium	AT SCREENING ONLY: Glucose Cholesterol
Hematology	Hemoglobin Hematocrit RBC MCH	MCHC RBC morphology & MCV WBC Neutrophils	Lymphocytes Monocytes Eosinophils Basophils	Platelets	
24 Hour Urine	Creatinine Calcium Citrate	Uric Acid Sodium Magnesium	Phosphate pH Oxalate	Urine volume	

A listing of subjects who experience abnormal clinical laboratory results (ie, outside of reference ranges) and/or clinically significant abnormalities after study drug administration will be presented by clinical laboratory measurement.

Data listings for laboratory, including data from scheduled and unscheduled laboratory tests, will be provided. Listing of abnormal labs will be provided separately.

Local lab results from lab visits LV1-3 and LV4-12 will be presented in a listing by period.

10.11.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, and weight) and changes from baseline values at each visit and at the end of study will be presented by period.

A listing of vital signs will be provided.

10.11.4. Electrocardiogram

ECG parameters (heart rate, QT interval, and QTcF interval) will be presented in a listing. ECGs will be performed at screening only and at unscheduled visit if necessary.

10.11.5. Local Tolerability Assessment

Local Tolerability is assessed based on presence of injection site reactions (ISRs). An ISR is defined as a reaction at the site of administration that is deemed abnormal from those ordinarily observed in subcutaneous (SC) injections (including pain intensity, pruritus, swelling, induration, ulceration, lipoatrophy, lipodystrophy, and infection). Asymptomatic transient erythema is not considered an ISR.

The local tolerability is performed by trial staff using Local Tolerability Scale at the time of the first blinded study drug injection and at least 15 minutes post-dose.

At Visit 3, the first dose of open-label study drug is administered on-site only for subjects currently taking active vitamin D. An assessment of local tolerability is performed by trial staff using the Local Tolerability Scale at the time of the study drug injection and at least 15 minutes post-dose.

The Local Tolerability Scale as well as any ISR will be summarized descriptively and presented in tables and listings as appropriate.

10.11.6. Antibody Parameters

The appropriateness of the approach taken to analyze, and report anti-drug antibody data should be evaluated on a case-by-case basis (FDA 2016), following recent regulatory guidance and white papers (Shankar 2014). Statistical analysis of antibodies against drug (ADA) will include (but not be limited to) the following tabulated summaries of antibody frequencies and population percentages:

1. Incidence of pre-existing anti-PTH binding antibodies (positive baseline)
2. Incidence of treatment induced anti-PTH binding antibodies by positive types (treatment emergent positive and treatment boosted positive) and overall
3. Incidence of treatment induced anti-PTH neutralizing antibodies by positive types and overall
4. Incidence of pre-existing anti-PEG antibodies (positive baseline)
5. Incidence of treatment induced anti-PEG binding antibodies by positive types and overall

Neutralizing antibodies are defined as confirmed binding anti-PTH antibodies that are confirmed positive in a cell-based neutralizing antibody assay.

In addition, treatment induced anti-PTH binding, anti-PTH neutralizing antibodies, and anti-PEG antibodies will also be summarized by visit and positive types and overall. Anti-PTH neutralizing antibodies and anti-PEG antibodies will be evaluated for clinically meaningful impact.

Treatment induced ADA will include two positive types:

- Treatment emergent positive: if baseline (pre-treatment sample) is negative for ADA and post-treatment sample is positive for ADA
- Treatment boosted positive: if baseline (pre-treatment sample) is positive and post-treatment sample has a titer which is at least 4-fold higher than the pre-treatment sample.

10.12. PHARMACOKINETIC ANALYSIS

The primary PK analysis of interest is the Free PTH [PTH (1-34) and PTH (1-33)] level, which represents active PTH released from the pro-drug. Free PTH will be assessed in approximately 24 subjects. The PK plasma concentration data for Free PTH, Free PTH (1-34) and Free PTH (1-33) will primarily be used to describe the time to steady-state and plasma concentration achieved at steady-state. Similarly, the PK plasma concentrations of Total PTH and mPEG (assessed in all subjects) will primarily be used to describe the time to steady-state and plasma concentration achieved at steady-state. Potential impact of any anti-PTH and anti-PEG antibodies detected will be included in the evaluation.

Summaries will be provided for Free PTH, Free PTH (1-34), Free PTH (1-33), Total PTH and mPEG plasma concentrations at scheduled visits.

