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: Protocol Amendment 3: 10 March 2021

CLINICAL STUDY PROTOCOL
AMENDMENT 3

PRODUCT NAME:	TransCon PTH
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EUDRACT NUMBER:	2018-004815-33
PHASE:	2
PROTOCOL 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
AMENDMENT 3 DATE:	10 March 2021
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AMENDMENT 3 SUMMARY

Section(s)	Change(s)	Rationale
Title Page	[redacted]	Administrative change
Section 9 Treatments Section 10.1.4 Extension Period (Week 4-214)	Changed maximum dosing to 60 µg/day in pen presentation	Updated to allow a dose range of 6-60 µg/day
Section 9.6.1 Required Stopping	Deleted inappropriate criteria for required stopping	Clarification
Section 9.6.2 Possible Stopping or Change to Administration	Revised text to change instructions for investigator on possible stopping or change to administration of study drug	Clarification of stopping/treatment interruptions criteria
Section 12 Adverse Event Assessment and Reporting	Replaced with new standard text and added severe hypo and hypercalcemia as AESI	The Adverse Event Assessment and reporting Section incl. outcome assessment were updated to for alignment across Ascendis Pharma clinical trial
Section 13 Safety Monitoring	Replaced with new standard text	Safety monitoring was updated to for alignment across Ascendis Pharma clinical trial
Appendix 9 PD-PK sub-set study	Addition of Appendix 9	Inclusion of sub-set study to ensure collection of 24h sCa and Free PTH at steady-state

AMENDMENT 2 SUMMARY

This amendment to the protocol is being issued to extend the open-label Extension Period from 1 year to 4 years following analysis of the 4-week Blinded Treatment Period data. This extension allows subjects continued access to the investigational drug while establishing the long-term safety and efficacy profile of the investigational drug.

The results of the 4-week, fixed-dose Blinded Treatment Period showed 50% of the subjects on TransCon PTH versus 15% of the subjects on placebo (p =0.0305) achieved the primary endpoint. Additionally, TransCon PTH was shown to be well-tolerated. There were no severe or serious adverse events thus far in the PaTH Forward trial and no discontinuations from the study treatment or trial during the Blinded Treatment Period.

Section(s)	Change(s)	Rationale
Title Page	[redacted]	Administrative change
Title Page	[redacted]	Administrative change
1.1 Approval Signature	[redacted]	Administrative change
Synopsis: Objectives: Exploratory Synopsis: Endpoints: Exploratory Endpoints 14.2.3. Exploratory Endpoints	Change from "Patient Reported Outcomes" and "PROs" to "Clinical Outcomes Assessments" and "COAs"	Update to reflect that the exploratory objective will assess the treatment effect of daily TransCon PTH on both patient-reported outcome and clinician-reported outcome measures
Synopsis: Trial Population Synopsis: Trial Design 8. Subject Population Appendix 1. SOC Dose Adjustment	Change "alphacalcidol" to "alfacalcidol"	Consistency
Synopsis: Trial Design Synopsis: Blinding Synopsis: Trial and Treatment Duration 7.1 Overall Trial Design and Plan	Change "58 weeks" of trial duration to "214 weeks" Change "54 weeks" of an open-label Extension Period to "210 weeks" Change "40 weeks" of stable dosing on TransCon PTH during the Extension Period to "196 weeks"	Addition of 3 years (156 weeks) to the Extension Period of the trial to include: • Laboratory assessments of sCa and phosphate every 3 months and in-person assessments every 6 months

Section(s)	Change(s)	Rationale
9.5.3. Extension Period (Visits 3-21; Weeks 4-214) 10.1. Trial Duration 10.1.1 Trial Periods and Visits 10.1.4. Extension Period (Week 4-214) 10.1.4.5. Laboratory Visits 7-12 (LV7-LV12; Weeks 71-201; Day 497-201 ±14 days) procedures 10.1.4.6. Visits 16-21 (Weeks 84-214; Day 588-1498 ±14 days) procedures 11.12.1.8. Visit 9-21 (V9-21) Laboratory Assessments Appendix 4. Schedule of Events Appendix 5. Schedule of Laboratory Assessments	Change Extension Period from Visits 3-15 or Visit 3+ to Visit 3-21 Change Extension Period from Weeks 4-58 or Weeks 4+ to Weeks 4-214 Update to the Study Design image to capture change in duration of Extension Period Addition of the following study visits: Visit 15A (Week 66, Day 462, ±7 days) Laboratory Visit 7 (Week 71, Day 497, ±14 days) Visit 15B (Week 74, Day 518, ±7 days) Visit 16 (Week 84, Day 588, ±14 days) Visit 16A (Week 92, Day 644, ±7 days) Laboratory Visit 8 (Week 97, Day 679, ±14 days) Visit 16B (Week 100, Day 700, ±7 days) Visit 17 (Week 110, Day 770, ±14 days) Visit 17A (Week 118, Day 826, ±7 days) Laboratory Visit 9 (Week 123, Day 861, ±14 days) Visit 17B (Week 126, Day 882, ±7 days) Visit 18 (Week 136, Day 952, ±14 days) Visit 18A (Week 144, Day 1008, ±7 days) Laboratory Visit 10 (Week 149, Day 1043, ±14 days) Visit 18B (Week 152, Day 1064, ±7 days) Visit 19 (Week 162, Day 1134, ±14 days) Visit 19A (Week 170, Day 1190, ±7 days) Laboratory Visit 11 (Week 175, Day 1225, ±14 days)	to align with current standard of care practices for hypoparathyroid patient • Interim dispensation of 8- or 10-week supply of study drug between in-person study visits (Visits A and B) to align with estimated maximum refrigerated storage capacity at subjects' homes and minimize risk of misuse due to inappropriate storage, confusion between kits, or kit expiry

Section(s)	Change(s)	Rationale
	Visit 19B (Week 178, Day 1246, ±7 days) Visit 20 (Week 188, Day 1407, ±14 days) Visit 20A (Week 196, Day 1372, ±7 days) Laboratory Visit 12 (Week 201, Day 1316, ±14 days) Visit 20B (Week 204, Day 1428, ±7 days) Visit 21 (Week 214, Day 1498, ±14 days) Addition of the following protocol sections: 10.1.4.5. Laboratory Visits 7-12 (LV7-LV12; Weeks 71-201; Day 497-201 ±14 days) procedures 10.1.4.6. Visits 16-21 (Weeks 84-214; Day 588-1498 ±14 days) procedures 11.12.1.9. Laboratory Visits 7-12 (LV7-LV12) Laboratory Assessments	
Synopsis: Trial Design Synopsis: Investigational Product 9.2. Treatment Administered 9.3. Selection of Trial Doses 9.5.3.1. Study Drug Dose Adjustments during Extension Period 10.1.4. Extension Period (Week 4-214)	"Dose range…will be 6-30 µg/day" to "Dose range…is expected to be 6-30 µg/day" Change from "a dose range of 6-30 µg/day" to "an expected dose range of 6-30 µg/day" Change from "an optimal dose of 6-30 µg PTH/day" to "an expected optimal dose of 6-30 µg PTH/day" "with the availability of a larger dose range from 6 to 30 µg/day in 3 pen presentations…" to "with the availability of 3 pen presentations …, allowing for an expanded dose range."	Clarification that the dose range during the Extension Period is expected to be 6-30mcg/day, but that dosing <6 mcg/day or >30 mcg/day is allowed
Synopsis: Trial Design 9.5.3.1. Study Drug Dose Adjustments during Extension Period	Addition of "However, dose adjustments should continue as needed based on sCa results and following Appendix 2 and Appendix 3" and "dose adjustments should continue as needed based on sCa results and following Appendix 2 and Appendix 3"	Clarification that adjustments to TransCon PTH and SOC doses is allowed per protocol throughout the Extension Period and such adjustments should be based on Appendix 2 and Appendix 3

Section(s)	Change(s)	Rationale
9.5.3.2. SOC Dose Adjustments during Extension Period, 10.1.4. Extension Period (Week 4-214) 10.1.4.3. Visits 9-11 (Weeks 18-26; Day 126-182 ±3 days) procedures 10.1.4.4. Visits 12-15 (Weeks 34-58; Day 238-406 ±7 days) procedures 10.1.4.5. Laboratory Visits 7-12 (LV7-LV12; Weeks 71-201; Day 497-201 ±14 days) procedures 10.1.4.6. Visits 16-21 (Weeks 84-214; Day 588-1498 ±14 days) procedures Appendix 4. Schedule of Events	Addition of "Titration of TransCon PTH and/or SOC dose adjustment, if needed (See Section 9.5.3)" to Visits 9+ procedures	
Synopsis: Trial Design 9.5.3.1. Study Drug Dose Adjustments during Extension Period 10.1.4. Extension Period (Week 4-214)	Change "Due to the extended length of time between visits after Visit 9 (4-8 weeks), the TransCon PTH dose may be adjusted to control persistent hypo- or hypercalcemia between clinic visits with prior approval of the Medical Monitor/Medical Expert" to "Due to the extended length of time between visits after Visit 9, the TransCon PTH dose may be adjusted to control persistent hypo- or hypercalcemia between clinic visits" Change "Due to the extended length of time between visits (4 and 8 weeks) after Visit 9, the TransCon PTH dose may be adjusted between clinic visits with the approval of the Medical Monitor/Medical Expert" to "Due to the extended length of time between visit after Visit 9, the TransCon PTH dose may be adjusted between clinic visits"	With the additional visits added to the Extension Period, visits will occur less frequently than every 4-8 weeks. Since approval from the Medical Monitor/Medical Expert is not needed prior to adjusting TransCon PTH doses at visits, it is unnecessary requirement to have for dose adjustments between Extension Period visits as sCa level from local laboratories and symptoms will be guiding such adjustments in either situation.
Synopsis: Trial and Treatment Duration	Change from "stable dosing" to "individualized dosing"	Clarification that adjustments to TransCon PTH and SOC doses

Section(s)	Change(s)	Rationale
7.1 Overall Trial Design and Plan Section 10.1. Trial Duration		is allowed per protocol throughout the Extension Period, though generally subjects are expected to remain stable on their individualized dosing
Synopsis: Endpoints: Secondary Efficacy Endpoints: Other Secondary Efficacy Endpoints 14.2.1.2.2. Other Secondary Efficacy Endpoints	Addition of "For the analysis of these endpoints in the Extension Period, the 24-hour urine calcium excretion will be used."	Clarification of analysis to be performed during the Extension Period
Synopsis: Endpoints: Secondary Efficacy Endpoints: Other Secondary Efficacy Endpoints 14.2.1.2.2. Other Secondary Efficacy Endpoints	Addition of "At predefined timepoints over the Extension Period: 24-hour urine calcium excretion"	Clarification of analysis to be performed during the Extension Period
Synopsis: Endpoints: Safety & Tolerability Endpoints 14.2.2. Safety & Tolerability Endpoints	Change from "Physical examinations (AE-directed), including vital signs" to "Physical examinations, including vital signs"	Update to include physical examinations performed at Visits 16-21 in addition to those performed in evaluation of potential AEs
Synopsis: Endpoints: Exploratory Endpoints 14.2.3. Exploratory Endpoints	Addition of annual assessments (weeks 110, 162, and 214) of: • BMD and TBS by DXA • Bone turnover markers (serum P1NP and CTx) • Clinical Outcomes Assessments (COAs) Addition of every 6-month assessments (weeks 84, 110, 136, 162, 188, and 214) of: • Albumin-adjusted sCa, magnesium, phosphate, and sCa x sP product • 24-hour urine calcium excretion	Addition of timepoints for exploratory endpoint analyses throughout the Extension Period with the addition of the 3 years to the Extension Period
Synopsis: Endpoints: Exploratory Endpoints	Change from "Albumin-adjusted or ionized sCa" to "Albumin-adjusted sCa"	Correction that analysis of this endpoint will be performed with albumin-adjusted sCa only

Section(s)	Change(s)	Rationale
14.2.3. Exploratory Endpoints		
4. List of Abbreviations	Addition of "COA" for "clinical outcomes assessment"	Administrative change
9.1.2. Accountability, Storage, and Dispensing	Addition of "Study drug may be shipped from site or depot to subjects using an Ascendis-approved courier service. In such cases, accountability for study drug remains the responsibility of the principal investigator until subject has confirmed receipt of study drug. Documentation of study drug shipments must be maintained by the site and include, at minimum, the following: date of shipment from site, kit numbers shipped, date of receipt by subject, and temperature monitoring during shipment."	Clarification that shipments of study drug to subjects is acceptable per protocol
9.6. Study Drug Stopping or Change to Administration	Change "Stopping" to "Study Drug Stopping" Change "Dose Reductions" to "or Change to Administration"	Clarification of topics covered in the section
9.6.1. Required Stopping	Removal of the following from "Required Stopping" section: "If during the Extension Period, albumin-adjusted sCa level remains >ULN while subject is taking TransCon PTH 6 µg/day (the minimum allowable TransCon dose) and the subject has discontinued active vitamin D and calcium supplements and notes symptoms of hypercalcemia, after discussion with the Sponsor Medical Monitor/Medical Expert, study drug should be permanently discontinued and SOC treatment resumed."	Correction that subjects are not required to stop taking the study drug if they need <6 µg/day of TransCon PTH
9.6.2. Possible Stopping or Change to Administration	Change "Possible Stopping/Dose Reduction" to "Possible Stopping or Change to Administration"	Clarification of topics covered in the section
9.6.2. Possible Stopping or Change to Administration	Change of "The investigator may stop or reduce the dose of study drug at any time during the trial" to "The	Clarification that reductions are not allowed during Blinded Period

Section(s)	Change(s)	Rationale
	investigator may stop study drug at any time during the trial"	
9.6.2. Possible Stopping or Change to Administration	Change "If during the Extension Period sCa level remains <LLN while subject is taking TransCon PTH 30 µg/day (the maximum allowable dose), and the subject notes symptoms of hypocalcemia…active vitamin D and/or calcium supplements may be resumed" to "If during the Extension Period sCa level remains <LLN while subject is taking TransCon PTH 30 µg/day the TransCon PTH dose may be increased."	Clarification that while 30mcg/day is the maximum available dose per injection, >30 mcg/day dosing is allowed Clarification that increase in TransCon PTH is the expected action if sCa level remains <LLN rather than resuming SOC
9.6.2. Possible Stopping or Change to Administration	Addition of "If during the Extension Period, albumin-adjusted or ionized sCa level remains >ULN while subject is taking TransCon PTH 6 µg/day and has discontinued active vitamin D and calcium supplements, after discussion with the Medical Monitor/Medical Expert, the TransCon PTH dose may be decreased."	Clarification that while 6mcg/day in the minimum available dose per injection, <6 mcg/day dosing is allowed
10.1.2. Screening Period (Week -4 to -1, Day 28 to -7)	Change "Rescreened subjects should keep the same Subject Number as they had during their initial screening" to "Rescreened subjects should receive a new Subject Number"	Alignment with logistical need to provide new Subject Numbers for rescreened subjects
10.1.2. Screening Period (Week -4 to -1, Day -28 to -7) 10.1.3.1 Visit 1 (Week 0, Day 1) procedures 10.1.3.4 Visit 3 (Week 4, Day 28 ±2 days) procedures 10.4.1.2 Visits 4-8 (Weeks 6-14; Days 42, 56, 70, 84, 98 ±2 days) procedures 10.4.1.3 Visits 9-11 (Weeks 18-26; Day 126-182 ±3 days) procedures	Change from "PRO validation battery" to "HPES validation battery"	Update to reflect that validation battery includes a clinician-reported outcome measure and not only patient-reported outcome measures

