Official Title: PaTHway Trial: A Phase 3, 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

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STATISTICAL ANALYSIS PLAN

Title	**PaTHway TRIAL:** A Phase 3, 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:	TCP-304
Investigational Product:	TransCon PTH
Phase:	3
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TABLE OF CONTENTS

LIST OF TABLES 4
LIST OF FIGURES 4
ABBREVIATIONS 5
1. INTRODUCTION 7
2. STUDY DESIGN 7
2.1. Blinding and Randomization Methods 8
3. STUDY OBJECTIVE(S) 9
3.1. Primary Objective(s) 9
3.2. Secondary Objective(s) 9
3.3. Exploratory Objectives 9
4. SAMPLE SIZE CONSIDERATIONS 9
5. INTERIM ANALYSIS 10
6. DATA MONITORING COMMITTEE 10
7. ANALYSIS ENDPOINTS 10
7.1. Efficacy Endpoints 10
7.1.1. Primary Efficacy Endpoint 10
7.1.2. Secondary Efficacy Endpoints 11
7.1.2.1. Key Secondary Efficacy Endpoints 11
7.1.2.2. Other Secondary Efficacy Endpoints 11
7.2. Safety Endpoints 12
7.3. Exploratory endpoints 12
8. DEFINITIONS 12
8.1. Treatment 12
8.2. Baseline 12
8.3. Study Day 13
8.4. Age 13
9. ANALYSIS POPULATIONS 13
9.1. Screened Population 13
9.2. Randomized Population 13
9.3. Intent to Treat (ITT) Population 13
9.4. Safety Analysis Population 13
9.5. Pharmacokinetic Population 13

10. DATA SCREENING AND ACCEPTANCE 14
10.1. General Principles 14
10.2. Handling of Missing and Incomplete Data 14
10.2.1. Missing Key Secondary Endpoints Data 14
10.2.2. Missing Hypoparathyroidism Disease History 15
10.2.3. Missing Birth Dates 15
10.2.4. Missing Date Imputation for Adverse Events and Concomitant Medications 15
10.2.5. Missing Causal Relationship to Study Drug for Adverse Events 16
10.2.6. Incomplete Lab and PK Data 16
10.3. Visit Time Windows 16
10.4. Testing/Validation Plan 18
10.5. Software 18
11. STATISTICAL METHODS OF ANALYSES 18
11.1. General Principles 18
11.2. Subgroup Analysis 19
11.3. Subject Accountability and disposition 19
11.4. Protocol Deviations 20
11.5. Investigational Product Administration 20
11.5.1. Extent of Exposure 20
11.5.2. Measurement of Treatment Compliance 20
CCI [redacted] 20
11.6. Demographic and Baseline Characteristics 21
11.7. Prior and Concomitant Medication 21
11.8. Medical History 21
11.9. hypoparathyroidism Disease Characteristics and History 21
11.10. Efficacy Analysis 21
11.10.1. General Analysis Methods 22
11.10.2. Analysis of Primary Efficacy Endpointin the Blinded Treatment Period 22
11.10.2.1. Primary Analysis 22
11.10.2.2. Sensitivity Analyses 23
11.10.3. Analysis of Primary Efficacy Endpointin the Extension Period 25
11.10.4. Analyses of Key Secondary Efficacy Endpoint(s) 26
11.10.4.1. Multiplicity Adjustment 26

11.10.5. Analyses of Other Efficacy Endpoint(s) 27
11.11. Safety Analysis 28
11.11.1. Adverse Events 28
11.11.1.1. Adverse Event of Special Interest 29
11.11.2. Clinical Laboratory Parameters 29
11.11.3. Vital Signs 30
11.11.4. Electrocardiogram 30
11.11.5. Local Tolerability Assessment 30
11.11.6. Antibody Parameters 30
11.12. Pharmacokinetic Analysis 31
11.13. Exploratory Analysis 31
12. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL 31
13. REFERENCES 32
14. APPENDICES 33
15. SAP AMENDMENT LIST OF CHANGES 43

LIST OF TABLES

Table 1: Analysis Visit Time Windows 17
Table 2: Schedule of Events – Blinded Treatment Period 33
Table 3: Schedule of Events - Extension Period 36
Table 4: Schedule of Laboratory Assessments – Blinded Treatment Period 39
Table 5: Schedule of Laboratory Assessments – Extension Period 41

LIST OF FIGURES

Figure 1: Trial Design 8
Figure 2: Graphical Illustration of the Sequential Tests for Primary and Key Secondary Endpoints 26

ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse events
AESI	adverse events of special interest
ANOVA	analysis of variance
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CGI-S	clinical global impression of severity
ClinRO	clinician-reported outcome
CMH	Cochran–Mantel–Haenszel
COA	clinical outcome assessment
eCRF	electronic case report form
CTx	c-telopeptide of type 1 collagen
CxP	calcium-phosphate product
DCO	data cut-off
DMC	data monitoring committee
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EDC	electronic data capture
EOT	end of trial
EQ-5D	euroQol 5-dimensional
EQ-VAS	euroQol visual analogue scale
FSH	follicle stimulating hormone
hCG	human chorionic gonadotropin
HPES	hypoparathyroidism patient experience scale
ICF	informed consent form
ITT	Intent-To-Treat
ISR	injection site reaction
LS Mean	least squares mean
LV	laboratory visit
IWRS	interactive web randomization system
MCMC	Markov Chain Monte Carlo
MCS	mental component
MedDRA	medical dictionary for regulatory activities

Abbreviation	Definition
MAR	missing at random
P1NP	procollagen type 1 amino-terminal propeptide
PCS	physical component
CCI	[redacted]
PD	pharmacodynamics
PEG	polyethylene glycol
PK	pharmacokinetics
PTH	parathyroid hormone
PRN	Pro re nata
PRO	patient-reported outcome
PT	preferred term
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓)
SAE	serious adverse events
SC	subcutaneous
SD	standard deviation
SE	standard error
SAP	statistical analysis plan
sCa	serum calcium
SF-36	36-item short form survey
sMg	serum magnesium
SoC	standard of care (active vitamin D plus calcium)
SOC	system organ class
sP	serum phosphate
TBS	trabecular bone score
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
uCa	urine calcium
uP	urine phosphate
WHO	world health organization
CCI	[redacted]

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 and safety data as outlined and/or specified in the study TCP-304 protocol version 5.0 (dated 17 DEC 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.

2. STUDY DESIGN

TCP-304 is a phase 3, 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. The total length of the trial will be up to approximately 190 weeks including the following 3 periods. The trial design is presented in Figure 1.

- **Screening Period (supplement optimization):** Up to approximately 4 weeks (plus a recommended period of up to approximately 2 weeks between randomization and Visit 1)
- **Blinded Treatment Period (study drug stable with SoC optimization):** 26 weeks
- **Extension Period (open-label TransCon PTH treatment):** 156 weeks (plus follow up telephone contact 2 weeks after last study drug administration)

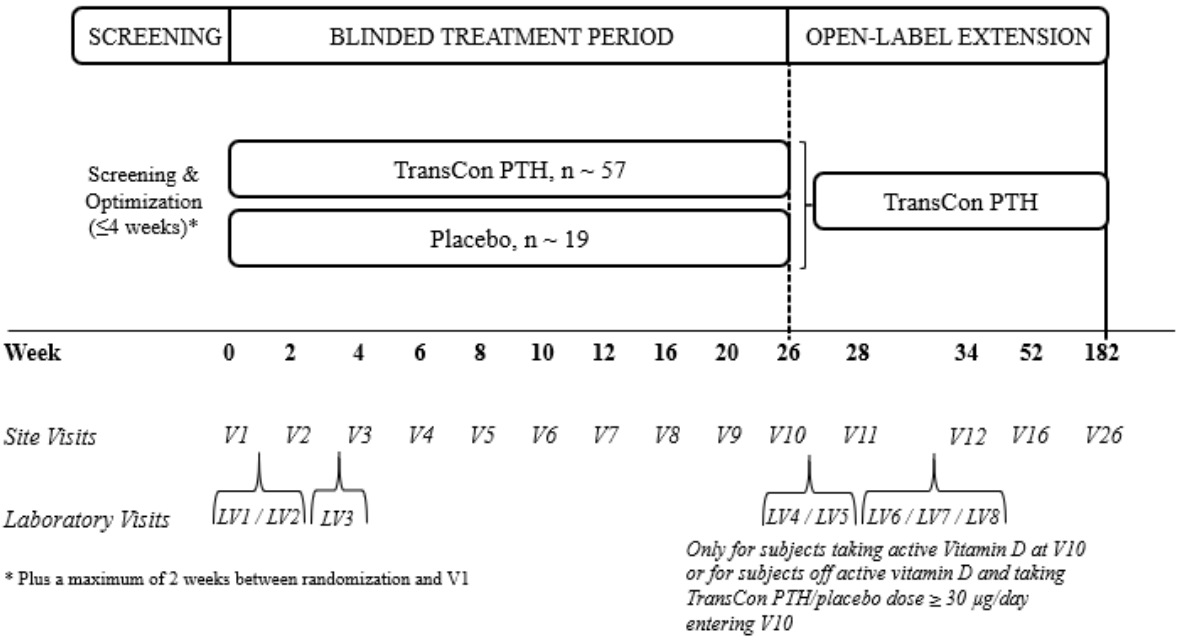
Approximately 76 subjects meeting the inclusion criteria will be randomized in a 3:1 ratio into 2 treatment groups:

- TransCon PTH 18 µg/day, co-administered with SoC
- Placebo for TransCon PTH (excipient solution), co-administered with SoC

In Blinded Treatment Period, all subjects will start with study drug at 18 µg/day and will be individually and progressively titrated to an optimal dose in dose increments of 3 µg/day.