10.13. PD-PK SUB-SET STUDY ANALYSIS

PK plasma concentration for Free PTH, Free PTH (1-34) and Free PTH (1-33) as well as albumin-adjusted serum calcium and serum phosphate will be summarized for the timepoints collected over the 24-hour period of hospital stay for the PD-PK sub-set study (refer to Appendix 13.1 for schedule of assessments, Table 7). Outputs will include table summaries and figures for nominal and actual time from dosing and time from first sample collection for each of the parameters. Similarly, urine parameters will be summarized in tables and figures.

Vital signs measured during the study will be summarized in a table by timepoint of collection.

Additionally, PK plasma concentrations, 24-hour urine parameters, and vital signs will be presented in listings.

11. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

- Removed “Albumin-adjusted or ionized sCa, magnesium, phosphate, and sCA x sP product at 8, 18, 26, 42, and 58 weeks” from exploratory endpoints as these are all included in other secondary efficacy endpoints and it is redundant to appear under both.

12. REFERENCES

Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (Draft Guidance), April 2016:
https://www.fda.gov/downloads/Drugs/Guidances/UCM192750.pdf

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https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Pink%20Sheet%20DAILY/2014/September/Natpara_FDA_brfg.pdf.

Khurana M, Zadezensky I, Lowy N, et al. Use of a systems pharmacology model based approach toward dose optimization of Parathyroid hormone therapy in hypoparathyroidism. Clinical Pharmacology & Ther. 2018

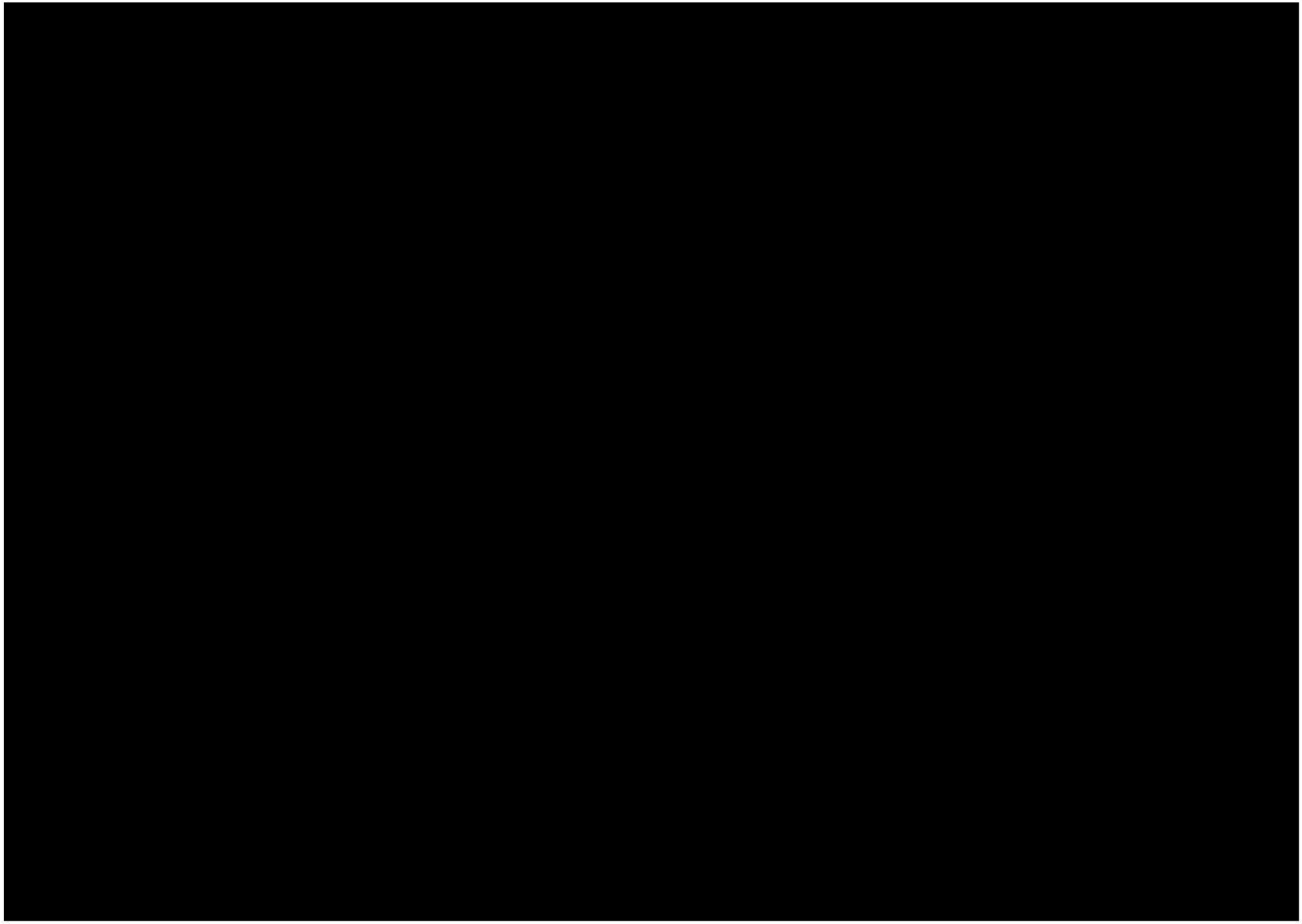
Shankar et al. (2014) Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations, AAPS J. 2014 Jul;16(4):658-73