Section(s)	Change(s)	Rationale
10.4.1.4 Visits 12-15 (Weeks 34-58; Day 238-406 ±7 days) procedures 10.4.1.6 Visits 16-21 (Weeks 84-214; Day 588-1498 ±14 days) procedures		
10.1.4.4. Visits 12-15 (Weeks 34-58; Day 238-406 ±7 days) procedures	Change "24-hour urine collection (only the week prior to Visit 15)" to "24-hour urine collection (only within a week of Visit 15)" Change "DXA and TBS (only the week prior to Visit 15)" to "DXA and TBS (only within a week of Visit 15)"	As Visit 15 is no longer the final study visit, 24-hour urine collection and DXA can occur within a week of the visit rather than only the week prior to the visit
11.7. Hypoparathyroidism Patient Experience Scale Validation Battery	Change from "Patient-Reported Outcome Measures" to "Hypoparathyroidism Patient Experience Scale Validation Battery"	Update to reflect that validation battery includes a clinician-reported outcome measure and not only patient-reported outcome measures
11.7. Hypoparathyroidism Patient Experience Scale Validation Battery	Change "The Hypoparathyroid Experience Scale" to "The Hypoparathyroidism Patient Experience Scale"	Update to reflect finalized title of the patient-reported outcome measure
11.7. Hypoparathyroidism Patient Experience Scale Validation Battery	Change from "The data collected in this trial will be combined with similar data collected via a web-study and a clinic-based study" to "The data collected in this trial will be combined with similar data collected via a web-study" Change from "A separate Statistical Analysis Plan based on the data collected from all three studies will be prepared" to "A separate Psychometric Analysis Plan based on the data collected from the two studies will be prepared" Change from "Data from the validation battery will be used to assess the measurement properties of the HPES" to "Data from the validation battery, and a subset thereof at various time	Update to reflect finalized HPES validation study

Section(s)	Change(s)	Rationale
	points, will be used to assess the measurement properties of the HPES"	
11.7. Hypoparathyroidism Patient Experience Scale Validation Battery	Change from "The Validation Battery consists of the HPES and other questionnaires" to "The Validation Battery consists of the following Clinical Outcome Assessments (COAs): the HPES, other PROs, and a clinician-reported outcome measure	Update to reflect that validation battery includes a clinician-reported outcome measure and not only patient-reported outcome measures
11.7. Hypoparathyroidism Patient Experience Scale Validation Battery	Addition of "In addition, one of the PROs will also be used for resource utilization evaluation."	Clarification that one of the PROs will be used for resource utilization evaluation in addition to HPES validation
11.7. Hypoparathyroidism Patient Experience Scale Validation Battery	Change from "A subset of the Validation Battery PROs will also be completed later in the trial for exploratory purposes" to "The Validation Battery, or a subset, will also be completed later in the trial for exploratory purposes"	Removal of "PRO" to reflect that validation battery includes a clinician-reported outcome measure and not only patient-reported outcome measures Clarification that the complete Validation Battery or a subset will be used in Exploratory Endpoint analyses
11.12.1.4. Visit 2 (V2) Laboratory Assessments 11.12.1.5. Visit 3 (V3) Laboratory Assessments 11.12.1.7. Visit 4-8 (V4-8) Laboratory Assessments 11.12.1.8. Visit 9-21 (V9-21) Laboratory Assessments	Change from "performed centrally on blood collected" to "performed centrally on blood and urine collected"	Correction to include urine collection to perform urine laboratory assessments listed
11.12.1.8. Visit 9-21 (V9-21) Laboratory Assessments	Change "Visit 9-15 (V9-15)" to "Visit 9-21 (V9-V21)" Change "Urine calcium and creatinine (only at Visits 9, 11, and 15)" to "Urine calcium and creatinine (only at Visits 9, 11, and 16-21) Change "Bone turnover markers (only at Visits 11, and 15)" to "Bone turnover	Addition of timepoints for laboratory assessments throughout the Extension Period with the addition of the 3 years to the Extension Period

Section(s)	Change(s)	Rationale
	markers (only at Visits 11, 15, 17, 19, and 21)	
11.12.1.8. Visit 9-21 (V9-21) Laboratory Assessments	Change from "The following laboratory assessments will be performed locally at Visits 9-15" to "The following laboratory assessments will be performed locally on urine collected at Visits 10, 12, and 14" Removal of "(only at Visits 10, 12 and 14)" for urine hCG	Readability
11.12.1.8. Visit 9-21 (V9-21) Laboratory Assessments	Change from "at Visits 9 and all subsequent visits" to "at Visits 9, 11, 13, 15, and 16-21" Removal of "(only at Visit 9 and every other visit after Visit 9)" for 25(OH) Vitamin D, 1,25(OH)2 vitamin D, Total PTH and mPEG, Antibodies against PTH and PEG, Chemistry panel, Hematology panel, and serum hCG	Readability
11.12.1.8. Visit 9-21 (V9-21) Laboratory Assessments	Change "24-hour urine collection will be performed…within a week of Visit 11 and within the week prior to Visit" to "24-hour urine collection will be performed…within a week of Visits 11, 15, 16-20, and within the week prior to Visit 21"	Addition of timepoints for 24-hour urine assessments throughout the Extension Period with the addition of the 3 years to the Extension Period As Visit 15 is no longer the final study visit, 24-hour urine collection can occur within a week of the visit rather than only the week prior to the visit
12.1.1. Definition	Change from "An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product" to "An AE is defined as any untoward medical occurrence in a clinical investigation subject who has been administered a pharmaceutical product"	Readability
12.2.2. Reporting of SAEs and/or SUSARs	[redacted]	Administrative change

Section(s)	Change(s)	Rationale
14.2.3. Exploratory Endpoints	Change from "14.2.3. Exploratory Endpoints:" to "14.2.3. Exploratory Endpoints"	Consistency
Appendix 2. TransCon PTH Titration for Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	Change from "TransCon PTH Dose Adjustment" to "Dose Adjustment"	Clarification as both TransCon PTH and SOC dose adjustments are indicated within the table
Appendix 2. TransCon PTH Titration for Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	Change from "Increase TransCon PTH by 3 µg (up to max of 30 µg/day)" to "Increase TransCon PTH by 3 µg" when sCa is <LLN with or without symptoms	Clarification that while 30mcg/day is the maximum available dose per injection, >30 mcg/day dosing is allowed
Appendix 2. TransCon PTH Titration for Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	Addition of SOC and TransCon PTH dose titration guidance for sCa WNL without symptoms, WNL with hypocalcemic symptoms, and WNL with hypercalcemic symptoms	Because the trial is assessing the potential for TransCon PTH to be a hormone replacement therapy, the goal is for subjects to achieve independence from standing doses of calcitriol and alfacalcidol, and to progressively reduce calcium supplements to ≤500 mg/day (a dose considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism). Thus, the guidance is updated to further adjust the TransCon PTH and SOC doses when sCa is WNL and subject remains on SOC.

Section(s)	Change(s)	Rationale
Appendix 2. TransCon PTH Titration for Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	Additional guidance to SOC and TransCon PTH dose titration for sCa <LLN and >ULN	Update to provide more detailed instructions to safely and adequately adjust the TransCon PTH and SOC doses when sCa is <LLN and >ULN
Appendix 2. TransCon PTH Titration for Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	Removal of "Do not adjust TransCon PTH more than once every 2 weeks"	Clarification that, for subject safety, adjustments to TransCon PTH may be required more often than every 2 weeks in order to alleviate hypercalcemic symptoms
Appendix 2. TransCon PTH Titration for Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	Addition of "If albumin-adjusted sCa is far below the normal range [≤7.3 mg/dL (1.82 mmol/L)] or far above the normal range [≥11.6 mg/dL (2.89 mmol/L)], additional adjustments to active vitamin D, calcium, or TransCon PTH may occur for the safety of the subject after discussion with the Medical Monitor"	Clarification that, for subject safety, further adjustments to TransCon PTH and/or SOC are acceptable if sCa levels are farther out of range than is expected
Appendix 2. TransCon PTH Titration for Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	Addition of "If ionized sCa is far below the normal range (≤1.03 mmol/L) or far above the normal range (≥1.45 mmol/L), additional adjustments to active vitamin D, calcium, or TransCon PTH may occur for the safety of the subject after discussion with the Medical Monitor"	Clarification that, for subject safety, further adjustments to TransCon PTH and/or SOC are acceptable if sCa levels are farther out of range than is expected
Appendix 2. TransCon PTH Titration for	Replacing the following from throughout the appendices:	Consistency in laboratory follow-up for any time SOC or

Section(s)	Change(s)	Rationale
Subjects Taking Daily Active Vitamin D (Starting at Visit 4) Appendix 3. TransCon PTH Titration for Subjects Not Taking Daily Active Vitamin D (Starting at Visit 3)	"performing an ULV approximately 9-11 days after dose adjustment" "performing an ULV approximately 3 days after every dose adjustment if symptoms persist, or 9-11 days after dose adjustment if symptoms resolved" With the following at the bottom of the appendices: • "If a TransCon PTH dose(s) is skipped, perform local laboratory testing of albumin-adjusted or ionized sCa 9-31 days after restarting TransCon PTH. These local laboratory assessments may occur at the next scheduled visit if one occurs within the 9-31 day window, otherwise an ULV should be performed. • If an adjustment(s) is made to active vitamin D, calcium, or TransCon PTH dose(s) without a TransCon PTH dose(s) skipped, perform local laboratory testing of albumin-adjusted or ionized sCa 9-31 days after dose adjustment. These local laboratory assessments may occur at the next scheduled visit if one occurs within the 9-31 day window, otherwise an ULV should be performed. • If symptoms persist despite an adjustment(s) made to active vitamin D, calcium, or TransCon PTH dose(s), perform local laboratory testing of albumin-adjusted or ionized sCa 2-3 days after restarting of TransCon PTH or dose adjustment. (Because symptoms persist, please do NOT wait 9-31 days.)"	TransCon PTH dose adjustments are performed Extend laboratory follow-up window from 9-11 days to 9-31 days, allowing investigator to determine appropriate follow-up for a given subject. Increasing the window also allows appropriate follow-up to occur at the next study visit rather than requiring an additional laboratory visit. The extension of the window is not considered a safety concern as the protocol requires additional ULVs for persistent hypo- or hypercalcemic symptoms.
Appendix 4. Schedule of Events	Split of Extension Period schedule into two separate tables	Readability
Appendix 4. Schedule of Events	Change in table header for Extension Period from "Titration: Study Drug Titration with SOC Optimization" and	Clarification that adjustments to TransCon PTH and SOC doses is allowed per protocol

Section(s)	Change(s)	Rationale
	"Follow-Up Study Drug & SOC Stable" to "Individualized Dosing"	throughout the Extension Period, though generally subjects are expected to remain stable on their individualized dosing
Appendix 4. Schedule of Events	Removal of rows for PRO validation battery, 24-hour urine collection, and local DXA from first section of the Extension Period table Adjustment of footnote numbering	Due to splitting of Extension Period schedule into two separate tables, these procedures do not occur during the timeframe that falls within the first section of the Extension Period table Footnotes associated with removed procedure rows required renumbering of footnotes within the first section of the Extension Period table
Appendix 4. Schedule of Events	Addition of "TransCon PTH dispensing" at Visit 15	As Visit 15 is no longer the final study visit, subjects must be dispensed study drug at this visit
Appendix 4. Schedule of Events	Addition of rows for procedures associated with Laboratory Visit 7 through Visit 21 to second section of the Extension Period table Adjustment of footnote numbering	Due to addition of study visits to the Extension Period of the trial, these procedures occur during the timeframe that falls within the second section of the Extension Period table Footnotes associated with added procedure rows required renumbering of footnotes within the second section of the Extension Period table
Appendix 5. Schedule of Laboratory Assessments	Changed "Calcium & Albumin or Ionized Calcium" to "Corrected Calcium (Calcium & Albumin or Ionized Calcium)"	Clarification required with the addition of separate serum Calcium to be assessed only if Ionized Calcium is used for Corrected Calcium. If Albumin-Adjusted Calcium is used for Corrected Calcium, Calcium is already assessed as part of Corrected Calcium and thus a separate(second) serum Calcium is not required.

Section(s)	Change(s)	Rationale
Appendix 5. Schedule of Laboratory Assessments	Change Visit "9+" to "9-15" and Weeks from "18+" to "18-58" Addition of columns for LV7-LV12 and V16-V21 Addition of rows for Calcium and Phosphate Adjustment of footnote numbering	Addition of timepoints and laboratory assessments throughout the additional 3 years of the Extension Period Footnotes associated with added procedure rows required renumbering of footnotes within the second section of the Extension Period table
Appendix 5. Schedule of Laboratory Assessments	Change from "hCG (pregnancy test) is assessed only at Visits 10, 12, and 14" to "Local urine hCG (pregnancy test) is assessed only at Visits 10, 12, and 14"	Clarification that urine hCG is expected to be performed at site/local laboratory rather than through the Central Laboratory
Appendix 5. Schedule of Laboratory Assessments	Change "24-hour urine collection will be performed… within a week of Visit 11and the week prior to Visit 15" to "24-hour urine collection will be performed… within the week prior to Visit 1, and within a week of Visits 11 and 15"	Clarification that 24-hour urine collection is to occur the week prior to Visit 1 rather than at Visit 1 As Visit 15 is no longer the final study visit, 24-hour urine collection and DXA can occur within a week of the visit rather than only the week prior to the visit
Appendix 6. Laboratory Panel Analytes	Change from "Labataorty Panel Analysis" to "Laboratory Panel Analysis"	Correction to spelling
Appendix 6. Laboratory Panel Analytes	Change from "Phosphorous" to "Phosphate"	Correction to accurately reflect laboratory analyte tested
Appendix 8. Remote Study Visits	Addition of Appendix	Allow for remote visits when a subject is unable to attend Extension Period study visits in-person, while still ensuring subject safety

US ADDENDUM 1 SUMMARY

Rationale

This US-specific addendum to the protocol is being issued to incorporate feedback from clinical trial sites and patient advocacy groups for humanitarian reasons, to enable US patients on Natpara at the time of the Takeda recall on 5 September 2019 to be enrolled in the PaTH Forward Trial within the limited enrollment window. Amending the protocol globally would not affect the eligibility criteria for the majority of subjects in other regions because Natpara is neither readily accessible in the majority of other countries where this trial is being conducted, nor has it been recalled outside of the US. Furthermore, this country-specific addendum will not create a difference in study population between the US and other regions as hypoparathyroid patients in both regions may still be treated either exclusively with SOC or returned to SOC following treatment with PTH, if available.

This addendum shortens the washout period from PTH-like drugs from 12 weeks to 5 weeks. The current washout period of 12 weeks prior to Visit 1 was established out of an abundance of caution. The half-life of Natpara guarantees that, even with a shortened washout period of 5 weeks, the drug will be out of the body prior to first dose of study drug and therefore not likely to be considered an acute cause of adverse events experienced during study drug treatment. Shortening the washout period will not affect the potential for long-term adverse events from previous PTH use to appear during the trial as the protocol currently allows subjects who have previously taken PTH to enter the trial.