Following successful completion of the Blinded Treatment Period, subjects will be allowed to enter the open-label Extension Period where all subjects will receive TransCon PTH.

Figure 1: Trial Design



The schedule of evaluations is presented in Section 14, Table 2 and Table 3 for blinded and extension periods, respectively. The schedule of laboratory assessments for blinded and extension periods is also presented under Section 14, Table 4 and Table 5.

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 party to maintain blinding. Approximately 76 subjects will be randomized in a 3:1 ratio to TransCon PTH treatment and placebo groups and assigned to a treatment sequence group via an Interactive Web Randomization System (IWRS). The randomization will be stratified by etiology of hypoparathyroidism (post-surgical vs other).

The study will be double-blind so that neither the sponsor, subject, nor site personnel involved in study conduct will know the identity of a subject's treatment.

The investigator and site personnel will remain blinded to the randomization code during the study. Treatment assignment for an individual subject should be unblinded by the investigator only in an emergency e.g., 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 should contact the medical monitor or clinical trial 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 an IWRS, which will be available 24-hours a day, 7 days a week. Refer to study blinding plan for additional details.

3. STUDY OBJECTIVE(S)

3.1. PRIMARY OBJECTIVE(S)

The primary objective is to assess the treatment effect of daily TransCon PTH on serum calcium (sCa) levels, and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment.

3.2. SECONDARY OBJECTIVE(S)

The secondary objectives are

- To assess the safety and tolerability of daily TransCon PTH
- To assess the treatment effect of daily TransCon PTH on hypoparathyroidism patient experience scale (HPES) domain scores
- To assess the treatment effect of daily TransCon PTH on pharmacodynamics (PD) markers (including sCa) and active vitamin D and calcium doses
- To assess the treatment effect of daily TransCon PTH on serum phosphate (sP), CxP (albumin-adjusted sCa x sP product), and serum magnesium (sMg)
- To assess anti-PTH, anti-TransCon PTH and anti-polyethylene glycol (PEG) antibody responses
- To assess the treatment effect during Extension Period
- To assess the treatment effect of daily TransCon PTH on
  - Bone mineral density (BMD) and trabecular bone score (TBS) by DXA
  - Bone turnover markers (serum P1NP and CTx)
- To assess the impact of treatment on patient-reported health-related quality of life (QOL) and a clinician-reported outcome (ClinRO) assessment

3.3. EXPLORATORY OBJECTIVES

CCI [redacted]

4. SAMPLE SIZE CONSIDERATIONS

The sample size is determined based on considerations from both statistical power and adequate safety exposure perspectives. Assuming that the response rate is 70% for TransCon PTH and 15% for placebo for the primary endpoint at 26 weeks, 68 subjects randomized 3:1 to active TransCon PTH vs. placebo will have approximate statistical powers of 99% at alpha = 0.05, and 95% at alpha = 0.01 (two-sided) to demonstrate statistically significant difference between TransCon PTH and placebo. The assumption of 70% response rate for TransCon PTH is considered conservative, since approximately 86% of subjects taking TransCon PTH with efficacy data (N=56) would meet the primary endpoint proposed for study TCP-304 based on phase 2 study TCP-201 6-month data.

Taking into account of approximately 10% dropout, a total sample size of 76 is targeted.

5. INTERIM ANALYSIS

The 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 may be performed.

The final analysis will be conducted at the end of study (i.e., All subjects complete End of Trial (EOT) visits and the follow-up telephone contact)

6. DATA MONITORING COMMITTEE

An independent data monitoring committee (DMC) with relevant expertise in the conduct of clinical trials will act in an advisory capacity to monitor subject safety on a routine basis throughout the trial. The DMC may also provide advice to Ascendis in any determination of whether the study should be halted.

The detailed roles and responsibilities of the DMC are specified in the DMC Charter.

7. ANALYSIS ENDPOINTS

7.1. EFFICACY ENDPOINTS

7.1.1. Primary Efficacy Endpoint

Blinded Treatment Period:

At 26 weeks of treatment, the proportion of subjects with:

- Albumin-adjusted sCa measured within 4 weeks prior to and on Week 26 visit are within the normal range (8.3-10.6 mg/dL) *; **and**
- Independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of pro re nata (PRN, as needed/rescue) ≤ 7 days during the 4 weeks); **and**
- Independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses on ≤ 7 days during the 4 weeks). This dose of elemental calcium ≤600 mg/day in the form of tablets, powder, liquid suspension, or transdermal patch is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism; **and**
- No increase in prescribed study drug within 4 weeks prior to Week 26 visit. **

*Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.

** Dose decrease permitted for safety reasons.

Extension Period:

The primary efficacy endpoint in the Extension Period is the proportion of subjects that meet the following criteria at 52 weeks or other timepoints as needed:

- Albumin-adjusted sCa measured within the normal range (8.3-10.6 mg/dL); **and**
- Independence from active vitamin D (i.e., standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit or other visits of interest); **and**
- Independence from therapeutic doses of calcium (i.e., standing dose of elemental calcium ≤ 600mg on the day prior to the Week 52 visit or other visits of interest).

7.1.2. Secondary Efficacy Endpoints

7.1.2.1. Key Secondary Efficacy Endpoints

Key secondary endpoints include the change from baseline at 26 weeks of treatment for the following parameters:

- HPES Symptom - Physical domain score
- HPES Symptom - Cognitive domain score
- HPES Impact – Physical Functioning domain score
- HPES Impact – Daily Life domain score
- 36-Item Short Form Survey (SF-36) Physical Functioning subscale score

The change from baseline for the above scores will also be evaluated as key secondary endpoints at 52 weeks or other timepoints as needed for Extension Period.

7.1.2.2. Other Secondary Efficacy Endpoints

The following endpoints will be evaluated at predefined timepoints during the Blinded Treatment and the Extension Period:

- Calcium and active vitamin D doses
- Daily "pill burden" of active vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches) assessed
- sP
- Albumin-adjusted sCa x sP product, including proportion of subjects with albumin-adjusted sCa x sP product ≤55 mg^2/dL^2, ≤52 mg^2/dL^2, and ≤44 mg^2/dL^2
- Albumin-adjusted sCa
- BMD and TBS by DXA
- Bone turnover markers (serum P1NP and CTx)
- sMg
- EQ-5D

- CGI-S
- HPES: HPES Impact domain scores (Psychological Well-being and Social Life and Relationships) and HPES Symptom and Impact total scores
- SF-36: SF-36 subscale scores (Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health) and SF-36 component summary scores (Physical component score (PCS) and Mental component score (MCS))

7.2. SAFETY ENDPOINTS

The following safety endpoints will be assessed during the Blinded Treatment and Extension Periods:

- Incidence of adverse events (AEs), adverse events of special interest (AESI) and serious adverse events (SAEs)
- Serum chemistry and hematology
- 24-hour urine chemistry (including uCa and urine creatinine clearance)
- Clinical events of hypo- or hypercalcemia (emergency/urgent care visits and hospitalizations)
- Injection site tolerability (based on AEs)
- Evaluation of anti-PTH, anti-TransCon PTH and anti-PEG antibody responses
- Vital signs

7.3. EXPLORATORY ENDPOINTS

The following exploratory endpoints will be assessed at predefined timepoints:

CCI

[redacted]

8. DEFINITIONS

8.1. TREATMENT

Blinded study drug is defined as TransCon PTH or Placebo.

Open-label study drug is defined as TransCon PTH.

8.2. BASELINE

Baseline is defined as the last non-missing assessment prior to the first dose of blinded study drug unless otherwise specified.

8.3. 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 date of the first dose of blinded study drug, then
- Study day = (visit/assessment date – date of the first dose of blinded study drug) + 1
- If the visit or assessment is before the date of the first dose of blinded study drug, then

  Study day = visit/assessment date – date of the first dose of blinded study drug

8.4. AGE

The age recorded on electronic case report form (eCRF) will be used. If it is missing, the birth date will be imputed to calculate age (See Section 10.2.3 for the birth date imputation algorithm) using Age = (Inform Consent Date – Birth Date +1)/365.25.

9. ANALYSIS POPULATIONS

9.1. SCREENED POPULATION

The Screened Population will consist of all subjects who underwent a Screening Visit and received a subject identification number.

9.2. RANDOMIZED POPULATION

The Randomized Population will consist of all subjects who were randomized to a treatment group in the study.