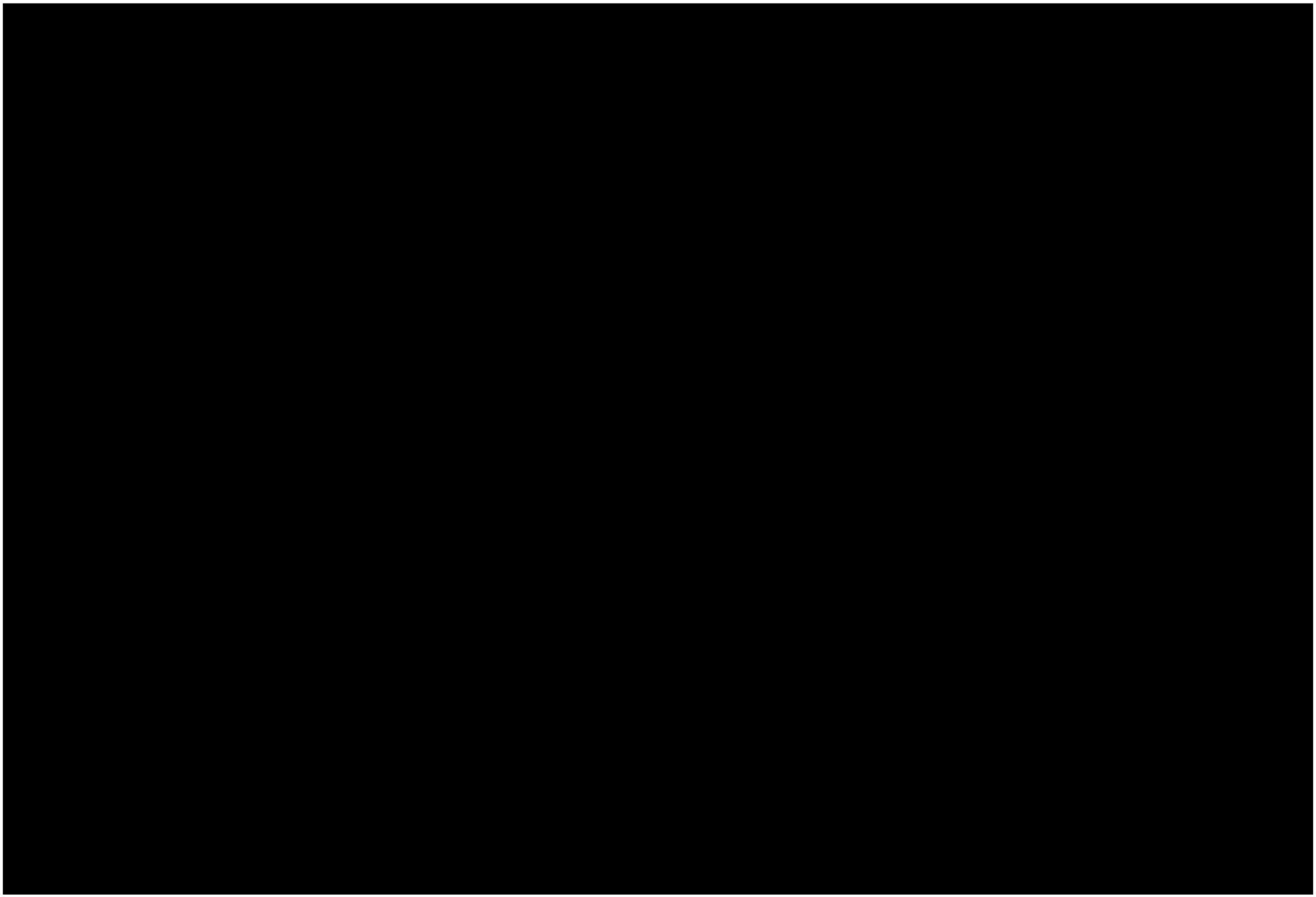
13. APPENDICES