Reducing the stabilization requirement for SOC from 12 weeks prior to Screening is not of clinical concern as subjects will still require optimization of their SOC during screening and prior to first study drug dosing (Visit 1). It should be noted however, that upon immediately discontinuing Natpara, patients may acutely require increased SOC doses due to "hungry bone syndrome" induced by the anabolic effect of intermittent Natpara. This generally resolves within one week. Thus, the protocol addendum still requires 4 weeks of stable SOC prior to Screening to reduce the likelihood of a meaningful difference between subjects who may enter the study after a decreased stabilization period after stopping Natpara due to the recall and those entering the study after a longer stabilization period.

Section(s)	Change(s)	Rationale
Synopsis: Eligibility Criteria: Inclusion Criteria #3 Section 8.1.1. Inclusion Criteria #3	Change "On a stable dose* for at least 12 weeks prior to Screening" to "On a stable dose* for at least 12 weeks (or 4 weeks if on Natpara as of September 2019) prior to Screening"	Reduce the wait period for US patients previously treated with the only marketed PTH for hypoparathyroidism which is currently unavailable due to the recall.
Synopsis: Eligibility Criteria: Exclusion Criteria #6 Section 8.1.2. Exclusion Criteria #6	Change "Use of PTH-like drugs…within 12 weeks prior to Visit 1" to "Use of PTH-like drugs…within 5 weeks prior to Visit 1"	Reduce the wait period for US patients previously treated with the only marketed PTH for hypoparathyroidism which is currently unavailable due to the recall.

CANADA ADDENDUM 1 SUMMARY

Rationale

This addendum to the protocol is being issued to incorporate feedback from Health Canada:

Section(s)	Change(s)	Rationale
Section 10.1.2 Screening Period (Week -4 to -1, Day -28 to -7) Section 10.1.4.3 Visits 9-11 (Weeks 18-26; Day 126-182 ±3 days) procedures Section 10.1.4.4 Visits 12-15 (Weeks 34-58; Day 238-406 ±7 days) procedures	Addition of bulleted statement: "TBS scoring will not be performed for subjects 18 to 20 years of age"	Remove TBS scoring for subjects 18 to 20 years old as requested by Health Canada
Section 11.5. Dual-Energy X-Ray Absorptiometry (DXA) and Trabecular Bone Score (TBS)	Addition of "TBS scoring will not be performed for subjects 18 to 20 years of age." Change "If the historical DXA did not include TBS, TBS analysis should be performed" to "If the historical DXA did not include TBS, TBS analysis should be performed unless subject is 18 to 20 years of age."	Remove TBS scoring for subjects 18 to 20 years old as requested by Health Canada

AMENDMENT 1 SUMMARY

Rationale

This amendment to the protocol is being issued to incorporate feedback from multiple Health Authorities.

Section(s)	Change(s)	Rationale
Title Page	[redacted]	Administrative change
Title Page	[redacted]	Administrative change
Synopsis: Objectives: Secondary Section 6.2. Secondary Objectives	Removal of "the long-term safety and tolerability (during the Extension Period)" from "To assess the safety and tolerability of daily TransCon PTH"	As requested by Health Authorities to align the objectives with the endpoints and clarify which objectives included analysis of data from the Extension Period
Synopsis: Objectives: Secondary Section 6.2. Secondary Objectives	Addition of a Secondary Objective: "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"	As requested by Health Authorities to align the objectives with the endpoints and clarify which objectives included analysis of data from the Extension Period
Synopsis: Objectives: Secondary Section 6.2. Secondary Objectives	Change the order of analytes from "serum magnesium, serum phosphate, and calcium x phosphate product" to "serum phosphate, serum magnesium, and calcium x phosphate product"	As requested by Health Authorities to align the objective with the endpoint
Synopsis: Eligibility Criteria: Exclusion Criteria #2 Section 8.1.2. Exclusion Criteria #2	Change "Impaired responsiveness to PTH (pseudohypoparathyroidism)" to "Impaired responsiveness to PTH (pseudohypoparathyroidism) which is characterized as PTH-resistance, with elevated PTH levels in the setting of hypocalcemia"	As requested by Health Authorities to describe how an investigator would differentiate between hypoparathyroidism and pseudohypoparathyroidism
Synopsis: Eligibility Criteria: Exclusion Criteria #11 Section 8.1.2. Exclusion Criteria #11 Section 11.13.2 Contraception	Addition of reference to Appendix 7 (guidance on highly effective contraception) Addition of the requirement for sexually active women of childbearing potential to use highly effective contraception "during the trial and for 2 weeks after the last dose of study drug"	As requested by Health Authorities to maintain use of highly effective until at least five times the half-life after the last study drug administration

Section(s)	Change(s)	Rationale
Synopsis: Eligibility Criteria: Exclusion Criteria #11 Section 8.1.2. Exclusion Criteria #11	Addition of "Sexually active women of childbearing potential who are unwilling to use highly effective contraception are excluded from the trial."	To clarify as requested by Health Authorities
Synopsis: Eligibility Criteria: Exclusion Criteria #17 Section 8.1.2. Exclusion Criteria #17	Change "Any disease or condition that, in the opinion of the investigator, may make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the investigational product or procedures, including treated malignancies that are likely to recur within the approximate 3-year duration of the trial" to "Any disease or condition that, in the opinion of the investigator, may make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the investigational product or procedures, including treated malignancies that are likely to recur within the approximate 1-year duration of the trial"	As requested by Health Authorities to reduce the Extension Period to 1 year
Synopsis: Trial Design	Reduction of Extension Period from "at least 3 years" to "54 weeks" Reduction of "Extension Period (Visits 3+; Week 4+)" to "Extension Period (Visits 3-15; Weeks 4-58)	As requested by Health Authorities to reduce the Extension Period to 1 year
Synopsis: Blinding Section 7.1 Overall Trial Design and Plan Section 10.1. Trial Duration	Reduction of the open-label extension period of "at least 158 weeks" to "54 weeks"	As requested by Health Authorities to reduce the Extension Period to 1 year
Synopsis: Trial & Treatment Duration Section 7.1 Overall Trial Design and Plan Section 10.1. Trial Duration Section 10.1.4 Extension Period	Reduction of the total duration of trial for an individual subject from "at least approximately 162 weeks" to "58 weeks" Reduction of "followed by approximately "144 weeks of stable dosing" in the Extension Period to "40 weeks of stable dosing" Reduction from "Extension Period (Week 4+)" to "Extension Period (Week 4-58)	As requested by Health Authorities to reduce the Extension Period to 1 year

Section(s)	Change(s)	Rationale
Synopsis: End of Trial	Addition of section to synopsis to capture definition of end of trial as last subject last visit	To highlight within the synopsis the addition requested by Health Authorities
Synopsis: Stopping Rules Section 12.2.1.3. Non-Serious Adverse Events Leading to Study drug Discontinuation Section 12.2.2. Reporting of SAEs and/or SUSARs	Change of "Medical Expert/Medical Monitor," "Medical Monitor," or "Medical Monitor/Expert" to "Medical Monitor/Medical Expert"	For consistency throughout document
Synopsis: Endpoints Section 14.2.1. Efficacy Endpoints	Addition of "Efficacy" to Primary and Secondary Endpoints Addition of "Primary and key secondary endpoints measured at predefined timepoints over the Extension Period" for Other Secondary Endpoints Addition of "and at predefined timepoints over the Extension Period" for the Other Secondary Efficacy Endpoints Moved "Safety & Tolerability Endpoints" below "Other Secondary Efficacy Endpoints" Addition of "The following safety endpoints will be assessed for both Blinded Treatment and Extension Periods" for Safety & Tolerability Endpoints	As requested by Health Authorities to align the objectives with the endpoints and clarify which endpoints include analysis of data from the Extension Period
Synopsis: Endpoints Section 14.2.3. Exploratory Endpoints	Removal of Exploratory Endpoint assessments after 58 weeks Addition of 24-hour urine calcium excretion at 58 weeks (in place of 74 weeks) Addition of PRO measure at 58 weeks (in place of "every 26 weeks thereafter")	To align endpoints with the procedures to be performed at the last visit of the Extension Period (V15) due to the reduction of the Extension Period to 1 year as requested by Health Authorities
Synopsis: Endpoints Section 14.2.3. Efficacy Endpoints	Change of albumin-adjusted or ionized sCa, magnesium, phosphate, and sCa x sP product at "every clinic visit" to "at 8, 18, 26, 42, and 58 weeks"	To match Schedule of Events and Schedule of Laboratory Assessments

Section(s)	Change(s)	Rationale
Synopsis: Statistical Methods Section 14.1. General	Change of finalization of SAP from before "database lock" to before "trial unblinding and database lock of the Blinded Treatment Period"	To clarify as requested by Health Authorities
List of Abbreviations	Addition of "Clinical Trial Facilitation Group" for "CTFG"	To provide the abbreviation for the group referenced in the protocol which provides the guidance for highly effective contraception as requested by Health Authorities
Section 5.3. Clinical Experience	Addition of "conducted under GCP, IEC, and Declaration of Helsinki guidelines" in regard to the TransCon PTH Phase 1 trial	To clarify as requested by Health Authorities
Section 5.5. Summary of Potential Risks and Benefits	Section split into 5.5.1. Potential Risks and 5.5.2. Potential Benefits	To increase readability
Section 5.5. Potential Risks	Change of "Some of the potential risks associated with PTH(1-34) and/or approved PTH therapies are provided below" to "The following risks have been seen in either the TransCon PTH Phase 1 volunteers or have been reported for approved PTH medications, and thus considered to be potential risks for TransCon PTH:"	To clarify as requested by Health Authorities
Section 5.5. Potential Risks	Addition of "Nausea" as a potential risk	To match TransCon PTH Investigator Brochure
Section 5.5. Potential Risks	Addition of hypercalcemia as a risk during the Blinded Treatment Period due to the requirement of subjects to remain on a fixed dose of study drug and methods of minimization and management Addition of hypocalcemia as a risk during the reduction in SOC following initiation of study drug at Visit 1 (and Visit 3 for those on active vitamin D at Visit 3) and methods of minimization and management	As requested by Health Authorities to address risks associated with protocol-required adjustments to therapies
Section 7.1. Overall Trial Design and Plan	Update to the Study Design image to capture change in duration of Extension Period	As requested by Health Authorities to reduce the Extension Period to 1 year

Section(s)	Change(s)	Rationale
Section 7.1.1. Measures Taken to Maximize Study Integrity and Minimize Bias	Addition of explanation that Appendices 1-3 act as methods of minimizing individual investigator bias by providing standardized guidelines based on objective laboratory tests and subjects' experience of hypo- or hypercalcemic symptoms. Addition of explanation that the Medical Monitor/Medical Expert will perform timely review of laboratory results and prescribed dosing to confirm investigator compliance with Appendices 1-3.	As requested by Health Authorities to revise section to include a discussion on the risk of bias associated as treatment allocation may be revealed based on evaluation of serum and urinary calcium levels
Section 9.6.1. Required Stopping	Section split into 9.6.1. Required Stopping and 9.6.2. Possible Stopping/Dose Reductions Change of wording to require investigators to stop study drug for evidence of severe hypersensitivity to TransCon PTH, drug-related SAE or drug-related severe AE (other than hypercalcemia), severe hypo- or hypercalcemia that cannot be corrected with protocol-allowable dose adjustments to SOC and/or TransCon PTH, neutralizing anti-PTH antibodies that correlate with reduced PD response, suspicion of osteosarcoma, and pregnancy Addition of "Suspicion of osteosarcoma (eg, persistent localized pain or occurrence of a new soft tissue mass tender to palpation that could be consistent with osteosarcoma, in association with an elevation of bone-specific alkaline phosphatase) Addition of "See Section 8.2.1 for further guidance on study drug discontinuation" to Section 9.6.1.	As requested by Health Authorities to discriminate between "may" and "must" criteria for subject discontinuation and to add a stopping rule for "suspicion of osteosarcoma"
Section 10.1.1. Trial Periods and Visits	Addition of "Visit 14 (Week 50, Day 350, ±7 days)" and "Visit 15 (Week 58, Day 406, ±7 days)" in place of "Visits every 8 weeks ±7 days until the end of the trial"	As requested by Health Authorities to reduce the Extension Period to 1 year

Section(s)	Change(s)	Rationale
Section 10.1.3.1. Visit 1 (Week 0, Day 1) procedures	Addition to vital signs of "including 30-minute post-dose orthostatic measurements"	As requested by Health Authorities to include orthostatic measurements
Section 10.1.3.4. Visit 3 (Week 4, Day 28 ±2 days) procedures	Addition of "For subjects on active vitamin D only: 30-minute post-dose orthostatic measurements"	As requested by Health Authorities to include orthostatic measurements
Section 10.1.4.2. Visits 4-8 (Weeks 6-14; Days 42, 56, 70, 84, 98 ±2 days) procedures Section 11.12.1.7. Visits 4-8 (V4-V8) Laboratory Assessments	Addition of *"Only for women of childbearing potential:* Urine collection for local hCG (only at Visits 6 and 8)" Addition of "*Only for women of child-bearing potential:* urine hCG (only at Visits 6 and 8)"	As requested by Health Authorities to increase number of pregnancy testing
Section 10.1.4.3. Visits 9+ (Weeks 18+; Day 126+) procedures	Split Section 10.1.4.3. into "Section 10.1.4.3. Visits 9-11 (Weeks 18-26; Day 126-182 ±3 days) procedures" and "Section 10.1.4.4. Visits 12-15 (Weeks 34-58; Day 238-406; ±7 days) procedures"	To group visits that have the same visit window for increased readability
Section 10.1.4.3. Visits 9+ (Weeks 18+; Day 126+) procedures	Removal of "Clinic Visits 9-11 will be performed every four (4) weeks ±3 days. Clinic Visits 12-15 will be performed every either (8) weeks ±7 days."	To remove redundancy due to splitting of Section 10.1.4.3. as these details are now provided in the section titles
Section 10.1.4.3. Visits 9-11 (Weeks 18-26; Day 126-182 ±3 days) procedures Section 11.12.1.8. Visits 9-15 (V9-15) Laboratory Assessments	Addition of *"Only for women of childbearing potential:* Urine collection for local hCG (only at Visit 10)" Addition of "The following laboratory assessments will be performed <u>locally</u> at Visits 9-15: *Only for women of child-bearing potential:* urine hCG (only at Visits 10, 12, and 14)"	As requested by Health Authorities to increase frequency of pregnancy tests
Section 10.1.4.4. Visits 12-15 (Weeks 34-58; Day 238-406 ±7 days) procedures Section 11.12.1.8. Visits 9-15 (V9-15) Laboratory Assessments	Addition of *"Only for women of childbearing potential:* Urine collection for local hCG (only at Visit 12 and 14)" Addition of "The following laboratory assessments will be performed <u>locally</u> at Visits 9-15: *Only for women of child-bearing potential:* urine hCG (only at Visits 10, 12, and 14)"	As requested by Health Authorities to increase frequency of pregnancy tests