9.3. INTENT TO TREAT (ITT) POPULATION

The Intent to Treat (ITT) Population will consist of all subjects in the Randomized Population who received at least one dose of blinded study drug. Subjects will be analyzed according to study treatment per randomization.

9.4. SAFETY ANALYSIS POPULATION

The Safety Analysis Population will consist of all subjects in the Randomized Population who received at least one dose of blinded study drug. Subjects will be analyzed according to actual study treatment received. If subjects take both TransCon PTH and placebo during the Blinded Treatment Period, they will be analyzed according to the treatment that was dosed majority of time (i.e., ≥50% dose days during the Blinded Treatment Period).

9.5. PHARMACOKINETIC POPULATION

Pharmacokinetic (PK) Population is defined as all subjects who received at least one dose of TransCon PTH and for whom the plasma concentration data are considered sufficient and interpretable (i.e., have at least one non-missing concentration).

10. DATA SCREENING AND ACCEPTANCE

10.1. GENERAL PRINCIPLES

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

10.2. 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 study. Missing and incomplete data will be identified for investigation, and possible resolution, by Data Management prior to the study database lock or snapshot.

Unless specified otherwise, no imputation will be applied to data not covered in Section 10.2. Only the observed data (not imputed data) will be presented in listings.

10.2.1. Missing Key Secondary Endpoints Data

Subjects with missing data for key secondary endpoints will have the post-baseline data imputed using a multiple imputation model stratified by treatment group, under the assumption of missing at random (MAR). Missing at random means that the missing data mechanism is assumed to not depend on unobserved missing values but may depend on any other available information collected in the trial (Schafer 1997, Schafer 1999).

The multiple imputation will be conducted in the following 3 steps:

Step I: Imputation of Missing Data

The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing post-baseline key secondary endpoint data by treatment group. The variable list for imputations will include etiology of hypoparathyroidism and baseline and all available post-baseline values of the key secondary endpoints. The SAS procedure PROC MI will be used to generate 100 imputed datasets. In each dataset, missing values are replaced with plausible possibilities. The set of possibilities represent the uncertainty about the unobserved 'true' value that is imputed.

Step II: Inference

For each of the 100 imputed datasets, the change from baseline in key secondary endpoints will be calculated based on the imputed values. The change from baseline will then be compared between TransCon PTH and Placebo groups using an ANCOVA model with unequal variance in the ITT population. Treatment assignment and etiology of hypoparathyroidism will be entered as fixed effects and baseline values of the key secondary endpoints will be entered as covariates in the ANCOVA model.

Step III: Pooling

The estimates from the 100 fitted models for each of the 100 imputed datasets will be combined to provide an overall estimate of the least square mean with a corresponding confidence interval for each treatment group. An overall estimate of the difference in least square means between

the two treatment groups with confidence interval and a p-value will also be provided (Little 2002).

10.2.2. 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.

If the resulting date is after informed consent form (ICF) date, assign the ICF date as imputed date.

10.2.3. Missing Birth Dates

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

- If 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.

10.2.4. Missing Date Imputation for Adverse Events and Concomitant Medications

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

Missing Start Dates

- If the day is unknown, then:
  - If the month and year match the first dose of blinded study drug start date month and year in this study, 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 blinded study drug date in this study, then impute the day and month of the first dose date in this study.
  - 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 end date, then the start date will be set as the same date as the end date.

Missing End Dates for "not ongoing" CM

- If the day is unknown, then assign the last day of the month.

- If both day and month are unknown, then assign 'December 31.'
- If the year is unknown, then the date will not be imputed and will be assigned a missing value, and the event will be considered ongoing.

If the resulting end date is after the date of study completion / discontinuation/ data cutoff, set the imputed end date to the date of study completion / discontinuation/ data cutoff, whichever is earlier.

10.2.5. Missing Causal Relationship to Study Drug for Adverse Events

If the causal relationship to the study drug is missing for an AE that started on or after the date of the first dose of blinded study drug, a causality of "Related" will be assigned. The imputed values for causal relationship to study drug will be used for the incidence summary; the values will be shown as missing in the data listings.

10.2.6. Incomplete Lab and PK Data

For lab data, if the raw data is "<xx", then the imputed value will be 0.9* xx. If the raw data is ">xx", then the imputed value will be 1.1*xx. For PK data, if the raw data is "<xx" or "<BLQ", then the imputed value will be 0. The imputed zero will be used for summary statistics with geometric mean and geometric CV% reported as "NC (Not Calculated)".

10.3. VISIT TIME WINDOWS

For laboratory parameters and other per visit assessments, both scheduled and unscheduled visits will be mapped to the scheduled visits based on windows (range of treatment days) in Table 1.

For by-visit summaries, 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, 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 vital signs with both pre- and post-dose assessments, this rule is applied to pre-dose assessments only.

For listings, all data points will be included.

Local laboratory visits during Blinded Treatment and Extension periods in the protocol will use nominal visit assigned in EDC, except that the albumin-adjusted sCa from local labs will be mapped to scheduled visits based on Table 1.

Table 1: Analysis Visit Time Windows

Period	Visit (Week)	Scheduled Visit Target Day	Window
Blinded Treatment Period	Baseline (Week 0)	Day 1	Days ≤ [prior to first dose of blinded study drug]
	Visit 1 (Week 0)	Day 1	Day 1
	Visit 2 (Week 2)	Day 15	Days [2-22]
	Visit 3 (Week 4)	Day 29	Days [23-36]
	Visit 4 (Week 6)	Day 43	Days [37-50]
	Visit 5 (Week 8)	Day 57	Days [51-64]
	Visit 6 (Week 10)	Day 71	Days [65-78]
	Visit 7 (Week 12)	Day 85	Days [79-99]
	Visit 8 (Week 16)	Day 113	Days [100-127]
	Visit 9 (Week 20)	Day 141	Days [128- (Study day of the first open-label drug dose -29)] *
	Visit 10 (Week 26)	Study day of the first open label study drug dose *	Days [(Study day of the first open-label drug dose -28) - Study day of the first dose of open-label study drug] *
Extension Period	Visit 11 (Week 28)	Day 197	Days [Study day after the first open-label study drug -218] *
	Visit 12 (Week 34)	Day 239	Days [219-253]
	Visit 13 (Week 38)	Day 267	Days [254-281]
	Visit 14 (Week 42)	Day 295	Days [282-309]
	Visit 15 (Week 46)	Day 323	Days [310-344]
	Visit 16 (Week 52)	Day 365	Days [345-410]
	Visit 17 (Week 65)	Day 456	Days [411-501]
	Visit 18 (Week 78)	Day 547	Days [502-592]
	Visit 19 (Week 91)	Day 638	Days [593-683]
	Visit 20 (Week 104)	Day 729	Days [684-774]
	Visit 21 (Week 117)	Day 820	Days [775-865]
	Visit 22 (Week 130)	Day 911	Days [866-956]
	Visit 23 (Week 143)	Day 1002	Days [957-1047]
	Visit 24 (Week 156)	Day 1093	Days [1048-1138]
	Visit 25 (Week 169)	Day 1184	Days [1139-1229]
	Visit 26 (Week 182)	Day 1275	Days >=1230

*If a subject does not have the first dose of open-label study drug administration, study day of scheduled Week 26 visit will be used as the target day for Week 26. If scheduled Week 26 visit is missing, study day 183 will be used as the target day for Week 26.
Local lab visits will not be summarized by visit in tables. They will only be presented in listings except that local album-adjusted sCa within 4 weeks prior to Week 26 will be included in primary analysis.

For analysis of local tolerability and DXA assessment, 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 date of active TransCon PTH, i.e., first blinded dose date, **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 date of active TransCon PTH, i.e., first open-label dose date, **Visit 10, Week 26**.

Weeks from dosing will be derived using nominal visits. For local lab visits (LV), weeks will be assigned as partial weeks. For example, LV1 – Week 0.4, LV2 – Week 1.1, LV3 – Week 3.1, etc.

For SoC, the dose (standing plus PRN, if applicable) taken on the day prior to Visit X will be considered as dose at Visit X for each subject in summary tables. 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 date is missing, the target date of the visit in Table 1 will be used for analyses.

10.4. TESTING/VALIDATION PLAN

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

10.5. SOFTWARE

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

11. STATISTICAL METHODS OF ANALYSES

11.1. GENERAL PRINCIPLES

The efficacy analyses will be based on the ITT Population. Safety analyses will be based on the Safety Analysis Population. PK analyses will be conducted using the PK Population. When the last randomized subject reaches the last visit in Blinded Treatment period (Visit 10), a Blinded Treatment Period analysis will be triggered using the last subject's Visit 10 date as data cut-off (DCO) date. Subsequent analyses may be conducted as needed and considered as Extension Period analyses. A final analysis will be conducted when all subjects are off the study.

For Extension Period analyses, selected outputs may be presented for TransCon PTH Period defined as the period of exposure to TransCon PTH drug. TransCon PTH Period for subjects randomized to the TransCon PTH arm at trial enrollment will be the time from exposure to first dose of blinded active TransCon PTH until time of analysis. 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.