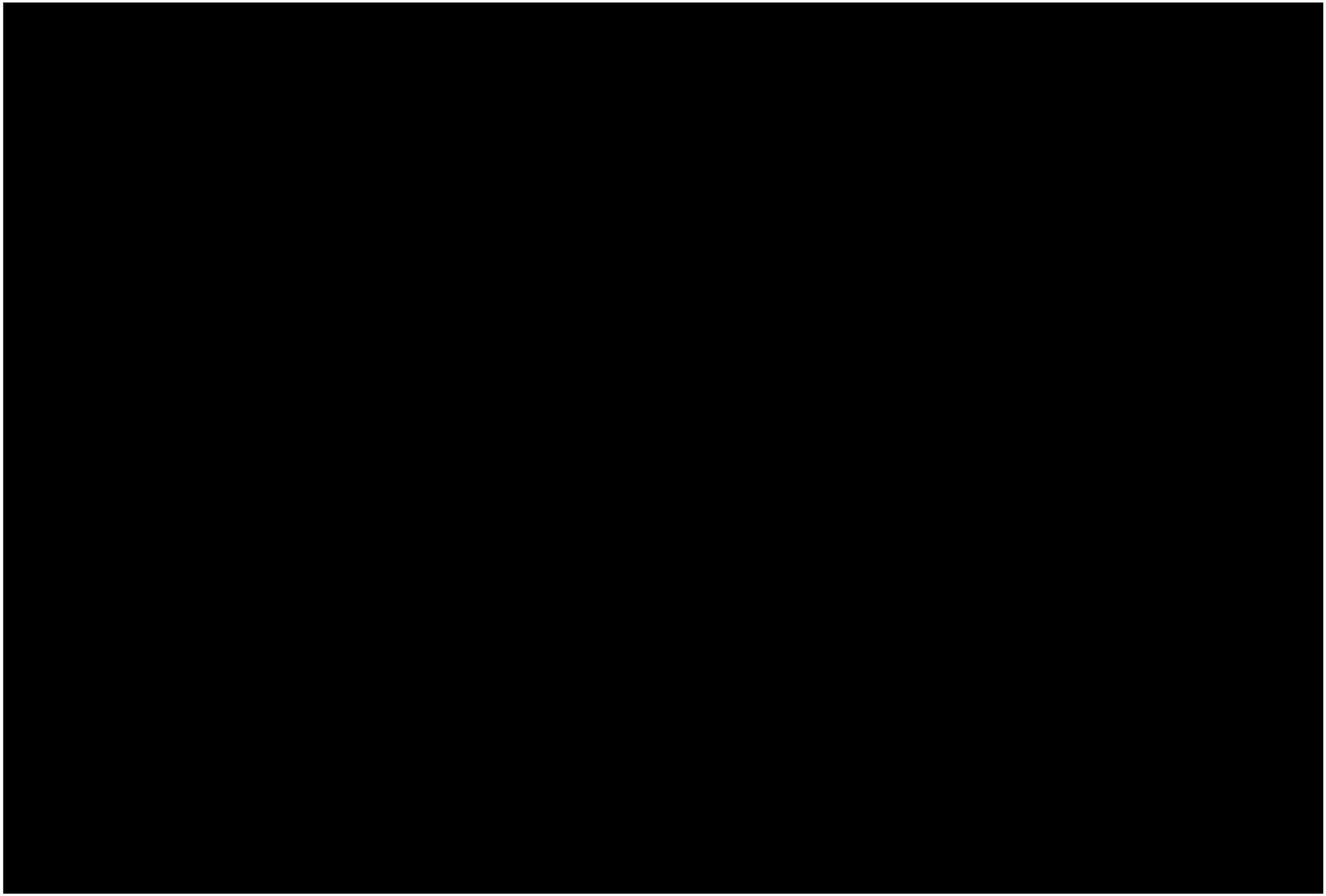
[redacted]