Section(s)	Change(s)	Rationale
Section 10.1.4.4. Visits 12-15 (Weeks 34-58; Day 238-406 ±7 days) procedures	Change of "24-hour urine collection (only within a week of Visit 17)" to "Change of "24-hour urine collection (only the week prior to Visit 15)"	To align procedures to the last visit of the Extension Period (V15) due to the reduction of the Extension Period to 1 year as requested by Health Authorities
Section 10.1.7. End of Study (EOS) Visits	Change of "If EOS Visits occur *after* Visit 3, the structure and assessments of the EOS Visit should be as similar as possible to Visit 11" to "If EOS Visits occur *after* Visit 3, the structure and assessments of the EOS Visit should be as similar as possible to Visit 15"	To align procedures to the last visit of the Extension Period (V15) due to the reduction of the Extension Period to 1 year as requested by Health Authorities
Section 10.1.7. End of Study (EOS) Visits	Addition of "Additionally, correspondence (eg, phone call, email) with the subject 2 weeks (+7 days) after last study drug administration is required to evaluate the subject for any further AEs during the 2 weeks since last study drug administration.	As requested by Health Authorities to include follow-up with subject after at least five times the half-life of study drug from the date of last study drug administration
Section 11.1 Vital Sign Measurements	Change of order of vital sign measurements to list "Respiratory Rate" and "Body Temperature" before "Orthostatic Blood Pressure & Heart Rate"	As requested by Health Authorities to include orthostatic measurements
Section 11.1 Vital Sign Measurements	Removal of Heart Rate and Blood Pressure Addition of "Orthostatic Blood Pressure & Heart Rate" Addition of "Blood pressure and heart rate are measured while subject is sitting. Subject is then asked to stand up and, within 3 minutes of doing so, blood pressure and heart rate are measured again."	As requested by Health Authorities to include orthostatic measurements
Section 11.1.1. Post-Dose Orthostatic Measurement	Addition of Section 11.1.1. Post-Dose Orthostatic Measurement Addition of a 30-minute post-dose measurement of orthostatic blood pressure and heart rate at Visit 1 and Visit 3 (for those on active vitamin D at Visit 3)	As requested by Health Authorities to include orthostatic measurements

Section(s)	Change(s)	Rationale
Section 11.5. Dual-Energy X-Ray Absorptiometry (DXA) and Trabecular Bone Score (TBS)	Change of "To evaluate bone density, a DXA of the spine, hip, and forearm must be performed" to "To evaluate bone density and quality, a DXA scan of the spine, hip, and forearm, as well as TBS scoring must be performed"	To clarify intent and analysis for DXA assessments
Section 11.10. Local Tolerability Assessment	Addition of "induration" as an injection site reaction (ISR) ordinarily observed in subcutaneous (SC) injections	To provide further guidance to investigators for potential ISRs
Section 11.10. Local Tolerability Assessment	Removal of "An ISR noted during the local tolerability assessment is only reported as an AE if it meets the criteria for an AE as described in Section 11.11.1."	To remove reference to a section that has been removed as requested by Health Authorities
Section 11.11.1. Injection Site Reactions (ISRs) as Adverse Events (AEs)	Removal of section	As requested by Health Authorities to remove restrictions on AE assessment by investigators
Section 11.11.2. Erythema as Adverse Events (AEs)	Removal of section	As requested by Health Authorities to remove restrictions on AE assessment by investigators
Section 11.12. Laboratory Assessments	Addition of "On the day of lab assessments, subjects should be instructed to take their SOC (as applicable) and eat their usual breakfast prior to blood collection"	To clarify that, while fasting is not required, consistency of either fasting or not fasting is important when comparing laboratory test results between visits
Section 11.12.1.2. Visit 1 (V1) Laboratory Assessments Section 11.12.1.4. Visit 2 (V2) Laboratory Assessments Section 11.12.1.5. Visit 3 (V3) Laboratory Assessments Section 11.12.1.7. Visit 4-8 (V4-V8) Laboratory Assessments Section 14.3. Statistical Analysis: Pharmacokinetic analysis	Increase of cohort size for assessment of Free PTH[PTH(1-34) and PTH(1-33)] from "12 subjects" to "approximately 24"	As requested by Health Authorities to increase the sample size for PK analysis

Section(s)	Change(s)	Rationale
Section 11.12.1.3. Laboratory Visits 1-3 (LV1-LV3) Laboratory Assessments	Addition of "If, at selected sites where the Free PTH assessment will be performed at Visit 1, subjects return to the site's own local laboratory for LV1-LV3, an additional assessment of Free PTH [PTH(1-34) and PTH(1-33)] will be performed centrally."	As requested by Health Authorities to increase the sampling timepoints for PK analysis
Section 11.12.1.8. Visits 9-15 (V9-15) Laboratory Assessments	Changed from "Visits 9+ (V9+) Laboratory Assessments" to "Visits 9-15 (V9-V15) Laboratory Assessments"	As requested by Health Authorities to reduce the Extension Period to 1 year
Section 11.12.1.8. Visits 9-15 (V9-15) Laboratory Assessments	Addition of "The following laboratory assessments will be performed locally at Visits 9-15: *Only for women of child-bearing potential:* urine hCG (only at Visits 10, 12, and 14)"	As requested by Health Authorities to increase frequency of pregnancy tests
Section 11.12.1.8. Visits 9-15 (V9-15) Laboratory Assessments	Removal of laboratory assessments after 58 weeks	As requested by Health Authorities to reduce the Extension Period to 1 year
Section 11.12.1.8. Visits 9-15 (V9-15) Laboratory Assessments	Change of "*Only for female subjects*" to "*Only for women*"	For consistency throughout document
Section 11.12.1.8. Visits 9-15 (V9-15) Laboratory Assessments	Change of 24-hour urine collection being performed "within a week of Visits 11 and 17" to "within a week of Visit 11 and within the week prior to Visit 15"	To align procedures to the last visit of the Extension Period (V15) due to the reduction of the Extension Period to 1 year as requested by Health Authorities
Section 11.13.2 Exercise Modification	Addition of section on avoiding exercise prior to visits which include blood collection	As requested by Health Authorities to align instructions given to subjects between Section 11.12. Laboratory Assessments and Section 11.13
Section 11.13.3.1. Blinded Treatment Period Administration Section 11.13.3.2. Extension Period Administration	Addition of orthostatic hypotension to adverse reactions which may be observed within the 30 minutes after study drug administration at the study visit	As requested by Health Authorities to include orthostatic measurements
Section 12.1.3. Reporting Procedures for All Adverse Events	Addition of "from the time of signed consent to 2 weeks after the last study drug administration" for reporting of AEs	As requested by Health Authorities to collect AEs until at least five times the half-life after the last study drug administration

Section(s)	Change(s)	Rationale
Section 12.2.2. Reporting of SAEs and/or SUSARs	Change of "within the time frames required by applicable regulations" to "in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries"	As requested by Health Authorities
Section 14.2.1.Efficacy Endpoints	Split Section 14.2.1. Efficacy Endpoints into "Section 14.2.1.1. Primary Efficacy Endpoint," and "14.2.1.2. Secondary Efficacy Endpoints"	As requested by Health Authorities to align the objectives with the endpoints
Section 14.2.2. Safety & Tolerability Endpoints	Addition of section Moved Safety & Tolerability Endpoints into new section from Section 14.2.1 Efficacy Endpoints	As requested by Health Authorities to align the objectives with the endpoints
Section 14.2.3. Exploratory Endpoints	Addition of section Moved Exploratory Endpoints into new section from Section 14.2.1 Efficacy Endpoints	As requested by Health Authorities to align the objectives with the endpoints
Section 14.8. Unblinding Procedures	Addition of section	As requested by Health Authorities to include unblinding procedures
Section 15.6. Trial Termination or Completion	Addition of "End of trial is defined as last subject last visit"	As requested by Health Authorities to include definition of end of trial
Section 15.6. Trial Termination or Completion	Addition of "including insufficient efficacy and unanticipated safety concerns" to "reason for Sponsor to terminate the trial at any time"	As requested by Health Authorities
Section 17. References	Addition of Clinical Trial Facilitation Group reference	Reference for guidance on highly effective contraception as requested by Health Authorities
Appendix 1	Addition of guidance if, at Visit 2, subject is on calcium >500 mg/day and has sCa within normal range	To give further guidance to investigators on SOC dose adjustment
Appendix 2 Appendix 3	Change of "skip one dose" for subjects with sCa >ULN and symptoms to "skip at least one dose"	To clarify guidance to investigators on TransCon PTH titration as skipping a single dose may not reduce sCA levels enough to adequately alleviate symptoms

Section(s)	Change(s)	Rationale
Appendix 4	Addition of footnote for vital sign measurements to perform orthostatic blood pressure and heart rate should also be performed 30 minutes after study drug administration at Visit 1	As requested by Health Authorities to include orthostatic measurements
Appendix 4	Addition of footnote for vital sign measurements to perform orthostatic blood pressure and heart rate should also be performed 30 minutes after study drug administration at Visit 3 only for subjects taking active vitamin D at Visit 3	As requested by Health Authorities to include orthostatic measurements
Appendix 4	Addition of Blood & urine collection for central lab assessments at LV1-LV3 Addition of footnote for LVI-LV3 for Blood & urine collection for central lab assessments to clarify that this is to only be performed only for subjects who, at selected sites where the Free PTH assessment will be performed at Visit 1, return to the site's own local laboratory for LV1-LV3, to have an additional assessment of Free PTH [PTH(1-34) and PTH(1-33)]	As requested by Health Authorities to increase the sampling timepoints for PK analysis
Appendix 4	Change of vital sign footnotes from "heart rate, blood pressure, respiratory rate and temperature" to "respiratory rate, temperature, and orthostatic blood pressure and heart rate"	As requested by Health Authorities to include orthostatic measurements
Appendix 4	Separated out Visits 12-15 into separate columns from a single column labelled Visit 12-28+ Update to footnotes accordingly	To increase readability
Appendix 4	Addition of Urine collection for local lab assessments for local urine hCG tests Addition of footnote "Urine collection only for female subjects of childbearing potential" for Urine collection for local lab assessments	As requested by Health Authorities to increase number of pregnancy testing
Appendix 4	Change of footnotes to capture removal of assessments after 58 weeks	As requested by Health Authorities to reduce the Extension Period to 1 year

Section(s)	Change(s)	Rationale
Appendix 4	Change of footnotes to capture addition of 24-hour urine calcium excretion "within the week prior to Visit 15" (in place of "within a week of Visit 17")	To align procedures to the last visit of the Extension Period (V15) due to the reduction of the Extension Period to 1 year as requested by Health Authorities
Appendix 4	Addition of footnote to capture addition of "Correspondence with subject (eg, phone call, email) should be made 2 weeks (+7 days) after last study drug administration to evaluate for AEs during the 2 weeks after last study drug administration for Adverse event review at Visit 15	As requested by Health Authorities to include follow-up with subject after at least five times the half-life of study drug from the date of last study drug administration
Appendix 4	Addition of footnote referring to Appendix 6	To provide reference to a complete list of analytes for Chemistry, Hematology, and 24-hour Urine Panels as requested by Health Authorities
Appendix 6	Addition of Appendix 6 Laboratory Panel Analytes	As requested by Health Authorities to include a complete list of analytes for Chemistry, Hematology, and 24-hour Urine Panels
Appendix 7	Addition of Appendix 7 Contraception	As requested by Health Authorities to include guidance on highly effective contraception methods

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Conference on Harmonisation (ICH) E6 (R2) and regional regulations
- Regional subject data protection laws and regulations
- Other applicable regional and local regulations
- US Federal Regulations, as applicable

1. APPROVAL SIGNATURES

1.1. SPONSOR

I agree to conduct this trial in accordance with the requirements of this Clinical Trial Protocol and also in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Conference on Harmonization (ICH) E6 (R2) and regional regulations
- Regional subject data protection laws and regulations
- Other applicable regional and local regulations
- Clinical trial contractual obligations
- US Federal Regulations, as applicable

CLINICAL TRIAL 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

[redacted]

10 March 2021
Date

Ascendis Pharma, Inc.

2. SYNOPSIS

PRODUCT NUMBER/NAME	TransCon PTH
PROTOCOL NUMBER	TransCon PTH TCP-201
IND NUMBER	133469
EUDRACT NUMBER	2018-004815-33
DEVELOPMENT PHASE	2
PROTOCOL 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
INDICATION	Hypoparathyroidism (HP) in Adults
OBJECTIVES	**Primary:** • 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 **Secondary:** • 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 **Exploratory:** • 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 – Clinical Outcomes Assessments (COAs) – Bone turnover markers (serum P1NP and CTx) – Vascular calcifications, nephrocalcinosis, and nephrolithiasis • To assess the usability of the pre-filled injection pen

PLANNED TRIAL SITES	Up to 40 sites worldwide
PLANNED NUMBER OF SUBJECTS	Approximately 40
TRIAL POPULATION	Male and female adults with 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 of alfacalcidol) and ≥400 mg BID calcium for at least 12 weeks prior to Screening
ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Males and females aged ≥18 years 2. Subjects with postsurgical chronic HP or auto-immune, genetic, or idiopathic HP for at least 26 weeks. Diagnosis of HP is established based on hypocalcemia in the setting of inappropriately low serum parathyroid hormone (PTH) levels. 3. On a stable dose* for at least 12 weeks (*US only:* or 4 weeks if on Natpara as of September 2019) prior to Screening of: • ≥0.25 µg BID of calcitriol (active vitamin D) or ≥0.5 µg BID or ≥1.0 µg daily of alfacalcidol (active vitamin D) **and** • ≥400 mg BID calcium citrate or carbonate If subject has a history of hypercalcemia on such doses, subject may be taking <0.25 µg BID of calcitriol, <0.5 µg BID or <1.0 µg daily of alfacalcidol, or <400 mg BID of calcium citrate or carbonate, with approval of Medical Monitor/Medical Expert **Does not preclude occasional (<3/week) rescue doses of active vitamin D and/or calcium for symptomatic hypocalcemia* 4. Optimization of supplements prior to randomization to achieve the target levels of: – 25(OH) vitamin D levels of 30-70 ng/mL (75-175 pmol/mL) **and** – Magnesium level within the normal range* **and** – Albumin-adjusted or ionized serum calcium (sCa) level in the lower half of the normal range * If subject has a history of inability to be successfully managed within the normal range for magnesium level, a level slightly below the normal range is acceptable with approval of the Medical Monitor/Medical Expert 5. BMI 17-40 kg/m^2 at Visit 1 6. If ≤25 years of age, radiological evidence of epiphyseal closure based on x-ray of non-dominant wrist and hand 7. eGFR >30 mL/min/1.73m^2 during Screening 8. Thyroid-stimulating hormone (TSH) within normal laboratory limits within the 12 weeks prior to Visit 1; if on suppressive therapy for thyroid cancer, TSH level must be ≥0.2 µIU/mL 9. If treated with thyroid hormone replacement therapy, the dose must be stable for at least 12 weeks prior to Visit 1

	10. Able to perform daily subcutaneous self-injections of study drug (or have a designee perform injection) via a pre-filled injection pen 11. Written, signed, informed consent of the subject **Exclusion Criteria** 1. Known activating mutation in the calcium-sensing receptor (CaSR) gene 2. Impaired responsiveness to PTH (pseudohypoparathyroidism) which is characterized as PTH-resistance, with elevated PTH levels in the setting of hypocalcemia 3. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HP, such as active hyperthyroidism; Paget's disease; hypomagnesemia; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus; severe and chronic cardiac, liver, or renal disease; Cushing syndrome; rheumatoid arthritis; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer or basal cell skin cancer); parathyroid carcinoma within 5 years prior to Screening; acromegaly; multiple endocrine neoplasia types 1 and 2 4. Use of loop diuretics, phosphate binders (other than calcium carbonate/calcium citrate), digoxin, lithium, methotrexate, or systemic corticosteroids (other than replacement therapy) 5. Use of thiazide diuretic within 4 weeks prior to the Screening 24-hour urine collection or the first dose adjustment of SOC during Screening 6. Use of PTH-like drugs (whether commercially available or through participation in an investigational trial) including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein within 12 weeks (*US only:* 5 weeks) prior to Visit 1 7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (> 0.5 mg/day), strontium, or cinacalcet hydrochloride within 12 weeks prior to Visit 1 8. Use of bisphosphonates (oral or IV) or denosumab within 2 years prior to Visit 1 9. Non-hypocalcemic seizure disorder with a history of a seizure within 26 weeks prior to Visit 1 **<u>NOTE</u>: History of seizures that occur in the setting of hypocalcemia is not exclusionary**