Unless otherwise specified, summaries will be performed descriptively by treatment group. Continuous variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), standard error (SE) of the mean, median, minimum, and maximum values. The mean for each visit will be calculated including only the subjects who are in the analysis set and have data for that visit.

Categorical variable summaries will include the frequency and percentage of subjects in the particular category. Unless otherwise specified, the calculation of proportions will include the missing category. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the analysis set. (i.e., Counts of missing observations will be included in the denominator and presented as a separate category)

All statistical tests will be two-sided and tested at statistically significant level of 0.05. P-values will be rounded and displayed in four decimals. If a p-value less than 0.0001, it will be shown in tables as <0.0001. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

11.2. SUBGROUP ANALYSIS

To assess the robustness of the treatment effect across subgroups, subgroup analyses may be conducted for the primary and key secondary efficacy endpoints. Demographics will also be summarized by subgroup.

The following subgroups of interest will be considered provided that sufficient number of subjects falls in each category (e.g., >=10% of analysis population in all categories) to perform appropriate statistical analysis:

- Age category (<50 vs >= 50)
- Prior treatment with PTH therapy (yes vs no)
- Gender (Female vs Male)
- Etiology of hypoparathyroidism (Post-surgical vs. Other (Auto-immune, Idiopathic and genetic))
- Duration of hypoparathyroidism (< 5 years, >=5 and < 10 years, >=10 and < 20 years, >= 20 years)
- Region (North America vs. Other)
- Menopausal status among female (Premenopausal vs postmenopausal)

In primary and key secondary efficacy analyses, forest plots will be used to display the odds ratio of response rate with 95% CI for binary endpoints and difference in LS means with 95% CI for continuous endpoints for each subgroup.

11.3. SUBJECT ACCOUNTABILITY AND DISPOSITION

The number and percentage of subjects in each of the analysis populations (Screened, Randomized, ITT, Safety, and PK) will be summarized. Subjects excluded from the analysis sets will be listed.

Screen-failure subjects (i.e., subjects screened but not randomized) and the associated reasons for failure to randomize will be summarized and listed.

The number and percentage of subjects who complete or prematurely discontinue study drug and/or the trial will be presented for each treatment group and Total for the ITT Population. The reasons for premature discontinuation from treatment and/or the trial as recorded on eCRFs will be summarized. Disposition data will be listed by subject for the Randomized Population.

11.4. PROTOCOL DEVIATIONS

Major protocol deviations will be summarized by deviation category for each treatment group. Both major and minor protocol deviations will be listed.

11.5. INVESTIGATIONAL PRODUCT ADMINISTRATION

11.5.1. Extent of Exposure

Exposure will be summarized by treatment group for the Safety Analysis Population, with the following parameters to be presented:

- Duration of exposure (days) (i.e., Total number of planned doses)
- Total number of actual doses
- Average actual daily dosage (mcg)
- Total actual dose (mcg)

The summary may be conducted for Blinded Treatment Period and Extension Period analyses. For Blinded Treatment Period analysis, duration of exposure is defined as the duration 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. For Extension Period analysis, duration of 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.

For Extension Period analysis, if a subject hasn't completed the End of Treatment eCRF at the time of analysis, the last dose date will be imputed as DCO date.

11.5.2. Measurement of Treatment Compliance

Compliance is defined as total number of actual doses received divided by the duration of exposure (i.e., total number of planned doses) multiplied by 100.

Descriptive statistics for study drug compliance will be presented by treatment group for the Safety Analysis Population.

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11.6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic parameters (age; age group; race; sex; weight; height, body mass index [BMI]) and other baseline characteristics (e.g., menopausal status) will be summarized descriptively by treatment group for the ITT Population.

11.7. PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as any medication started before the date of the first dose of blinded study drug (medication start date prior to the first blinded study drug dose date). Prior medication may be summarized by treatment groups.

The summary of concomitant medication may be conducted for Blinded Treatment Period and TransCon PTH Period. In Extension Period analyses, concomitant medication will be analyzed for TransCon PTH Period. For Blinded Treatment Period analysis, concomitant medication is defined as any medication that has (1) end date on or after the first blinded study drug dose date [or ongoing], and (2) start date prior to or on the last blinded study drug dose date. The TransCon PTH Period, concomitant medication is defined as any medication with end date on or after the first dose of TransCon PTH [or ongoing] and start date prior to or on the last dose of TransCon PTH. For both periods, 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.

Both prior and concomitant medications will be coded by drug name and therapeutic class using WHO Drug dictionary (version WHO Drug B3 Global 2021Q1 or newer) and summarized for the Safety Analysis Population. 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.

11.8. MEDICAL HISTORY

Subjects' medical history will be summarized by system organ class and preferred terms using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or newer for the ITT Population.

11.9. HYPOPARATHYROIDISM DISEASE CHARACTERISTICS AND HISTORY

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

11.10. EFFICACY ANALYSIS

Efficacy analyses will be conducted for ITT population according to the randomized treatment assignment.

11.10.1. General Analysis Methods

In Blinded Treatment Period analysis, Cochran–Mantel–Haenszel (CMH) test controlling for randomization stratification factor (etiology of hypoparathyroidism: post-surgical vs other) will be used for the primary analysis and other categorical endpoints. The continuous efficacy endpoints will be analyzed using ANCOVA model with unequal variance and Satterthwaite approximation for degrees of freedom. In general, the continuous endpoint of interest or change from baseline will be included in the model as a response variable. Treatment assignment and etiology of hypoparathyroidism will be entered as fixed effects and baseline value of the variable of interest will be entered as a covariate, unless otherwise specified.

For Extension Period, all endpoints will be summarized descriptively, and no statistical tests will be conducted.

11.10.2. Analysis of Primary Efficacy Endpointin the Blinded Treatment Period

11.10.2.1. Primary Analysis

The estimand for the primary analysis is defined by the following components.

Population:

The target study population comprises hypoparathyroidism patients who meet the inclusion and exclusion criteria as specified in Protocol Sections 8.1. The analysis population is the ITT population as defined in Section 9.3.

Variable:

The variable is the primary endpoint, defined as the proportion of subjects who meet the following criteria at 26 weeks of blinded treatment:

- Albumin-adjusted sCa measured within 4 weeks prior to and on Week 26 visit are within the normal range (8.3-10.6mg/dL) *; **and**
- Independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND use of PRN ≤ 7 days during the 4 weeks); **and**
- Independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND use of PRN doses on ≤ 7 days during the 4 weeks); **and**
- No increase in prescribed study drug within 4 weeks prior to Week 26 visit. **

*Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is “abnormal” requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.

**Dose decrease permitted for safety reasons.

Intercurrent events and their handling rules are as follows:

Subjects with no Week 26 albumin-adjusted sCa will be considered as non-responders.

Subjects with >25% (i.e., >7 days) missing diary data of active vitamin D or calcium during the 4 weeks will be considered as non-responders.

Analysis:

As primary analysis, the 2-sided CMH test controlling for etiology of hypoparathyroidism (post-surgical vs other) will be conducted to test the following hypothesis for the primary efficacy endpoint with alpha=0.05:

$$H_0: OR_{Post}=OR_{Other}=1,$$

where OR_{Post} and OR_{Other} are the odds ratios (i.e., the odds of meeting the primary endpoint in TransCon PTH group compared to the odds in the placebo group) within post-surgical and other groups, respectively. The p-value from the CMH test will be reported. The common odds ratio between treatment group and primary endpoint controlling for etiology of hypoparathyroidism with 95% CI will also be reported (Mantel 1959).

Population-level Summary:

The number and proportion of subjects meeting the primary endpoint will be provided by treatment group. The 2-sided 95% exact confidence interval will be calculated for the proportion of subjects for each treatment group.

The estimand framework for the secondary endpoint will be handled using the same approach as described above for the primary endpoint.

11.10.2.2. Sensitivity Analyses

To assess the robustness of the primary analysis, the following sensitivity analyses of the primary endpoint will be performed on the ITT population (except for Sensitivity Analysis 1). In all sensitivity analyses (except for Sensitivity Analysis 1), subjects with missing data on one or more of the criteria for the sensitivity analysis endpoints will be considered as non-responders. The CMH test controlling for etiology of hypoparathyroidism will be conducted for all sensitivity analyses (except for Sensitivity Analysis 3).

Sensitivity Analysis 1

In sensitivity analysis 1, the primary endpoint will be analyzed for the Completer Population. The Completer Population is defined as subjects in the ITT population who complete 26 weeks of blinded study treatment and have data on all components for the primary endpoint.

Sensitivity Analysis 2

In sensitivity analysis 2, the primary endpoint is defined as the proportion of subjects who meet the following criteria at 26 weeks of blinded treatment:

- Albumin-adjusted sCa measured within 4 weeks prior to and on Week 26 visit are within the normal range (8.3-10.6mg/dL) *; **and**
- Not taking any standing dose of active vitamin D within 4 weeks prior to Week 26 visit AND use of PRN ≤ 7 days during the 4 weeks); **and**
- Not taking any standing dose of calcium within 4 weeks prior to Week 26 visit AND use of PRN doses on ≤ 7 days during the 4 weeks); **and**

- No increase in prescribed study drug within 4 weeks prior to Week 26 visit. **

*Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.