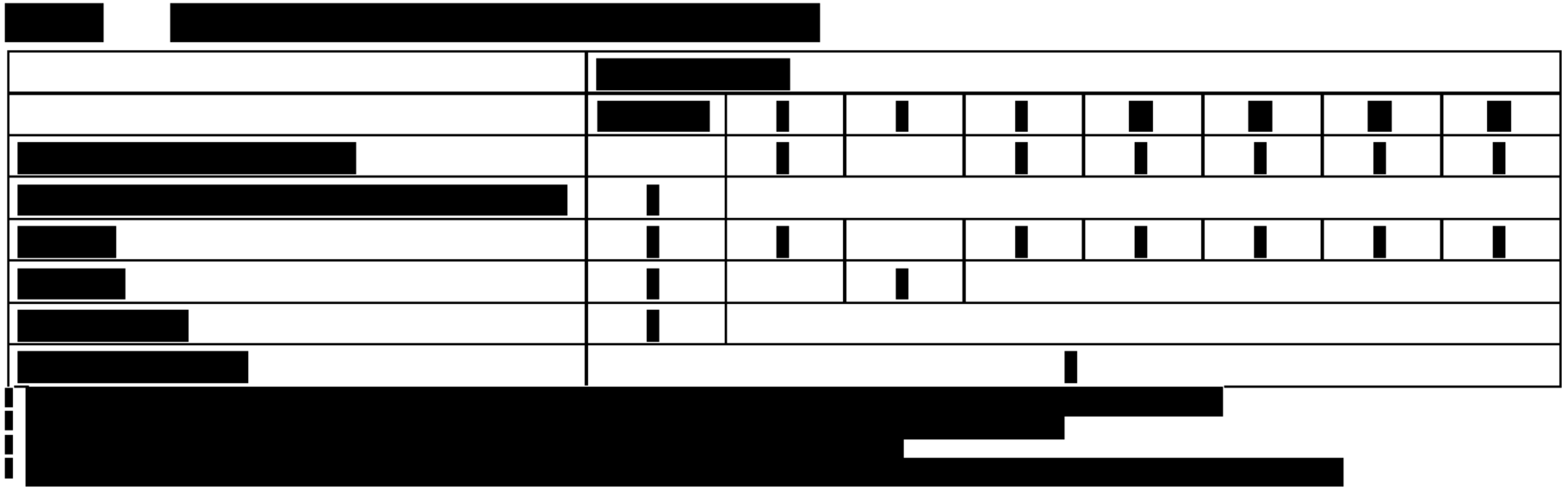
13.1. SCHEDULE OF ASSESSMENTS

[redacted]









14. SAP AMENDMENT LIST OF CHANGES

AMENDMENT 1 SUMMARY

The major changes to the analyses specified in the original SAP version 1 (dated 21 August 2019) are:

Section(s)	Change(s)
7.2 Baseline	Clarify the baseline definition for PRO measures and select lab parameters.
9.3 Visit Time Window	Add more details for window mapping of standard of care supplements.
10.10.2 Analysis of Primary Efficacy Endpoint	Added two sensitivity analyses to the primary endpoint.

AMENDMENT 2 SUMMARY

The major changes to the analyses specified in the SAP Amendment 1 version 1.1 (dated 27 March 2020) are:

Section(s)	Change(s)
2. Trial Design	Updates to accommodate changes based on Protocol Amendment 2. Extended number of visits.
9.3 Visit Time Window	Add analysis windows for the extension period triggered by Protocol Amendment 2. Clarify analyses of PK and antibody data.
10.1 General Principles	Added definition of TransCon Period that is used for summaries of certain endpoints.
10.10.5 Analyses of Efficacy Endpoints in the Extension Period	Added a new section to describe the analysis for efficacy to be conducted at the Extension Period timepoints.
13. Appendices	Updated appendices per Protocol Amendment 2 with extended visits and schedule of assessments.

AMENDMENT 3 SUMMARY

The major changes to the analyses specified in the SAP Amendment 1 version 1.2 (dated 21 August 2020) are:

Section(s)	Change(s)
8.5. PD-PK Sub-Set Study Population	Defined a new analysis population for the PD-PK subset study.
10.10.5.1. Primary and Sensitivity Extension Period Endpoints	Added a new sensitivity analysis.

Section(s)	Change(s)
10.11.1. Adverse Events	Added the definition of AESIs, and TEAEs of special interest and the planned analyses.
10.13. PD-PK Sub-Set Study Analysis	Added details on the analysis for the PD-PK subset study.
13 Appendices	Added Table 7 of Schedule of Laboratory Assessments for PD-PK subset study.

Approval Signatures

Document Name: TCP-201 SAP v1.3 Amend3

Document Number: VV-SUB-030304

Version: 2.0

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Approved	SIGNATURE INFORMATION: [redacted] 28-Oct-2021 23:49:29 GMT+0000
Approved	SIGNATURE INFORMATION: [redacted] 28-Oct-2021 23:51:26 GMT+0000