	10. Increased risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, hereditary disorders predisposing to osteosarcoma, or with a prior history of substantial external beam or implant radiation therapy involving the skeleton 11. Pregnant or lactating women. **NOTE: Highly effective contraception (see Appendix 7) is required for sexually active women of childbearing potential during the trial and for 2 weeks after the last dose of study drug, and pregnancy testing will be performed throughout the trial. Sexually active women of childbearing potential who are unwilling to use highly effective contraception are excluded from the trial.** 12. Diagnosis of drug or alcohol dependence within 3 years prior to Visit 1 13. Disease processes that may adversely affect gastrointestinal absorption including but not limited to short bowel syndrome, bowel resection, gastric bypass, tropical sprue, active celiac disease, active ulcerative colitis, gastroparesis, AIRE gene mutations with malabsorption, and active Crohn's disease 14. Chronic or severe cardiac disease within 26 weeks prior to Visit 1 including but not limited to congestive heart failure, myocardial infarction, QTcF >430 msec (males) or >450 msec (females), severe or uncontrolled arrhythmias, bradycardia (resting heart rate <50 beats/minute), symptomatic hypotension, systolic BP <80 mm Hg or diastolic <40 mm Hg, or poorly controlled hypertension (systolic BP >150 mm Hg or diastolic >95 mm Hg) 15. Cerebrovascular accident within 5 years prior to Visit 1 16. History of renal colic or acute gout within 52 weeks prior to Visit 1 17. Any disease or condition that, in the opinion of the investigator, may make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the investigational product or procedures, including treated malignancies that are likely to recur within the approximate 1-year duration of the trial 18. Known allergy or sensitivity to PTH or any of the excipients [metacresol, mannitol, succinic acid, NaOH/(HCl)] 19. Participation in another clinical trial in which receipt of investigational drug or device occurred within 8 weeks (or at least 5.5 times the half-life of the investigational drug) prior to Visit 1 20. Likely to be non-compliant with respect to trial conduct 21. Any other reason that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule

TRIAL DESIGN	This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group, 4-week trial with an open-label extension of 210 weeks of daily TransCon PTH in male and female adults with 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 alfacalcidol) and ≥400 mg BID calcium for at least 12 weeks prior to Screening. **NOTE: If during the Blinded Treatment Period clinical symptoms of hypo- or hypercalcemia occur, an Unscheduled Laboratory Visit (ULV) should be scheduled to assess albumin-adjusted or ionized sCa levels to guide calcium and/or active vitamin D dose adjustments. During either the Blinded Treatment Period or Extension Period, rescue doses of active vitamin D and/or calcium are allowable, even prior to the ULV. However, unlike in the Blinded Treatment Period when study drug dose must remain stable, if symptoms of hypo- or hypercalcemia are persistent during the Extension Period, the TransCon PTH dose should be adjusted at the following clinic visit. Due to the extended length of time between visits after Visit 9, the TransCon PTH dose may be adjusted to control persistent hypo- or hypercalcemia between clinic visits.** **Screening Period (Week -4 to Week -1):** The Screening Period consists of determining eligibility, documenting baseline status, and optimizing vitamin D and magnesium levels, and doses of standard of care (SOC; active vitamin D and calcium) prior to study drug dosing to achieve the following target levels: • 25(OH) vitamin D: 30-70 ng/mL • Magnesium: within the normal range* • Albumin-adjusted or ionized sCa: within the lower half of the normal range SOC doses are adjusted only after initial Screening laboratory results are received. Follow-up laboratory assessment of the above values, with exception of vitamin D level, are performed approximately 3 days after SOC dose adjustment. If required, additional SOC dose adjustments, with follow-up laboratory assessments approximately 3 days later may be performed throughout the Screening Period. For additional guidance see Section 9.5.1. When laboratory results are within the above optimization ranges* with at least one confirmation laboratory result, and all other entry criteria including the Screening 24-hour urine collection are met, the subject is eligible to move to the Blinded Treatment Period and be randomized following Medical Monitor/Medical Expert or designee confirmation. **If subject has a history of inability to be successfully managed within the normal range for magnesium level, a level slightly below the normal range is acceptable with approval of Medical Monitor/ Medical Expert.*

	<u>Blinded Treatment Period (Visits 1-3; Weeks 0-4)</u>: At Visit 1, subjects are randomized into one of 4 treatment groups (1:1:1:1): • TransCon PTH 15 µg/day* • TransCon PTH 18 µg/day • TransCon PTH 21 µg/day • Placebo for TransCon PTH (excipient solution) **Dose of TransCon PTH refers to dose of PTH(1-34) administered* To maintain blinding, the placebo group will be sub-randomized into 3 groups (1:1:1) to mimic doses of 15, 18, and 21 µg/day. Subjects are to remain on the same dose of study drug throughout the 4-week Blinded Treatment Period; however, SOC doses will be optimized as follows *assuming sCa remains ≥LLN but ≤ULN*: **Visit 1:** Decrease active vitamin D dose by 33-50% (eg, skip 2nd dose of the day if taking BID, skip last dose of the day if taking TID, or reduce once daily dose of alfacalcidol ≥1.0 µg by ≥0.5 µg) **Day 3-4:** Discontinue active vitamin D **Day 6-7:** Decrease calcium by ≥50% (≥400 mg/day) if taking ≤2000 mg/day or decrease calcium by ≥800 mg/day if taking >2000 mg/day **Day 9-10:** Discontinue or decrease calcium to ≤500 mg/day if taking ≤2000 mg/day or decrease calcium by ≥800 mg/day if taking >2000 mg/day Complete guidance on SOC optimization is provided in Section 9.5.2.2 and Appendix 1. **<u>NOTE</u>: If during the Blinded Treatment Period clinical symptoms of hypo- or hypercalcemia occur, an Unscheduled Laboratory Visit (ULV) should be scheduled to assess albumin-adjusted or ionized sCa levels to guide calcium and/or active vitamin D dose adjustments. Rescue doses of active vitamin D and/or calcium are allowable, even prior to the ULV.** **<u>Extension Period (Visits 3-21; Weeks 4-214)</u>:** At Visit 3, subjects will be assigned to open-label treatment as follows: • **If taking active vitamin D:** Start TransCon PTH at a dose of 15 µg/day, and undergo titration of SOC as performed during the 4-week Blinded Treatment Period • **If not taking active vitamin D:** Start TransCon PTH at the same dose of study drug taken during the Blinded Treatment Period. Exception should be made if hypo- or hypercalcemic symptoms are present at Visit 3, in which case TransCon PTH dose may be adjusted by 3 µg/day. Subsequently, at every clinic visit (every 2 weeks) up to and including Visit 8, the TransCon PTH dose is increased by 3µg/day if the albumin-adjusted or ionized sCa level is <LLN or subject is experiencing persistent hypocalcemic symptoms. Conversely, if a subject not taking SOC experiences persistent hypercalcemic symptoms

	in the setting of an elevated adjusted or ionized sCa value, the TransCon PTH dose is decreased by 3µg/day. Dose range for the Extension Period is expected to be 6-60 µg/day in 3 pen presentations (6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively). Starting at Visit 9, TransCon PTH, active vitamin D, and calcium doses are expected to remain stable. However, dose adjustments should continue as needed based on sCa results and following Appendix 2 and Appendix 3. **NOTE: Rescue doses of active vitamin D and/or calcium are allowable throughout the Extension Period. However, if symptoms of hypo- or hypercalcemia are persistent, the TransCon PTH dose should be adjusted at the following clinic visit. Due to the extended length of time between visits after Visit 9, the TransCon PTH dose may be adjusted to control persistent symptomatic hypo- or hypercalcemia between clinic visits. Due to the long half-life of TransCon PTH, the full effect of a dose change cannot be determined until 8 to 10 days after the dose change.**
INVESTIGATIONAL PRODUCT	Name: TransCon PTH TransCon PTH drug product is supplied as a clear solution containing TransCon PTH with a nominal PTH(1-34) content of 0.3 mg/mL in a pre-filled pen intended for SC injection. Excipients include metacresol, mannitol, succinic acid, and NaOH/(HCl). The TransCon PTH delivery system consists of a multi-use cartridge integrated into a device to constitute a pre-filled injection pen. The cartridge contains a liquid formulation of TransCon PTH with a fill volume sufficient for 14 doses. Three pre-filled pen presentations are available. For the Blinded Treatment Period, the mid-dose pen will be used, which allows for a dose range of 15-21 µg/day (15, 18, and 21 µg/day). For the Extension Period, all three pen presentations will be available, which allows for an expected dose range of 6-60 µg/day (6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day), respectively. The TransCon PTH drug product concentration is 0.3 mg PTH(1-34)/mL.
REFERENCE PRODUCT(S)	Placebo for TransCon PTH (excipient solution in the mid-dose pen) to mimic doses of 15, 18, and 21 µg/day within the Blinded Treatment Period
TREATMENT REGIMEN	Daily treatment with TransCon PTH or placebo for TransCon PTH (excipient solution) delivered by a modified Ypsomed Uno Pen Fix using 31G, 5 mm needles to deliver doses of 15, 18, or 21 µg/day in volumes of 50, 60, and 70 µL, respectively, to either abdomen or anterior thigh, rotating injections sites. All treatment groups should continue to take stable doses of magnesium and vitamin D3 to maintain the defined ranges, as well as active vitamin D and/or calcium supplements with dose adjustments as required.

BLINDING	This trial consists of a 4-week randomized, double-blind, placebo-controlled treatment period followed by an open-label extension period of 210weeks. To maintain the double-blind during the Blinded Treatment Period, the placebo group will be sub-randomized into 3 groups (1:1:1) to mimic doses of 15, 18, and 21 μg/day delivered by the mid-dose pen.
TRIAL AND TREATMENT DURATION	The total duration of the trial for an individual subject is 214 weeks plus a screening period of up to approximately 4 weeks. • Blinded Treatment Period (study drug stable with 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 Only subjects who successfully complete the Blinded Treatment Period on blinded study drug (TransCon PTH or placebo for TransCon PTH) may enter the open-label Extension Period (TransCon PTH only).
END OF TRIAL	The end of trial is defined as the last subject last visit
STOPPING RULES	Study drug may be temporarily held for symptomatic hypercalcemia or permanently discontinued for a drug-related AE at investigator discretion, with notification of the sponsor Medical Monitor/Medical Expert. If study drug is permanently discontinued prior to Visit 3, subjects are expected to continue within the trial off study drug until Visit 3. If study drug is permanently discontinued after Visit 3, subjects are withdrawn following an Early Termination Visit.
ENDPOINTS	**Primary Efficacy Endpoint:** At 4 weeks of treatment, the proportion of subjects with: • Albumin-adjusted or ionized sCa within the normal range **and** • Spot morning fractional excretion of calcium (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 **Secondary Efficacy Endpoints:** <u>Key Secondary Efficacy Endpoint:</u> 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 <u>Other Secondary Efficacy Endpoints</u>:

	• Primary and key secondary endpoints measured at predefined timepoints over the Extension Period. For the analysis of these endpoints in the Extension Period, the 24-hour urine calcium excretion will be used. 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 mg2/dL2, ≤52 mg2/dL2, and ≤44 mg2/dL2 • Albumin-adjusted or ionized sCa At predefined timepoints over the Extension Period: • 24-hour urine calcium excretion **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, adverse event of special interest (AESI), and serious adverse events (SAEs) • 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, including vital signs **Exploratory Endpoints** 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 at 26, 58, 110, 162, and 214 weeks • 24-hour urine calcium excretion at 26,58, 84, 110, 136, 162, 188, and 214 weeks • Clinical Outcome Assessments (COAs) at 6, 8, 12, 26, 58, 110, 162, and 214 weeks

<table>
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Bone turnover markers (serum P1NP and CTx) at 8, 12, 26, 58, 110, 162, and 214 weeks
Albumin-adjusted sCa, magnesium, phosphate, and sCa x sP product at 8, 18, 26, 42, 58, 84, 110, 136, 162, 188, and 214 weeks

</td></tr>
<tr><td>STATISTICAL METHODS</td><td>Details of applicable statistical methods will be provided in a statistical analysis plan (SAP) which will be finalized before trial unblinding and database lock of the Blinded Treatment Period. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record.</td></tr>
<tr><td>SAMPLE SIZE DETERMINATION</td><td>Based on clinical experience, the proportion of subjects on SOC meeting the primary endpoint will be rare and close to 0. According to simulation data from the FDA, 66% of subjects with continuous infusion of PTH will have normal sCa. The phase 1 study data predict that a large proportion of HP subjects, around 90%, on TransCon PTH will have 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 the following table.
Power calculation for 10 subjects per arm with alpha level at 0.05 and 0.10 (two-sided)
<table>
<tr><th rowspan="2">Proportion for TransCon PTH</th><th rowspan="2">Proportion for Placebo</th><th colspan="2">Power</th></tr>
<tr><th>α=0.05 (2-sided)</th><th>α=0.10 (2-sided)</th></tr>
<tr><td>40%</td><td>1%</td><td>40.7%</td><td>53.2%</td></tr>
<tr><td>50%</td><td>1%</td><td>58.8%</td><td>70.4%</td></tr>
<tr><td>60%</td><td>1%</td><td>74.8%</td><td>83.8%</td></tr>
<tr><td>80%</td><td>1%</td><td>94.7%</td><td>97.3%</td></tr>
</table>
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4. LIST OF ABBREVIATIONS

Abbreviation	Definition
AC	arterial calcification
AE	adverse events
AESI	adverse event of special interest
BID	twice daily
BMD	bone mineral density
BMI	body mass index
CaSR	calcium-sensing receptor
COA	clinical outcomes assessment
CRO	contract research organization
CTFG	Clinical Trial Facilitation Group
CTx	c-telopeptide of type 1 collagen
CxP	calcium-phosphate
DLT	dose-limiting toxicity
DXA	dual-energy x-ray absorptiometry
ECG	Electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ER	emergency room
FECa	fractional excretion of calcium
HP	Hypoparathyroidism
HPES	hypoparathyroid experience scale
ISR	injection site reaction
LLN	lower level of normal
MAD	multiple ascending dose
mPEG	methoxypolyethylene glycol
MTD	maximal tolerated dose
NOAEL	no-observed-adverse-effect level
P1NP	procollagen type 1 amino-terminal propeptide
PD	Pharmacodynamics
PI	principal investigator
PK	Pharmacokinetics

Abbreviation	Definition
pQCT	peripheral quantitative computed tomography
PTH	parathyroid hormone
PRO	patient-reported outcome
qHS	every night at bedtime
SAD	single ascending dose
SAE	serious adverse events
SAP	statistical analysis plan
SC	Subcutaneous
sCa	serum calcium
sMg	serum magnesium
SOC	standard of care (active vitamin D plus calcium)
SOP	standard operating procedure
sP	serum phosphate
TBS	trabecular bone score
TID	three times daily
TPTx	Thyroparathyroidectomized
TSH	thyroid-stimulating hormone
uCa	urine calcium
ULN	upper level of normal

5. INTRODUCTION

5.1. BACKGROUND AND RATIONALE

5.1.1. Parathyroid Hormone

Parathyroid hormone (PTH) is a product of endocrine secretion from the four parathyroid glands. It is synthesized by chief cells as a prohormone peptide, eventually cleaved to 84 amino acids, ie, PTH(1-84), which is secreted. Although PTH(1-84) is the biologically active form of PTH, receptor-mediated activities require only the 34 amino acid N-terminus fragment, PTH(1-34). PTH(1-84) is fairly quickly cleaved to PTH(1-34) both by the parathyroid glands and by hepatic Kuppfer cells (*Hamilton 1983*). PTH(1-33) appears to equipotent to PTH(1-34) (*Morley 1999*).