**Dose decrease permitted for safety reasons.

Sensitivity Analysis 3

In sensitivity analysis 3, the 2-sided CMH test controlling for gender (Female vs Male) will be conducted to test the primary endpoint.

Sensitivity Analysis 4

In sensitivity analysis 4, the primary endpoint is defined as the proportion of subjects who meet the following criteria at 26 weeks of blinded treatment:

- Albumin-adjusted sCa measured within 4 weeks prior to and on Week 26 visit are within the range of 7.5-10.6mg/dL*; **and**
- ≥50% reduction from baseline in the dose of active vitamin D **and**
- ≥50% reduction from baseline in the dose of calcium supplements.

The % reduction is calculated based on total daily dose (standing plus PRN, if applicable) at baseline (i.e., last non-missing prior to the first dose of blinded study drug) and the average total daily dose during 4 weeks prior to Week 26 visit.

*Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.

Sensitivity Analysis 5

In sensitivity analysis 5, the primary endpoint is defined as the proportion of subjects who meet the following criteria at 26 weeks of blinded treatment:

- Albumin-adjusted sCa measured within 4 weeks prior to and on Week 26 visit are within the normal range (8.3-10.6mg/dL) *; **and**
- Independence from active vitamin D within 4 weeks prior to Week 26 visit (i.e., all daily standing dose of active vitamin D equal to zero AND no use of PRN during the 4 weeks); **and**
- Independence from therapeutic doses of calcium within 4 weeks prior to Week 26 visit (i.e., average daily standing dose of elemental calcium ≤600 mg AND no use of PRN during the 4 weeks); **and**
- No increase in prescribed study drug within 4 weeks prior to Week 26 visit. **

*Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.

**Dose decrease permitted for safety reasons.

11.10.3. Analysis of Primary Efficacy Endpointin the Extension Period

The primary efficacy endpoint in the Extension Period is the proportion of subjects that meet the following criteria at 52 weeks or other timepoints as needed:

- Albumin-adjusted sCa measured within the normal range (8.3-10.6 mg/dL); **and**
- Independence from active vitamin D (i.e., standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit or other visits of interest); **and**
- Independence from therapeutic doses of calcium (i.e., standing dose of elemental calcium ≤600 mg on the day prior to the Week 52 visit or other visits of interest).

The primary analysis is descriptive and will present proportion of subjects meeting the primary endpoint with 2-sided 95% exact confidence interval at each Extension Period analysis timepoint. The analysis will be performed using ITT Population excluding subjects who have missing data on any criteria.

The following sensitivity analysis will be performed on the same population. The proportion of subjects meeting the endpoint with 2-sided 95% exact confidence interval will be provided for each sensitivity analysis.:

Extension Period Primary Endpoint Sensitivity Analysis 1

In sensitivity analysis 1, the primary endpoint is defined as the proportion of subjects who meet the following criteria at 52 weeks or other timepoints as needed in the Extension Period:

- Albumin-adjusted sCa measured within the normal range (8.3-10.6 mg/dL); **and**
- Not taking any standing dose of active vitamin D; **and**
- Not taking any standing dose of calcium.

Extension Period Primary Endpoint Sensitivity Analysis 2

In sensitivity analysis 2, the primary endpoint is defined as the proportion of subjects who meet the following criteria at 52 weeks or other timepoints as needed in the Extension Period:

- Albumin-adjusted sCa measured within the range of 7.5-10.6mg/dL; **and**
- ≥50% reduction from baseline in the dose of active vitamin D **and**
- ≥50% reduction from baseline in the dose of calcium supplements.

Extension Period Primary Endpoint Sensitivity Analysis 3

In sensitivity analysis 3, the primary endpoint is defined as the proportion of subjects who meet the following criteria at 52 weeks or other timepoints as needed in the Extension Period:

- Albumin-adjusted sCa measured within the range of 7.5-10.6 mg/dL; **and**
- Independence from active vitamin D (i.e., standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit or other visits of interest); **and**
- Independence from therapeutic doses of calcium (i.e., standing dose of elemental calcium ≤600 mg on the day prior to the Week 52 visit or other visits of interest).

11.10.4. Analyses of Key Secondary Efficacy Endpoint(s)

For Blinded Treatment Period analysis, the changes from baseline to Week 26 in the following specific HPES and SF-36 scores will be considered as key secondary endpoints with alpha-protection:

Key Secondary Endpoint 1: HPES Symptom - Physical domain score

Key Secondary Endpoint 2: HPES Symptom - Cognitive domain score

Key Secondary Endpoint 3: HPES Impact - Physical Functioning domain score

Key Secondary Endpoint 4: HPES Impact - Daily Life domain score

Key Secondary Endpoint 5: SF-36 - Physical Functioning subscale score

ANCOVA models with unequal variance will be used to analyze the above key secondary endpoints after potential multiple imputation as described in Section 10.2.1. The change from baseline in variable of interest at week 26 will be included in the model as response variables. The following null hypothesis will be tested for each of the key secondary endpoint:

$$H_0: \pi^{PTH} - \pi^{PBO} = 0,$$

where π^{PTH} and π^{PBO} are the mean change from baseline in key secondary endpoint for TransCon PTH and placebo groups, respectively.

Treatment assignment and etiology of hypoparathyroidism will be entered as fixed effects and baseline value of the variable of interest will be entered as a covariate. A 2-sided 95% confidence interval will be calculated for the difference in least square means between the 2 treatment groups. The estimates from the 100 fitted ANCOVA models for each of the 100 imputed datasets will be combined to provide an overall estimate of the between treatment group difference with a corresponding confidence interval and a p-value. The ANCOVA model will also be repeated in subjects with both baseline and post-baseline data (i.e., observed cases) without multiple imputation.

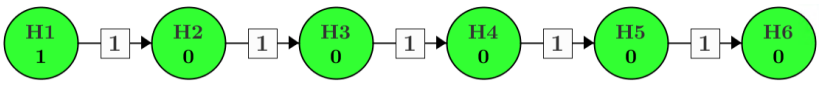
Multiplicity adjustment is applied to control the family-wise type-I error rate for all key secondary endpoints. The order of testing and the significance level for each test are detailed in Section 11.10.4.1.

For Extension Period analyses, the changes from baseline for the above 5 scores will be summarized descriptively as key secondary endpoints at 52 weeks or other timepoints as needed.

11.10.4.1. Multiplicity Adjustment

For Blinded Treatment Period analysis, the primary and five key secondary endpoints will be tested sequentially to control the overall significance level at 0.05. Assume that H1 denotes the null hypothesis of primary endpoint; H2 - H6 denote the null hypotheses of Key Secondary Endpoints 1 - 5, respectively. The testing order is illustrated in Figure 2.

Figure 2: Graphical Illustration of the Sequential Tests for Primary and Key Secondary Endpoints



When a null hypothesis cannot be rejected, the statistical significance for the associated endpoint will not be declared, but the test results will still be reported.

No adjustments are planned for multiple testing/comparisons in the other secondary and exploratory endpoints.

11.10.5. Analyses of Other Efficacy Endpoint(s)

- Calcium and active vitamin D doses
- Daily "pill burden" of active vitamin D and calcium
- sP
- Albumin-adjusted sCa x sP product, including proportion of subjects with albumin-adjusted sCa x sP product ≤55 mg^2/dL^2, ≤52 mg^2/dL^2, and ≤44 mg^2/dL^2
- Albumin-adjusted sCa
- sMg
- BMD and TBS by DXA
- Bone turnover markers (serum P1NP and CTx)
- EuroQol 5-Dimensional Questionnaire (EQ-5D)
  - 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
  - 1 scale to evaluate overall health status: EuroQol visual analogue scale (EQ-VAS)
- Clinician Global Impression of Severity (CGI-S) (filled by investigator)
  - Overall hypoparathyroidism symptoms
  - Hypoparathyroidism physical symptoms
  - Hypoparathyroidism cognitive symptoms
- HPES
  - HPES Impact domain scores*:* Psychological Well-being and Social Life and Relationships
  - HPES Symptom and HPES Impact total scores
- SF-36
  - SF-36 subscale scores: Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health
  - SF-36 component summary scores: PCS and MCS

In the Blinded Treatment Period analysis, all continuous endpoints will be analyzed using an ANCOVA model with unequal variance specified in Section 11.10.1. For calcium and active vitamin D dose, the sum of standing dose and PRN dose on a calendar day will be considered as

daily dose. For bone turnover marker endpoints, the % change from baseline at each post-baseline visit will also be presented by treatment group, and ANCOVA model with unequal variance will be used to compare the % change from baseline between the treatment groups.

In the Extension Period analyses, all other secondary endpoints will be summarized by scheduled visit.

11.11. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Analysis Population for both Blinded Treatment Period and Extension Period. The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG) parameters, local tolerability, and antibody parameters. For safety endpoints, all analyses will be based on the observed data (i.e., with no imputation of missing data), unless otherwise stated.

11.11.1. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or newer. The World Health Organization (WHO) toxicity grading scale will be used for assessing AE severity.

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 was not present prior to the first dose, or it was present at the first dose but increased in severity during the study, and the AE start date was within 14 days after last dose of study drug. TEAE occurring prior to first dose open-label treatment is defined as Blinded Treatment 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 for each treatment group and total Safety Population:

- Summary of TEAEs
- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- TEAE by, SOC, PT, and greatest severity
- Serious TEAEs by SOC and PT
- Non-serious TEAEs by SOC and PT
- Serious Related TEAEs by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs leading to discontinuation of study by SOC and PT
- TEAEs leading to discontinuation of treatment by SOC and PT
- TEAE related to hypocalcemia/hypercalcemia leading to ER/urgent care visit and/or hospitalization by SOC and PT
- TEAEs by PT

- Related TEAEs by PT
- Serious TEAEs by PT
- TEAEs related to special situation by PT
- TEAEs related to injection site reaction (ISR) by PT

For AE tables by SOT and PT, the AE terms will be sorted by descending frequency by SOC and then by PT based on the Total column. For AE tables by PT, the AE terms will be sorted by descending frequency of PT based on the Total column.

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

11.11.1.1. Adverse Event of Special Interest

The following Adverse Event of Special Interest (AESI) will be summarized by PT for each treatment group and total Safety Analysis Population. Data listings will also be provided for each of the AESI.

- Vasodilatory signs and symptoms which may include orthostatic dizziness, lightheadedness, weakness, blurring of vision, pre-syncope, syncope, headache, orthostatic hypotension, orthostatic tachycardia/palpitations
- Persistent severe hypocalcemia
- Persistent severe hypercalcemia

11.11.2. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in conventional and SI units) and changes from the baseline values at each scheduled assessment time point will be presented by treatment group and total Safety Analysis Population for the following laboratory parameters:

- Serum 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 and Cholesterol)
- 24-hour urine: Creatinine, Calcium, Citrate, Uric Acid, Oxalate, Phosphate, Sodium, Potassium, Magnesium, pH and Urine volume
- Hematology: Hemoglobin, Hematocrit, RBC, MCH, MCHC, RBC morphology & MCV, WBC, Neutrophils, Lymphocytes, Monocytes Eosinophils, Basophils, Platelets, and HbA1C

For 24h uCa at Week 26, the percentage of subjects meeting each of the following criteria will be summarized based on (1) Safety Analysis Population, (2) Subgroup of subjects with 24-hour uCa excretion >250 mg/24h at baseline, and (3) Subgroup of subjects with 24-hour uCa excretion >300 mg/24h at baseline, respectively.

- With normal 24-hour uCa excretion (≤250 mg/24h)
- With normal 24-hour uCa excretion (≤250 mg/24h) or ≥50% reduction from baseline

Data listings for laboratory will be provided. Listings of abnormal labs and local lab results will be provided separately.

11.11.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, temperature, respiratory rate, heart rate and weight) and changes from baseline values at each visit will be presented by treatment group.

A listing of vital signs will be provided.

11.11.4. Electrocardiogram

ECG parameters (heart rate, QT interval, and QTcF interval) will be presented in a listing.

11.11.5. Local Tolerability Assessment

Local Tolerability is assessed based on presence of injection site reactions (ISRs).

At Visit 1, assessment of local tolerability including redness, itching and swelling is performed by trial staff at the time of the first blinded study drug injection and at least 15 minutes post-dose.

At Visit 10, the first dose of open-label TransCon PTH is administered on-site only for subjects still taking active vitamin D or subjects off active vitamin D and taking study drug dose ≥30 µg/day at the end of blinded treatment period. An assessment of local tolerability including redness, itching and swelling is performed by trial staff using the Local Tolerability Scale at the time of the TransCon PTH 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.

11.11.6. 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 2019), following recent regulatory guidance and white papers (Shankar 2014). Statistical analysis of anti-drug antibodies (ADAs) will include the following tabulated summaries of antibody frequencies and percentages:

- Incidence of pre-existing anti-PTH, anti-TransCon PTH, and anti-PEG antibodies (positive baseline)
- Incidence of treatment induced anti-PTH, anti-TransCon PTH, and anti-PEG antibodies (positive post-baseline) by positive types

Treatment induced ADA includes 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.

In addition, treatment induced anti-PTH, anti-TransCon PTH, and anti-PEG and their positive types and titer values will also be summarized by visit.

11.12. PHARMACOKINETIC ANALYSIS

The primary PK analysis of interest is the Free PTH [PTH (1-34) and PTH (1-33)] concentrations, which represents active PTH released from the pro-drug. Free PTH will be assessed in a minimum of approximately 23 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. Summaries of Free PTH, Free PTH (1-34), and Free PTH (1-33) plasma concentrations will be provided for PK population at scheduled visits. The plasma concentrations-time profiles of Free PTH, Free PTH (1-34), and Free PTH (1-33) will be plotted for PK population. The individual and summary plasma concentrations at scheduled timepoints will also be plotted for PK population.

11.13. EXPLORATORY ANALYSIS

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12. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

The following are changes compared to protocol v5.0 dated 17 DEC 2021. These changes will be included in protocol amendment v6.0.

• The primary endpoint definition for the Extension Period and analysis of this endpoint are added.

13. REFERENCES

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14. APPENDICES

Table 2: Schedule of Events – Blinded Treatment Period

Period	**Screening** ***Supplement Optimization***	**Blinded Treatment Period and Start of OLE**												
Visit	**Screening**[1]	**V1**	**LV1**	**LV2**	**V2**	**LV3**	**V3**[2]	**V4**[2]	**V5**[2]	**V6**	**V7**[2]	**V8**[2]	**V9**	**V10**[3]**/ET**[4]
Week	-6 to -2	0	0	1	2	3	4	6	8	10	12	16	20	26
Day	-42 to -14	1	3	8	15	22	29	43	57	71	85	113	141	183
Window			+1 day		+2 days			± 2 days			± 3 days			
Informed consent	X													
COAs[5]	X	X								X			X	X[6]
Demographics	X													
Height, weight measurements	X													
Vital sign measurements[7]	X	X[8]			X		X	X	X	X	X	X	X	X[9]
Medical history	X													
Prior & Concomitant medication	X	X			X		X	X	X	X	X	X	X	X
Physical examination	X	X									X			X
12-lead ECG[10]	X													
DXA[11]	X													X[12]
X-ray of non-dominant wrist and left hand[13]	X													
24-hour urine collection[14]	X[14]	X[14]									X[14]			X[14]
Urine collection for local lab assessments[15]	X	X												
Blood collection for local lab assessments[16]	X[17]		X	X	X	X	X	X	X	X				
Blood collection for central lab	X	X			X		X	X	X	X	X	X	X	X
Dietary calcium questionnaire[18]	X	X												X
Subject diary activation and training	X													

Period	**Screening** ***Supplement Optimization***	**Blinded Treatment Period and Start of OLE**												
Visit	**Screening**[1]	**V1**	**LV1**	**LV2**	**V2**	**LV3**	**V3**[2]	**V4**[2]	**V5**[2]	**V6**	**V7**[2]	**V8**[2]	**V9**	**V10**[3]**/ET**[4]
Week	-6 to -2	0	0	1	2	3	4	6	8	10	12	16	20	26
Day	-42 to -14	1	3	8	15	22	29	43	57	71	85	113	141	183
Window			+1 day		+2 days			± 2 days			± 3 days			
Subject diary review		X			X		X	X	X	X	X	X	X	X
HP-related therapy optimization[19]	X													
SoC titration[20]		X	X	X	X	X	X	X	X	X	X	X	X	X[20]
Treatment assignment	X[21]													X[22]
Study drug training		X												
Study drug dispensing		X			X		X	X	X	X	X	X	X	X
Study drug receipt & compliance review					X		X	X	X	X	X	X	X	X
Adverse event review[23]		X			X		X	X	X	X	X	X	X	X
On site study drug administration		X[24]												X[23]
Local tolerability assessment		X[26]												X[27]
CCI [redacted]		X			X					X				X
TransCon PTH/placebo titration[28]				X	X	X	X	X	X	X	X	X	X	X

[1] Following randomization, it is recommended to start Visit 1 within 2 weeks from the time of randomization.
[2] In selected countries, home/virtual visits can be performed instead of on-site visits at Visit 3, 4, 5, 7 and 8.
[3] Visit 10 marks the end of the Blinded Treatment Period. Subjects still taking active vitamin D, or subjects off active vitamin D and taking study drug ≥ 30 µg/day entering this visit will start open-label TransCon PTH at a dose of 18 µg/day, with the 1st dose taken in clinic on Visit 10. Subjects off active vitamin D and taking study drug < 30 µg/day will start TransCon PTH at the same dose of study drug taken at the end of the Blinded Treatment Period (Exception: in cases of out-of-range sCa level at Visit 10, adjust the TransCon PTH dose and/or calcium doses as per Figure 8 and Appendix 2 in protocol).
[4] Early Termination (ET) Visit for the Subjects who discontinue the trial prior to Visit 10. The structure and assessments of this ET visit should be as similar as possible to Visit 10.
[5] COAs: PRO measures must be completed by the subject without assistance and prior to conducting any clinical assessments or supplement dose adjustments. On visit 6, 9 and 10/ET, additional CCI [redacted] needs to be completed by the subject. The CGI-S should be completed by the investigator after all clinical assessments are completed.
[6] In selected English speaking countries/sites, approximately 2 weeks prior to Visit 10, subjects will be contacted to set up a one-hour phone interview to occur within 2 weeks after Visit 10 to discuss their experience in the trial. Additionally, in case of subject discontinuation before or at Visit 10, the phone interview will be scheduled to be completed within 2 weeks after the early termination visit. The phone interview will be conducted by an external vendor, and not by the site or the sponsor.