PTH maintains the body's extracellular calcium and phosphate homeostasis, the former within a very narrow range. When serum calcium (sCa) levels drop, PTH is released from the parathyroid glands. An important effect of PTH at the renal PTH/PTHrP receptor is to increase calcium reabsorption, decrease phosphate reabsorption, and convert the prohormone 25-hydroxyvitamin D (25OHD) to the fully active steroid hormone, 1,25 dihydroxyvitamin D [$1,25(OH)_2$ vitamin D3 or calcitriol]. Active vitamin D increases calcium and phosphate absorption in the small intestine. Another direct action of PTH is to increase osteoclast activity causing calcium and phosphate to increase, and potentially osteocyte activity, increasing ionized calcium.

5.1.2. Hypoparathyroidism

Hypoparathyroidism (HP) is a rare disease of impaired PTH production or activity. The majority of cases (≥75%) are acquired, occurring secondary to anterior neck surgery in which approximately 0.12-4.6% of procedures cause the parathyroid gland(s) to be inadvertently injured or destroyed (*Brandi 2016*, *Clarke 2016*). Of these, 3-30% result in chronic HP, ie, features of HP lasting more than 6 months after the surgery (*Mannstadt 2013*, *Brandi 2016*, *Shoback 2016*). Autoimmune diseases are the second most common cause of acquired HP while less common causes include intrinsic genetic defects of the parathyroid glands, hemochromatosis, magnesium deficiency, as well as idiopathic disease (*Brandi 2016*, *Clarke 2016*).

The US prevalence rate of HP is estimated to range from 60,000-115,000, thus meeting orphan disease status (*Brandi 2016*). Given the predominance of cases secondary to anterior neck surgery, HP incidence rates depend on the number of anterior neck surgeries performed in a given locale, the expertise of the surgeons, and underlying pathology.

In HP, the sCa level drops and there is a lack of compensatory PTH secretion, and calcium-phosphate homeostasis is disrupted. The kidneys decrease calcium reabsorption, phosphate excretion, and conversion of 25D to active 1,25D. Given decreased 1,25D conversion in the kidneys, intestinal absorption of calcium and phosphate decline, and due to deficient PTH the bone osteoclast activity is decreased, further decreasing sCa and resulting in over-mineralized bone and higher-than-normal BMD. Despite decreased GI absorption of phosphate from decreased 1,25D production, patients with HP typically show either elevated or high-normal levels of serum phosphate due to decreased renal phosphate excretion.

5.1.3. Current Standard Therapy for Hypoparathyroidism

Current standard of care (SOC) for HP – specifically active vitamin D and calcium (calcium carbonate or calcium citrate) may improve hypocalcemia, particularly in patients with mild/moderate HP; active vitamin D stimulates calcium and phosphate absorption from the intestines, and calcium supplements increase sCa (*Brandi 2016*). Yet, chronic calcium and vitamin D therapy may also produce adverse effects beyond the original problems of HP because active vitamin D and calcium do not restore PTH-dependent renal calcium reabsorption, correct the elevated serum phosphate/decreased phosphate excretion in HP, or correct diminished bone turnover (*Winer 2012*, *Mannstadt 2017*). Patients on SOC may become hypercalciuric, with a subsequent risk for nephrolithiasis, nephrocalcinosis, and chronic kidney disease (*Winer 2012*, *Mannstadt 2017*). Decreased PTH activity also leads to decreased bone resorption, ie, a low bone turnover – high bone mass state. Finally, as SOC increases both sCa (which is low in HP) and serum phosphate (sP) (which is elevated in HP), SOC can also result in an increased calcium-phosphate (CxP) product, thereby increasing the risk for ectopic calcifications, including in the vascular system, the renal parenchyma, the lens of the eye, and the basal ganglia of the central nervous system (*Abate 2017*).

Based on the current SOC, there have been six goals of chronic HP therapy: 1) prevent signs and symptoms of hypocalcemia; 2) maintain sCa concentration slightly below or within the low-normal range; 3) maintain the CxP product below 55 mg^2/dL^2 (4.4 $mmol^2/L^2$); 4) avoid hypercalciuria (see Table 1); 5) avoid hypercalcemia; and 6) avoid renal (nephrocalcinosis/nephrolithiasis) and other extra-skeletal calcifications (*Bilezikian 2016*, *Brandi 2016*).

Table 1: Normal Urine Calcium Values

	24 Hour Urine	FECa	Urine Calcium/Creatinine Ratio
Females	≤250 mg	≤2%	0.05 to 0.20
Males	≤300 mg	≤2%	0.05 to 0.20

In the absence of a true PTH replacement therapy that replaces active PTH within the normal physiologic range 24 hours per day, achieving all six goals of HP therapy has been a challenge, especially in patients with moderately severe to severe deficiency of PTH. Furthermore, given that active vitamin D and calcium may cause paradoxical long-term morbidity and mortality, replacing the missing hormone in HP patients has long been desired. In 1996, Winer et al established the experimental basis for using biologically active PTH(1-34) to treat HP (*Winer 1996*). Since then, twice daily administration has been shown to achieve better calcemic control than daily, and continuous infusion has been shown to achieve better control than twice daily (*Winer 1998*, *Winer 2008*, *Winer 2012*). In addition to normalizing sCa, sP, and serum magnesium (sMg), PTH by continuous infusion has also demonstrated less sCa fluctuations, a reduction in urine calcium (uCa), and normalized bone turnover compared to twice daily PTH(1-34) administration, despite a 65% lower dose of infused vs twice daily (BID) PTH(1-34) (*Winer 2012*). While intermittent PTH administration results in high hormone fluctuations, with an initial supraphysiological PTH level (high C_{max}) followed by a rapid decline to subtherapeutic levels, continuous infusion maintains PTH levels in the physiological range throughout the day.

Although PTH(1-34) is currently only approved for osteoporosis, these studies provided proof of concept for its use in HP.

Recombinant PTH(1-84) (Natpara) was approved as an adjunct to active vitamin D and calcium by the Food and Drug Administration (FDA) in 2015 (*BLA #125511 2015*) using PTH to treat HP. In its Advisory Meeting Briefing Document, the FDA noted that "This [lack of control of urinary calcium excretion] is primarily due to the short half-life (~ 3 hours) of Natpara, which results in PTH concentrations returning to baseline by 10-12 hours", and also noted that Natpara did not reduce the clinical episodes of either hypocalcemia or hypercalcemia compared to placebo plus SOC (*Briefing Document 2014*, *Khurana 2018*). Using a calcium homeostasis systems pharmacology model, the FDA simulated effects following 100 µg daily or twice daily dosing of 50 µg and compared these regimens against a theoretical slow-release model. It concluded that PTH replacement therapy requires a physiologic profile, specifically a dosing regimen that is either more frequent than daily dosing or daily dosing with a slow-release formulation that achieves an infusion-like exposure within the physiological normal range, both of which the model predicted would decrease renal calcium excretion (*Khurana 2018*, Figure 1). In April 2017, once-daily SC administration of recombinant PTH(1-84) (Natpar) was approved in Europe as a new therapy and recommended for adult patients with HP who cannot be well controlled on conventional therapy alone (*CHMP 2017*). However, CHMP noted that this treatment has not demonstrated the ability to reduce the incidence of hypocalcemia, hypercalcemia, or hypercalciuria relative to the conventional therapy of oral calcium and active vitamin D analogues, due to its relatively short half-life of ~3 hours (*CHMP 2017*).

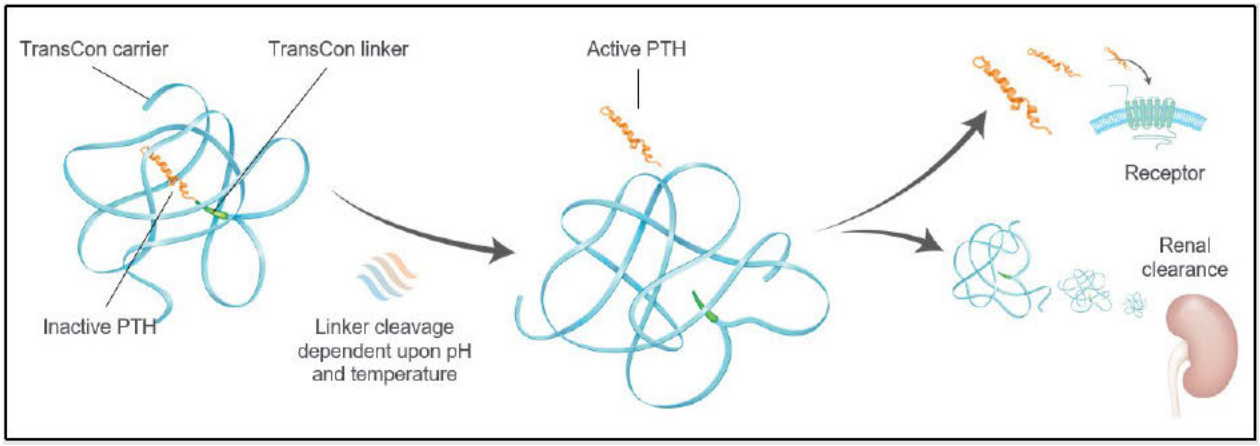
TransCon PTH (drug substance) is PTH(1-34) transiently conjugated to a branched 40 kDa methoxypolyethylene glycol (mPEG) moiety through a proprietary TransCon Linker as illustrated below:

Figure 1: Structure of TransCon PTH Drug Substance

As a consequence of attaching the branched 40 kDa (2x20 kDa) mPEG to PTH(1-34), TransCon PTH is essentially inactive and thus a prodrug. The TransCon Linker, and hence also TransCon PTH drug substance, is stable under the storage conditions used. The release of PTH(1-34) from the mPEG-linker moiety in TransCon PTH results from an auto-cleavage reaction, the 1st-order kinetics of which are controlled by physiologic pH and temperature.

After subcutaneous injection, the TransCon PTH prodrug enters the bloodstream where the inert mPEG acts as a carrier, extending PTH(1-34) circulation time in the body through a shielding effect that minimizes renal excretion and receptor binding (Figure 2). The auto-cleavage reaction is initiated at the end of the linker attached to the PTH, releasing active PTH with 1st order kinetics with a half-life of ~60 hours. The transient linkage allows TransCon PTH to fit the definition of a Type IIB prodrug (*Wu 2007*).

Figure 2: Schematic of TransCon PTH and the Release of PTH



5.2. RELEVANT FINDINGS FROM NONCLINICAL STUDIES

Please refer to the current version of the TransCon PTH Investigator's Brochure for a full discussion of nonclinical data.

A comprehensive nonclinical development program has been conducted for TransCon PTH to support clinical development. The testing strategy involved a range of in silico, in vitro and in vivo studies in Sprague Dawley rats, cynomolgus monkeys, and New Zealand White rabbits to characterize the PK, TK, PD, and safety profile of TransCon PTH. Bioanalytical assays, including immunogenicity assays were developed and validated according to relevant guidelines.

In vivo safety assessment was based on standard toxicological endpoints and assessment of bone turnover markers, peripheral quantitative computed tomography (pQCT), dual energy X-ray absorptiometry (DXA), and histomorphometry.

The pharmacological effect of TransCon PTH was demonstrated in single-dose PK/PD and in repeat-dose toxicity studies in rats, monkeys, and rabbits. The pharmacological effect was further confirmed in thyroparathyroidectomized (TPTx) rats, a disease model for HP.

In repeat-dose toxicity studies the no-observed-adverse-effect level (NOAEL) for subcutaneous daily administrations of TransCon PTH for up to 26 weeks was 10 µg PTH(1-34)/kg in rats and 0.5 µg PTH(1-34)/kg in monkeys. The adverse findings considered related to TransCon PTH were all considered exaggerated pharmacological effects of continuous administration of PTH resulting in sustained hypercalcemia. TransCon PTH did not induce any adverse effects on the central nervous, pulmonary, or cardiovascular system, and was not considered genotoxic as assessed in specific genotoxicity studies. Furthermore, the reproductive and developmental toxicity studies conducted so far have not identified any adverse effects on embryofetal development or fertility.

The nonclinical data are provided in further detail in the Investigator's Brochure.

5.3. CLINICAL EXPERIENCE

A Phase 1 clinical trial [a randomized, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) trial to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of TransCon PTH in healthy adult subjects] conducted under GCP, IEC, and Declaration of Helsinki guidelines has been completed.

A total of 132 male and female normal healthy subjects were randomized and received study treatment; 69 subjects in SAD cohorts (56 received TransCon PTH and 13 placebo) and 63 subjects in MAD cohorts (50 received TransCon PTH and 13 placebo).

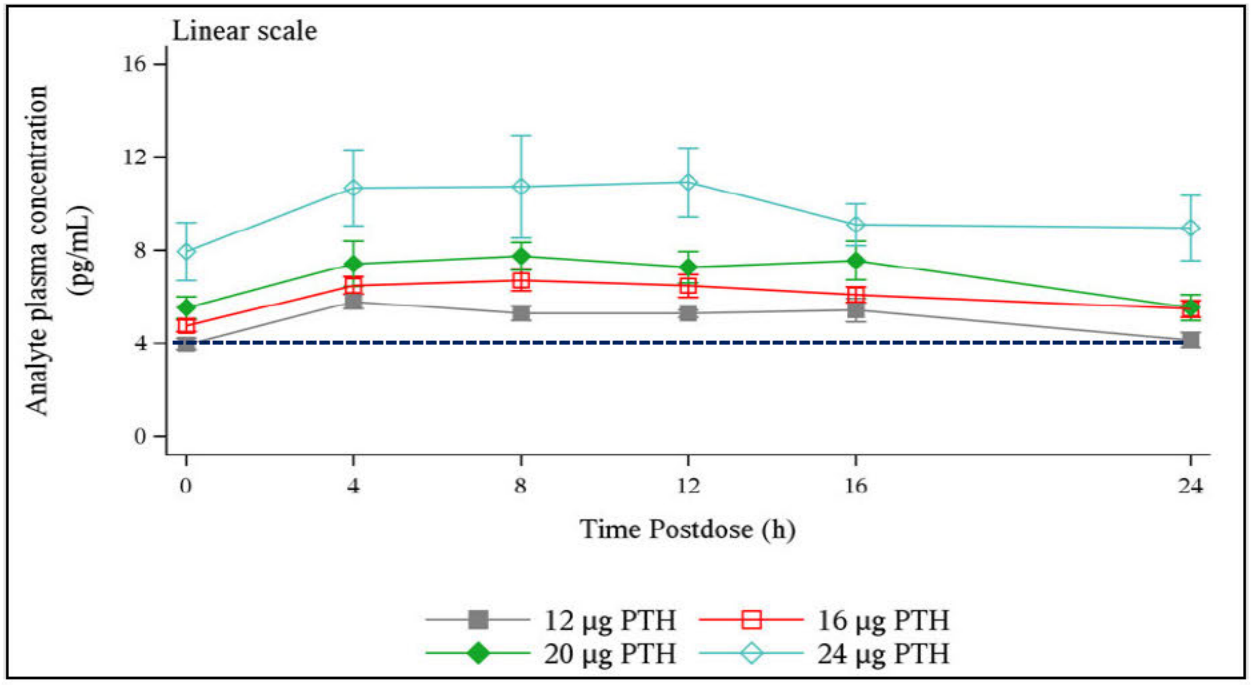
Cohorts of 10 subjects each (8 on TransCon PTH and 2 on placebo) were sequentially randomized to receive an ascending single dose of TransCon PTH in 7 SAD cohorts [3.5, 12, 32, 48, 72, 100, and 124 µg/day PTH] or an ascending daily dose of TransCon PTH for 10 days in 6 MAD cohorts [3.5, 7.0, 12, 16, 20, and 24 µg/day PTH].