[7] Subject should rest for at least 5 minutes before vital sign measurements, including respiratory rate, temperature, orthostatic BP and heart rate. BP and heart rate are performed while the subject is sitting. The subject is then asked to stand up, within 2 minutes of doing so, BP and heart rate are measured again.
[8] Orthostatic BP and heart rate should also be performed 30 minutes after study drug administration.
[9] Orthostatic BP and heart rate should also be performed 30 minutes after study drug administration only for subjects still taking active vitamin D or subjects off active vitamin D and taking study drug ≥ 30 µg/day at the end of the Blinded Treatment Period.
[10] Standard ECG must include QT interval and Heart Rate.
[11] A historical DXA may be utilized if it was performed within 6 months prior to Screening and report includes required elements per protocol Section 11.7.
[12] A DXA is performed at or within one week prior to Visit 10.
[13] An X-ray of the non-dominant wrist and hand with evidence of epiphyseal closure is only required for subjects who are ≤ 25 years old as of Screening. A historical X-ray may be utilized.
[14] 24-hour urine collection is performed within 52 weeks prior to Screening or during the Screening Period. After the investigator has confirmed the subject is eligible to move into the Blinded Treatment Period, 24-hour urine collection is performed within one week prior to Visit 1. The subject should also perform this collection at home within one week prior to Visit 10 while the subject could perform this collection at home within one week (+/- one week) of Visit 7.
[15] Only for female subjects of childbearing potential.
[16] Local lab assessments may always be performed at investigator's discretion e.g. for symptoms or to guide SoC or TransCon PTH/placebo titration if necessary, at any visits after Visit 6 during Blinded Treatment Period, or at any point in time as needed.
[17] Multiple local laboratory assessments over the approximate 4 weeks of the Screening Period are expected in order to optimize both the albumin-adjusted or ionized sCa to the normal range, as well as normalize the sMg and vitamin D level. Repeat TSH may be performed during the Screening Period if the baseline measurement is out of the allowable range.
[18] Based on review of dietary calcium questionnaire, subjects will be counseled to maintain a stable dietary calcium and to avoid unnecessary/excessive dietary sodium intake throughout the trial.
[19] During Screening, HP-related therapies (calcitriol, alfacalcidol, calcium, magnesium, and vitamin D3) will be optimized to achieve the protocol-specified ranges for sCa, 25(OH) vitamin D, and sMg. See protocol Section 9.5.1.
[20] See protocol Section 9.5.2.1, Section 9.5.3.1 (for Visit 10) and Appendix 2.
[21] Randomization may occur only after Medical Monitor or designee confirmation of eligibility.
[22] See protocol Section 9.4.2. At Visit 10, subjects still taking active vitamin D or subjects off active vitamin D and taking study drug ≥ 30 µg/day will start TransCon PTH at a dose of 18 µg/day while subjects off active vitamin D and taking study drug < 30 µg/day will continue their TransCon PTH dose taken at the end of the Blinded Treatment Period (Exception: in cases of out-of-range sCa level at Visit 10, adjust the TransCon PTH dose as per protocol Appendix 2).
[23] Adverse event review includes questions about general well-being, changes to health or medications, hypo- or hypercalcemic symptoms, vasodilatory symptoms as AESI, emergency/urgent care visits or hospitalizations, and abnormal results from physical examination, examination of injection sites, and laboratory results, as applicable.
[24] On-site drug administration to include on-site observation for at least 30 minutes for local tolerability assessment and adverse reactions, including light headedness.
[25] On-site drug administration only for subjects still taking active vitamin D at Visit 10 or subjects off active vitamin D and taking study drug ≥ 30 µg/day entering Visit 10.
[26] Local tolerability assessment including redness, itching, swelling and pain assessment to be performed at Visit 1 at time of the first study drug injection and at least 15 minutes post dose.
[27] Local tolerability assessment including redness, itching, swelling and pain assessment to be performed at Visit 10 only for subjects still taking active vitamin D at Visit 10 or subjects off active vitamin D and taking study drug ≥ 30 µg/day entering Visit 10, at time of the study drug injection and at least 15 minutes post dose.
[28] See protocol Section 9.5.2.2, Section 9.5.3.2 and Appendix 2.

Table 3: Schedule of Events - Extension Period

Period	**Extension**														
Visit	**LV4**[1]	**LV5**[1]	**V11**	**LV6**[1]	**LV7**[1]	**LV8**[1]	**V12**	**V13**[2]	**V14**[2]	**V15**[2]	**V16**	**V17**[2]	**V18**	**V19 to V25**[2]	**V26 (EoT)/ET**[3]
Week	26	27	28	29	30	32	34	38	42	46	52	65	78	91 to 169[4]	182
Day	185	190	197	204	211	225	239	267	295	323	365	456	547	638 to 1184	1275
	2-3 days post-V10	7-8 days post-V10	14-16 days post-V10	21-23 days post-V10	28-30 days post-V10	±2 days			±3 days		±7 days				
COAs[5]							X				X		X	X[6]	X
Vital sign measurements[7]			X				X	X	X	X	X	X	X	X[8]	X
Concomitant medication review			X				X	X	X	X	X	X	X	X[9]	X
Physical examination								X			X		X	X[10]	X
Weekly diary dispensing								X							
Subject diary review			X				X	X	X	X	X	X	X		
Blood Collection for local lab assessment[11]	X	X	X	X	X	X	X	X	X						
Blood collection for central lab assessments			X		X		X	X		X	X	X	X	X[12]	X
24-hour urine collection											X[13]			X[13]	X[13]

Period	**Extension**														
Visit	**LV4**[1]	**LV5**[1]	**V11**	**LV6**[1]	**LV7**[1]	**LV8**[1]	**V12**	**V13**[2]	**V14**[2]	**V15**[2]	**V16**	**V17**[2]	**V18**	**V19 to V25**[2]	**V26 (EoT)/ET**[3]
Week	26	27	28	29	30	32	34	38	42	46	52	65	78	91 to 169[4]	182
Day	185	190	197	204	211	225	239	267	295	323	365	456	547	638 to 1184	1275
	2-3 days post-V10	7-8 days post-V10	14-16 days post-V10	21-23 days post-V10	28-30 days post-V10	±2 days			±3 days		±7 days				
DXA											X[14]			X[14]	X[14]
TransCon PTH dispensing			X				X	X	X	X	X	X	X	X	
TransCon PTH receipt & compliance review			X				X	X	X	X	X	X	X	X	X
Adverse event review[15]			X				X	X	X	X	X	X	X	X[9]	X
SoC titration[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TransCon PTH titration		X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] LV4-LV8 are performed for subjects who are still taking active vitamin D at Visit 10 or subjects off active vitamin D and taking TransCon PTH/placebo dose ≥30 µg/day entering Visit 10.
[2] In selected countries, home/virtual visits may be performed at Visits 13, 14, 15, 17, 19, 21, 23, and 25.
[3] Early Termination (ET) Visit for the subjects who discontinue the trial after Visit 10. The structure and assessments of the ET visit should be as similar as possible to Visit 26.
[4] Visit 19 to 25 are performed in Week 91, 104, 117, 130, 143, 156 and 169.
[5] COAs: PRO measures must be completed by the subject without assistance and prior to conducting any clinical assessments. The CGI-S should be completed by the investigator after all clinical assessments are completed.
[6] COAs will be completed at Visits 20, 22, 24.
[7] Subject should rest for at least 5 minutes before vital sign measurements, including respiratory rate, temperature, orthostatic BP and heart rate. BP and heart rate are performed while the subject is sitting. The subject is then asked to stand up, within 2 minutes of doing so, BP and heart rate are measured again.
[8] Vital sign measurements are performed at Visit 20, 22 and 24.

[9] Correspondence (e.g., telemedicine, phone call, email) with subject is required to perform concomitant medication review, including PRN doses of SoC, and adverse event review if visit is not performed on-site.
[10] Physical Examination is performed at Visit 20, 22 and 24.
[11] Local lab assessments may be performed at the clinic visits, or at any time at the investigator's discretion e.g., for symptoms or to guide SoC or TransCon PTH titration.
[12] Blood Collection for central lab assessments only at Visit 19, 20 and every other visit after.
[13] 24-hour urine collection is performed by the subject at home within one week (+/- one week) of Visit 16, 20, 24, and within one week prior to Visit 26.
[14] DXA is performed at or within one week (+/- one week) of Visit 16, 20, and at or within one week prior to Visit 26.
[15] Adverse event review includes a question about general well-being, changes to health or medications, hypo- or hypercalcemic symptoms, vasodilatory symptoms as AESI, emergency/urgent care visits or hospitalizations, and abnormal results from physical examination, examination of injection sites, and laboratory results, as applicable. Two weeks (+ 7 days) after last study drug administration, a telephone contact will take place to evaluate AEs that were ongoing at the final study visit and to evaluate the subject for any further AEs during the 2 weeks since last study drug administration.
[16] See protocol Section 9.5.3.1 and Appendix 2.

Table 4: Schedule of Laboratory Assessments – Blinded Treatment Period

Visit	**Screening**		**1**		**LV1-LV2**	**2**		**LV3**	**3**		**4**		**5**		**6**		**7[1]**	**8-10[1]**
Week	***-6 to -2***		***0***		***0-1***	***2***		***3***	***4***		***6***		***8***		***10***		***12***	***16-26***
Laboratory Type	Local	Central	Local	Central	Local ONLY	Local	Central	Local ONLY	Local	Central	Local	Central	Local	Central	Local	Central	Central	Central
Calcium & Albumin or Ionized Calcium[1]	X	Included in Chem. Panel		Included in Chem. Panel	X	X	Included in Chem. Panel	X	X	Included in Chem. Panel	X	Included in Chem. Panel	X	Included in Chem. Panel	X	Included in Chem. Panel	Included in Chem. Panel	Included in Chem. Panel
25(OH) Vitamin D	X	X		X						X							X	X[2]
$1,25(OH)_2$ Vitamin D		X		X						X							X	X[2]
Chemistry Panel[3]		X		X			X			X		X		X		X	X	X
Hematology Panel[4]		X		X			X			X		X		X		X	X	X
Free PTH[5]				X						X				X			X	X[5]
Antibodies against PTH, TransCon PTH & PEG[6]				X						X				X			X	X[6]
Bone Turnover markers		X		X													X	X[7]
Magnesium	X																	
TSH		X		X						X							X	X[2]
PTH(1-84)		X																
Serum FSH[8]		X																
Urine hCG[9]	X		X[10]															

Visit	**Screening**		**1**		**LV1-LV2**	**2**		**LV3**	**3**		**4**		**5**		**6**		**7[1]**	**8-10[1]**
Week	***-6 to -2***		***0***		***0-1***	***2***		***3***	***4***		***6***		***8***		***10***		***12***	***16-26***
Laboratory Type	Local	Central	Local	Central	Local ONLY	Local	Central	Local ONLY	Local	Central	Local	Central	Local	Central	Local	Central	Central	Central
Serum hCG[9]				X						X				X			X	X
24-hour Urine Panel[11]		X[12]		X[13]													X[12]	X[12]

[1] Local lab assessments may be performed at the clinic visits, or at any time at the investigator's discretion e.g., for symptoms or to guide SoC or study drug titration.
[2] 25(OH) vitamin D, 1,25$(OH)_2$ vitamin D and TSH are assessed at Visit 10.
[3] Including but not limited to: 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: also Glucose, Cholesterol and HbA1C [Documented HbA1C result drawn within 12 weeks prior to Screening is acceptable.])
[4] Including but not limited to: Hemoglobin, Hematocrit, RBC, MCH, MCHC, RBC morphology & MCV, WBC, Neutrophils, Lymphocytes, Monocytes Eosinophils, Basophils, Platelets.
[5] Only for subjects at selected sites, where Free PTH assessment will be performed. Free PTH(1-34) and Free PTH(1-33) are assessed at Visit 1, 3, 5, 7 and 10.
[6] Anti-PTH, anti-TransCon PTH and anti-PEG antibodies are assessed at Visit 1, 3, 5, 7 and 10.
[7] Bone turnover markers are assessed at Visit 10.
[8] Follicle stimulating hormone (FSH) is assessed only for female subjects ≥ 45 years old as of Screening, without menses for at least 6 months prior to Screening without an alternative medical cause (e.g., surgically sterile) to determine if they are postmenopausal (i.e., do not require pregnancy testing).
[9] Human chorionic gonadotropin (hCG) (pregnancy test) is assessed only for female subjects of childbearing potential. Female subjects are considered NOT to be of childbearing potential if they are surgically sterile or postmenopausal, defined as age >50 with absent menses for ≥12 months, or age ≥45 years old as of Screening, without menses for at least 6 months prior to Screening and FSH >30 mIU/mL).
[10] Local urine hCG (pregnancy test) results must confirm subject is not pregnant prior to first study drug dose administration at Visit 1.
[11] 24-hour urine panel includes but not limited to: Creatinine, Calcium, Citrate, Uric Acid, Oxalate, Phosphate, Sodium, Potassium, Magnesium, pH and Urine volume, except for 24-hour urine collection within 52 weeks of Screening or during Screening for confirmation of eligibility which only includes Calcium, Creatinine, and urine volume.
[12] 24-hour urine collection is performed by the subject at home within 52 weeks prior to Screening or during the Screening Period, within one week (+/- one week) of Visit 7 and within one week prior to Visit 10.
[13] After the investigator has confirmed the subject is eligible to move into the Blinded Treatment Period, 24-hour urine collection is performed within one week prior to Visit 1.

Table 5: Schedule of Laboratory Assessments – Extension Period

Period		**Extension Period**											
Visit	**LV4-LV5[1]**	**11**		**LV6[1]**	**LV7[1]**		**LV8[1]**	**12**		**13**		**14**	**15[2]**	**16+[2]**
Week	26-27	28		29	30		32	34		38		42	46	52+
Laboratory Type	Local ONLY	Local	Central	Local ONLY	Local	Central	Local ONLY	Local	Central	Local	Central	Local ONLY	Central	Central
Calcium & Albumin or Ionized Calcium[2]	X	X	Included in Chem Panel	X	X	Included in Chem Panel	X	X		X	Included in Chem Panel	X	Included in Chem Panel	Included in Chem Panel
25(OH) Vitamin D						X					X		X	X[3]
$1,25(OH)_2$ Vitamin D						X					X		X	X[3]
TSH						X					X		X	X[3]
Chemistry Panel[3]			X			X					X		X	X[3]
Hematology Panel[3]			X			X					X		X	X[3]
Antibodies against PTH, TransCon PTH & PEG[4]						X			X		X			X[4]
Bone turnover markers											X			X[5]
Serum hCG						X					X		X	X[6]
24-hour Urine Panel														X[7]

[1] LV4-LV8 are performed only for subjects still taking active vitamin D at Visit 10 or for subjects off active vitamin D and taking TransCon PTH/placebo dose ≥ 30 µg/day at the end of the Blinded Treatment Period.
[2] Local lab assessment may be performed at clinic visits of V15+ or at any time at the investigator's discretion e.g., for symptoms or to guide SoC or TransCon PTH titration.
[3] 25(OH) vitamin D, $1,25(OH)_2$ vitamin D, TSH, chemistry panel, and hematology panel are assessed at Visit 16 and then every other visit.
[4] Anti-PTH, anti-TransCon PTH and anti- PEG antibodies are assessed at LV7, 12, 13, 16, 17, 18, 19, 20 and every other visit after.

[5] Bone turnover markers are assessed at Visit 16, and every other visit after.
[6] Serum hCG (pregnancy test) is assessed at Visit 16, 17, 18, 19, 20 and every other visit after.
[7] 24-hour urine collection is performed by the subject at home within one week (+/- one week) of Visit 16, 20, 24, and within one week prior to Visit 26.

15. SAP AMENDMENT LIST OF CHANGES

AMENDMENT 1 SUMMARY

The major changes to the analyses specified in the original SAP version 1 (dated 21 Jul 2021) are:

Section(s)	Change(s)
7.1.1, 11.10.2.1	Update the primary endpoint definition
7.1.2, 11.10.3, 11.10.4	Update the HPES and SF-36 score parts in key secondary and plain secondary endpoints
10.2.1	Add a subsection to specify the multiple imputation method for missing key secondary endpoints data
11.10.1, 11.10.3, 11.10.4, 11.13	For continuous endpoints analysis, change analysis model from ANCOVA model to ANCOVA model with unequal variance
11.10.2.1	Add the report of common odds ratio for primary endpoint as part of primary analysis
11.10.2.2	Update sensitivity analyses 2 and 5
11.10.3	Update analyses for key secondary endpoints to incorporate missing data multiple imputation
11.10.3.1	Update multiplicity adjustment approach based on the updated key secondary endpoints

AMENDMENT 2 SUMMARY

The changes to the analyses specified in the original SAP version 2 (dated 20 Dec 2021) are:

Section(s)	Change(s)

7.1.1	Add definition for the Extension Period primary endpoint
7.1.2.1	Add definition for the Extension Period key secondary endpoints
11.10.3	Add a new section to describe the Extension Period primary endpoint analysis and its sensitivity analyses
11.10.4	Add the analyses Extension Period key secondary endpoints

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