The primary goal of the trial was to identify the clinically effective dose range for the Phase 2 clinical trial (based on change in albumin-adjusted sCa from baseline), the effect of treatment on the fractional excretion of calcium (FECa), and to assess the PK profile, safety, tolerability, and immunogenicity of TransCon PTH.

In healthy volunteers in SAD cohorts, TransCon PTH demonstrated dose-dependent increases in Free PTH, corresponding to the sum of active Free PTH [intact Free PTH(1-34)] and the main metabolite Free PTH(1-33) in the calculated normal range, which correlated with dose-dependent increases in albumin-adjusted serum calcium and suppression of intact PTH(1-84) at all single doses of ≥32 µg. Despite moderate hypercalcemia over 3 days in the cohorts receiving single doses of TransCon ≥100 µg PTH, at the time of greatest serum calcium (mean ±SD of 10.3±0.23 to 10.97±0.56 mg/dL on Day 2), the urine FECa remained well-controlled below the ULN of the normal range (2%), demonstrating that active PTH within the normal range continuously over 24 hours can enhance the renal handling of calcium. The data from the MAD cohorts is summarized below.

Figure 3 shows a dose-dependent increase in Free PTH corresponding to the sum of active Free PTH [intact Free PTH(1-34)] and the main metabolite Free PTH(1-33) ; with a half-life of ~60 hours, resulting in an infusion-like profile at approximate steady-state (after the 10th daily dose), with a low peak-to-trough ratio of ~1.27 to 1.55 over 24 hours. The 1st MAD dose to significantly increase albumin-adjusted serum calcium (12 µg/day) resulted in a sustained, infusion-like Free PTH level at the low end of the calculated normal range. The normal physiologic range for intact PTH(1-84) is 10-65 pg/mL; as PTH(1-34) and PTH(1-33) comprise about 40% of the molecular mass of the intact hormone, the calculated normal range is about 4-26 pg/mL.

Figure 3: Arithmetic Mean Plasma Concentrations of Free PTH on Day 10



Note: Negative SE bars less than 0 are shown as 0

Figure 4 presents albumin-adjusted serum calcium result for the MAD cohorts dosed with 3.5 to 24 µg PTH/day for 10 days. The MAD cohorts demonstrated a sustained, dose-dependent increase in albumin-adjusted serum calcium over 10 days, which (as predicted by the long half-life) was maximal on Day 11 for doses ≥16 µg/day, and did not return to baseline for 3-4 days after the final dose, as shown below.

Figure 4: Albumin-Adjusted Serum Calcium: MAD Cohorts

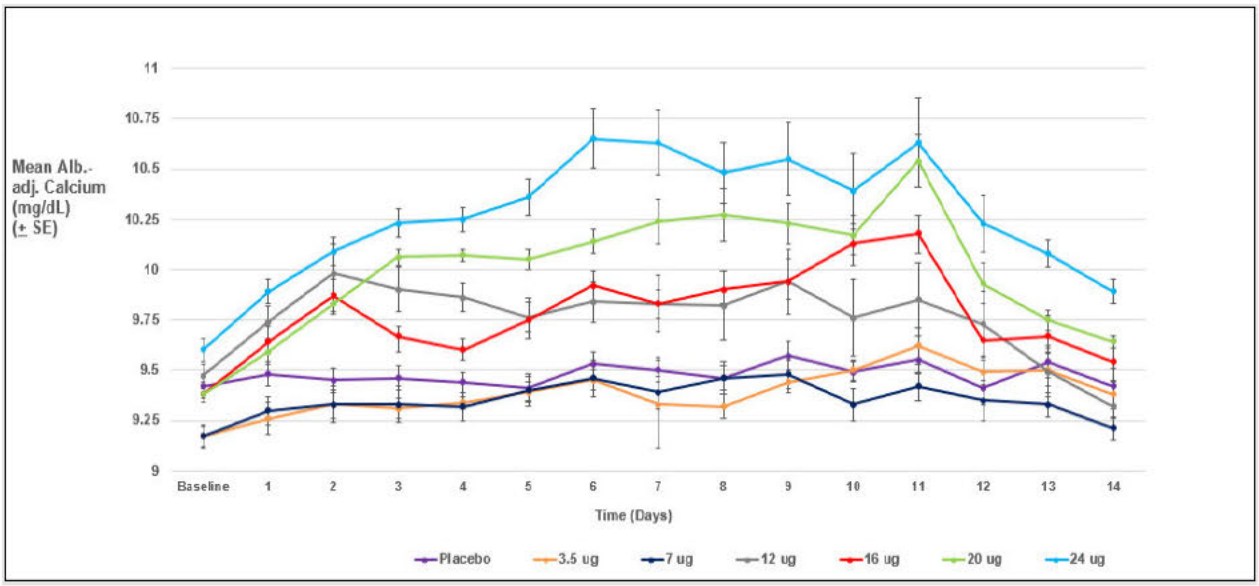
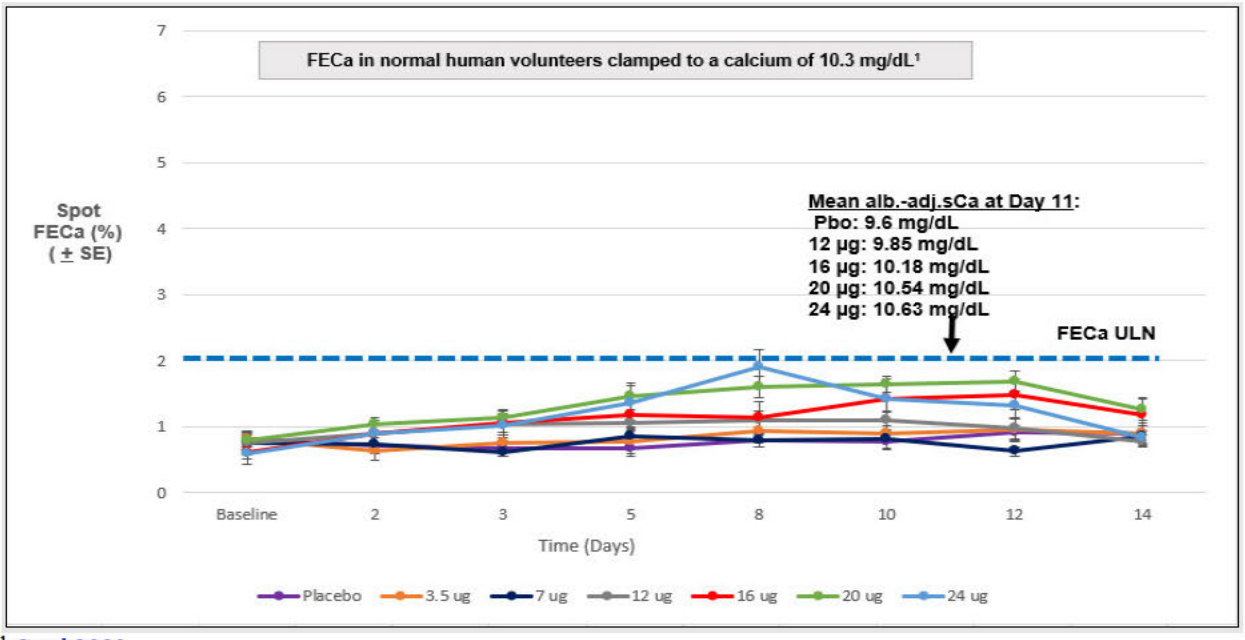


Figure 5 presents spot FECa for subjects in the MAD cohorts. Overall, in the MAD cohorts, mean spot FECa remained stable over the study. Despite the moderate hypercalcemia in the cohorts receiving doses of TransCon ≥20 µg PTH/day, at the time of greatest serum calcium (~10.5 to 11.2 mg/dL) on Day 11, the urine FECa remained well-controlled below the ULN of the normal range (2%), demonstrating that active PTH within the normal range continuously over 24 hours can enhance the renal handling of calcium.

This contrasts with the substantial increase in FECa (to ~6% to 7%), reported for NHVs "clamped" with IV calcium to a serum calcium of 10.3 mg/dL (shown in grey box in Figure 5) since the increase in serum calcium suppressed their endogenous PTH, resulting in renal calcium wasting (*Syed 2001*).

Figure 5: Spot Fractional Excretion of Calcium: MAD Cohorts

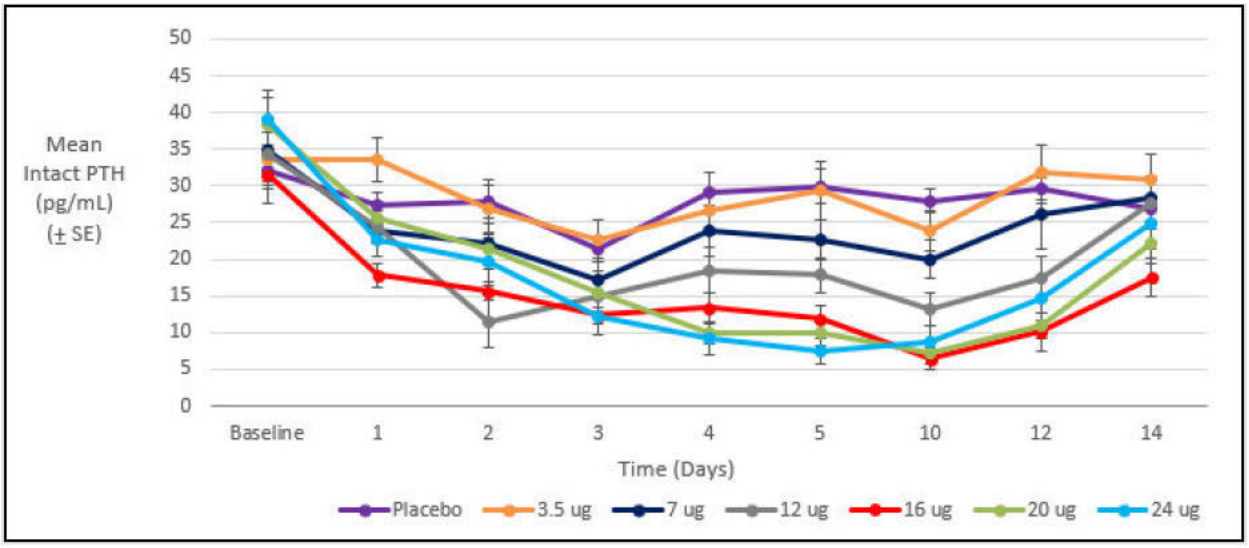


[1] *Syed 2001*

Figure 6 presents Intact PTH (1-84) for subjects in the MAD cohorts.

Intact PTH(1-84) decreased in a dose-dependent manner for each treatment group. Daily doses of TransCon PTH ≥16 µg PTH/day appeared to completely suppress endogenous PTH(1-84) to ≤10 pg/mL (the detection limit), likely due to the increased serum calcium in these cohorts.

Figure 6: Absolute Intact PTH(1-84): MAD Cohorts



[redacted]

TransCon PTH was generally well tolerated across the clinical dose range proposed for the Phase 2 clinical trial. There were no drug-related serious or severe adverse events (AEs).

No injection site reactions (ISRs) were seen in the trial. Transient asymptomatic erythema/hyperemia at injection sites was observed for subjects in both the SAD and MAD cohorts, especially at higher doses. None were captured as AEs, as the erythema was not associated with any symptoms and did not decrease dosing compliance; the asymptomatic erythema was attributed to PTH-mediated vasodilation from Free PTH released in the skin and was increased in frequency after higher doses.

For the SAD cohorts, the maximum tolerated dose (MTD) was 124 µg PTH due to asymptomatic hypercalcemia seen in the SAD 7 cohort (124 µg PTH) resulting from pharmacodynamic effects of PTH in these normal subjects, with no DLT (dose-limiting toxicity) seen.

For the MAD cohorts, the top dose of 24 µg PTH/day was associated with vasodilatory symptoms felt to represent DLT in 7 female subjects (5 on PTH and 2 on placebo), but not in male subjects, thus the MTD was 20 µg PTH/day.

Since participants were all healthy volunteers with normal baseline calcium levels, it is possible that higher doses of TransCon PTH may be well tolerated and effective in patients with HP.

In the MAD cohorts, no increase in P1NP or BSAP (bone formation markers) was observed, suggesting that by producing a flat-infusion-like profile of TransCon PTH within the calculated normal range the study drug is not anabolic. TransCon PTH modestly increased CTx but less than that seen in published data with short-acting PTH (*Rubin 2016*) and did not show a meaningful increase in NTx (bone resorption markers). These data are similar to published literature illustrating the effects of continuous PTH administration (*Horwitz 2011*, *Winer 2012*, *Winer 2014*).

In summary, TransCon PTH demonstrated a potent serum calcemic and renal calcium reabsorption effect in normal subjects, predicting control of both serum calcium (sCA) and urine calcium (uCa) in patients with HP. The effect of TransCon PTH on bone formation markers was consistent with results reported for continuous infusion of PTH(1-34) (*Horwitz 2011*, *Winer 2012*, *Winer 2014*) and lacked an anabolic effect.

Phase 1 data support the target product profile of TransCon PTH as a replacement therapy for HP patients, providing physiological levels of PTH 24 hours per day, and supports further advancement of TransCon PTH into Phase 2 clinical development.

5.4. TRIAL RATIONALE

A NIH study with once-daily SC administration of PTH(1-34) maintained the mean sCa level within the normal range over a 24-hour period and reduced uCa excretion (*Winer 1996*). Another study in adults demonstrated that twice daily PTH(1–34), at a significantly lower daily dose, provides improved metabolic control compared with once-daily PTH(1–34) therapy (*Winer 1998*). Long term effect of PTH(1–34) was further studied in patients with HP of various etiologies. The study demonstrated that long-term twice daily PTH administration maintained mean sCa within or just below the normal range over a 3-year period with concurrent normalization of mean uCa excretion (*Winer 2003*). Subsequently, a study of continuous PTH(1-34) delivery, by insulin pump, compared with twice daily SC injection in adult HP patients, showed that continuous exposure to PTH was superior in maintaining normal levels of sCa, sP and serum magnesium (sMg), normalizing uCa excretion, and restored bone turnover to normal levels while avoiding the anabolic overstimulation from daily or twice daily injection (*Winer 2012*). In addition, pump delivery led to a 65% reduction in the PTH(1-34) dose needed to maintain normal sCa levels in the HP patients. The study also hypothesized that pump delivery of PTH(1-34) would provide more physiological control of serum and urine calcium (compared with conventional treatment or intermittent PTH delivery), would reduce symptoms of hypoparathyroidism, improve quality of life, and lower the long-term risk of renal damage, without adverse effect on bone (*Winer 2012*). Similar benefits of continuous infusion of PTH(1-34) vs. twice-daily injections was demonstrated in children with HP (*Winer 2014*).

Recombinant PTH(1-84) (Natpara) was approved as an adjunct to active vitamin D and calcium by the Food and Drug Administration (FDA) in 2015 and by the Committee for Medicinal Products for Human Use (CHMP) in 2017 to treat HP. But in the Advisory Committee Natpara Briefing Document, the FDA also concluded that due to its short half-life (~ 3 hours), PTH concentrations returns to baseline by 10-12 hours and there is a lack of control of urinary calcium excretion. In addition, Natpara did not reduce the clinical episodes of either hypocalcemia or hypercalcemia compared to placebo plus SOC (*Briefing Document 2014*). FDA recently published these data (*Khurana 2018*). Similar comments were made by CHMP (*CHMP 2017*).

In comparison to short-lived PTH molecules that show supraphysiological PTH levels at T_{max} followed by a rapid decline to undetectable levels after 10-12 hours, TransCon PTH is designed for sustained-release of PTH with a $T_{½}$ of ~ 60 hours, ensuring a stable systemic concentration of the hormone with a flat, infusion-like profile within the physiological normal concentration range. The ability of TransCon PTH to maintain circulating PTH levels in the normal range has been confirmed in the non-IND Phase 1 clinical trial (TransCon PTH CT-103), as well as a lack of the anabolic effect seen with short-lived PTH molecules. Due to the well characterized correlation between PK and PD of PTH(1-34) established in subjects with and without intact parathyroid function, and the similarity of response in both groups, the Phase 1 clinical trial is considered adequate to start Phase 2 clinical trial.

5.5. SUMMARY OF POTENTIAL RISKS AND BENEFITS

5.5.1. Potential Risks

There were no significant risks identified in the Phase 1 clinical trial besides vasodilatory symptoms (such as headache, tachycardia/palpitations, dizziness, and syncope) seen in the top MAD cohort (24 µg PTH/day) in both active and placebo-treated subjects, which has also been seen with approved PTH compounds. Asymptomatic transient erythema at injection sites, especially at higher doses, was also observed. These symptoms/signs are known to be associated with all PTH therapies where they are usually transient in nature and tend to resolve with continued dosing. The vasodilatory effects can be managed by dosing at bedtime, while reclining.

The following risks have been seen in either the TransCon PTH Phase 1 volunteers or have been reported for approved PTH medications, and thus considered to be potential risks for TransCon PTH:

- Hypercalcemia
- Injection site erythema
- Orthostatic hypotension/presyncope/syncope/dizziness/tachycardia (palpitations)
- Headache
- Fatigue
- Nausea
- Osteosarcoma

Please refer to the current version of the TransCon PTH Investigator's Brochure for further details.

During the Blinded Treatment Period, there is an increased risk of hypercalcemia due to the requirement of subjects to remain on a fixed dose of study drug. This increased risk is limited to the brief period of time between achieving steady-state (9-11 days after Visit 1) and Visit 3, when TransCon PTH dose reduction can occur. Additionally, this risk can be managed in most situations by reducing or stopping SOC.

During the reduction in SOC following initiation of study drug at Visit 1 (and Visit 3 for those on active vitamin D at Visit 3), there is a risk of hypocalcemia. However, the following have been included in the protocol to limit the extent of this risk:

- Step-wise decreases of SOC occurring only after sCa levels are confirmed to be within appropriate pre-defined ranges, as per Appendix 1
- Returning subjects with symptomatic hypocalcemia to their previous SOC dose, as per Appendix 1
- Allowing subjects who experience hypocalcemic symptoms during this period (and throughout the trial) to use rescue doses of SOC

5.5.2. Potential Benefits

In healthy volunteers, an infusion-like profile of Free PTH PK translated into a predicted, sustained dose-dependent PD response, suggesting the ability to titrate patients with HP into the normal calcemic range, consistent with preclinical data. TransCon PTH demonstrated a potent serum calcemic and renal calcium reabsorption effect, predicting control of both serum calcium (sCA) and urine calcium (uCa) in normal healthy subjects.

6. OBJECTIVES

6.1. 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

6.2. SECONDARY OBJECTIVES

- 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

6.3. 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

7. TRIAL DESIGN

7.1. OVERALL TRIAL DESIGN AND PLAN

The double-blind, placebo-controlled, parallel group treatment period of this trial is expected to enroll approximately 40 subjects from up to approximately 40 sites worldwide.

Subjects are randomized into 4 treatment groups (1:1:1:1):

- TransCon PTH 15 µg/day*
- TransCon PTH 18 µg/day
- TransCon PTH 21 µg/day
- Placebo for TransCon PTH (excipients solution)

**Dose of TransCon PTH refers to dose of PTH(1-34) administered*

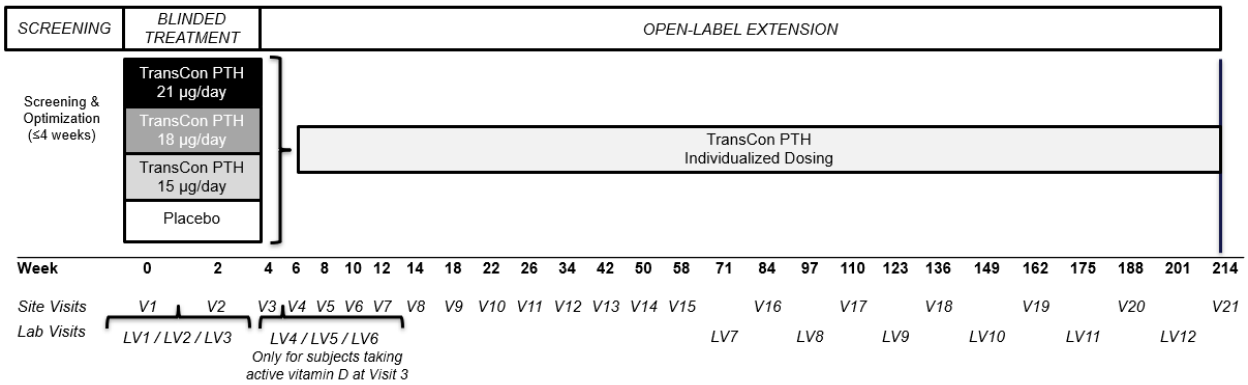
To maintain blinding, the placebo group will be sub-randomized into 3 groups (1:1:1) to mimic doses of 15, 18, and 21 µg/day.

Subjects are to remain on the same dose of study drug throughout the 4-week Blinded Treatment Period. Following successful completion of the Blinded Treatment Period, subjects enter the open-label Extension Period at which time all subjects will receive TransCon PTH.

Each subject's participation is expected to last up to 214weeks plus a screening period of up to approximately 4 weeks.

- Screening Period (supplement optimization): Up to approximately 4 weeks
- Blinded Treatment Period (study drug stable with 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

Study Design



7.1.1. Measures Taken to Maximize Study Integrity and Minimize Bias

Subject visits should be performed in the *morning* at approximately the same time of day. Also, assessments should be performed in a similar fashion at each visit. Additionally, all efforts will be made to keep missing data to a minimum, including the following:

- Investigators will be trained about the importance of subject retention
- Investigators will be instructed to encourage subjects to complete all Blinded Treatment Period visits, including any subjects who discontinue the study drug early
- The Informed Consent Form (ICF) will include a statement educating subjects about the scientific importance of their data even if the subject discontinues study drug early
- Special efforts will be made to provide assistance to subjects/families who might discontinue due to travel or cost barriers, such as offers of transportation to the clinic
- All study visits have visit windows to allow flexibility for clinic attendance (see Schedule of Events, Appendix 4)
- Every effort will be made to maintain contact with subjects or other family members
- The key components of the primary endpoint, sCa and urine calcium levels, are based on objective laboratory tests
- To minimize individual investigator bias, Appendices 1-3 provide standardized guidelines for withdrawal of SOC and titration of TransCon PTH based on objective laboratory tests and subjects' experience of hypo- or hypercalcemic symptoms. Additionally, the Medical Monitor/Medical Expert will perform timely review of albumin-adjusted serum calcium and/or ionized serum calcium results and prescribed dosing to confirm investigator compliance with Appendices 1-3.

7.2. TRIAL SITES

The trial will be conducted at up to approximately 40 sites worldwide. All sites are specialized treatment centers in the management of adult HP.

8. SUBJECT POPULATION

Approximately forty (40) male and female adults with either postsurgical HP or autoimmune, genetic, or idiopathic HP for at least 26 weeks, treated with a stable dose (requiring <3 rescue doses of active D/calcium per week) of ≥0.25 µg BID active vitamin D (or ≥1.0 µg/day of alfacalcidol) and ≥400 mg BID calcium for at least 12 weeks prior to Screening may enter the Screening Period.

8.1. TRIAL ENTRY CRITERIA

8.1.1. Inclusion Criteria

1. Males and females aged ≥18 years
2. Subjects with postsurgical chronic HP or auto-immune, genetic, or idiopathic HP for at least 26 weeks. Diagnosis of HP is established based on hypocalcemia in the setting of inappropriately low serum parathyroid hormone (PTH) levels.
3. On a stable dose* for at least 12 weeks (*US only:* or 4 weeks if on Natpara as of September 2019) prior to Screening of:
   - ≥0.25 µg BID of calcitriol (active vitamin D) or ≥0.5 µg BID or ≥1.0 µg daily of alfacalcidol (active vitamin D) **and**
   - ≥400 mg BID calcium citrate or carbonate
   - If subject has a history of hypercalcemia on such doses, subject may be taking <0.25 µg BID of calcitriol, <0.5 µg BID or < 1.0 µg daily of alfacalcidol, or <400 mg BID of calcium citrate or carbonate, with approval of Medical Monitor/Medical Expert
     **Does not preclude occasional (<3/week) rescue doses of active vitamin D and/or calcium for symptomatic hypocalcemia*
4. Optimization of supplements prior to randomization to achieve the target levels of:
   - 25(OH) vitamin D levels of 30-70 ng/mL (75-175 pmol/mL) and
   - Magnesium level within the normal range* and
   - Albumin-adjusted or ionized serum calcium (sCa) level in the lower half of the normal range
     *If subject has a history of inability to be successfully managed within the normal range for magnesium level, a level slightly below the normal range is acceptable with approval of the Medical Monitor/Medical Expert
5. BMI 17-40 kg/m^2 at Visit 1
6. If ≤25 years of age, radiological evidence of epiphyseal closure based on x-ray of non-dominant wrist and hand
7. eGFR >30 mL/min/1.73m^2 during Screening
8. Thyroid-stimulating hormone (TSH) within normal laboratory limits within the 12 weeks prior to Visit 1; if on suppressive therapy for thyroid cancer, TSH level must be ≥0.2 µIU/mL

9. If treated with thyroid hormone replacement therapy, the dose must be stable for at least 12 weeks prior to Visit 1
10. Able to perform daily subcutaneous self-injections of study drug (or have a designee perform injection) via a pre-filled injection pen
11. Written, signed, informed consent of the subject

8.1.2. Exclusion Criteria

1. Known activating mutation in the calcium-sensing receptor (CaSR) gene
2. Impaired responsiveness to PTH (pseudohypoparathyroidism) which is characterized as PTH-resistance, with elevated PTH levels in the setting of hypocalcemia
3. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HP, such as active hyperthyroidism; Paget's disease; hypomagnesemia; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus; severe and chronic cardiac, liver, or renal disease; Cushing syndrome; rheumatoid arthritis; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer or basal cell skin cancer); parathyroid carcinoma within 5 years prior to Screening; acromegaly; multiple endocrine neoplasia types 1 and 2
4. Use of loop diuretics, phosphate binders (other than calcium carbonate/calcium citrate), digoxin, lithium, methotrexate, or systemic corticosteroids (other than replacement therapy)
5. Use of thiazide diuretic within 4 weeks prior to the Screening 24-hour urine collection or the first dose adjustment of SOC during Screening
6. Use of PTH-like drugs (whether commercially available or through participation in an investigational trial) including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein within 12 weeks (*US only:* 5 weeks) prior to Visit 1
7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (> 0.5 mg/day), strontium, or cinacalcet hydrochloride within 12 weeks prior to Visit 1
8. Use of bisphosphonates (oral or IV) or denosumab within 2 years prior to Visit 1
9. Non-hypocalcemic seizure disorder with a history of a seizure within 26 weeks prior to Visit 1

   NOTE: History of seizures that occur in the setting of hypocalcemia is not exclusionary
10. Increased risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, hereditary disorders predisposing to osteosarcoma, or with a prior history of substantial external beam or implant radiation therapy involving the skeleton

11. Pregnant or lactating women.

    NOTE: Highly effective contraception (see Appendix 7) is required for sexually active women of childbearing potential during the trial and for 2 weeks after the last dose of study drug, and pregnancy testing will be performed throughout the trial. Sexually active women of childbearing potential who are unwilling to use highly effective contraception are excluded from the trial.

12. Diagnosis of drug or alcohol dependence within 3 years prior to Visit 1
13. Disease processes that may adversely affect gastrointestinal absorption including but not limited to short bowel syndrome, bowel resection, gastric bypass, tropical sprue, active celiac disease, active ulcerative colitis, gastroparesis, AIRE gene mutations with malabsorption, and active Crohn's disease
14. Chronic or severe cardiac disease within 26 weeks prior to Visit 1 including but not limited to congestive heart failure, myocardial infarction, QTcF >430 msec (males) or >450 msec (females), severe or uncontrolled arrhythmias, bradycardia (resting heart rate <50 beats/minute), symptomatic hypotension, systolic BP <80 mm Hg or diastolic <40 mm Hg, or poorly controlled hypertension (systolic BP >150 mm Hg or diastolic >95 mm Hg)
15. Cerebrovascular accident within 5 years prior to Visit 1
16. History of renal colic or acute gout within 52 weeks prior to Visit 1
17. Any disease or condition that, in the opinion of the investigator, may make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the investigational product or procedures, including treated malignancies that are likely to recur within the approximate 1-year duration of the trial
18. Known allergy or sensitivity to PTH or any of the excipients [metacresol, mannitol, succinic acid, NaOH/(HCl)]
19. Participation in another clinical trial in which receipt of investigational drug or device occurred within 8 weeks (or at least 5.5 times the half-life of the investigational drug) prior to Visit 1
20. Likely to be non-compliant with respect to trial conduct
21. Any other reason that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule

8.2. PREMATURE SUBJECT WITHDRAWAL

Premature subject withdrawal occurs when an enrolled subject ceases participation in the trial, regardless of the circumstances, prior to the expected completion of the trial.

In the case of premature subject withdrawal, the investigator should schedule an End of Study (EOS) Visit to collect data, particularly AE follow-up data (if applicable), and to collect blood for final laboratory evaluations. This visit should contain all appropriate assessments and the reason(s) for trial discontinuation should be documented. See Section 10.1.7.

The investigator/site staff should make every attempt to contact the subject via phone to arrange the appropriate follow-up assessment(s) for such subjects.

8.2.1. Study Drug Discontinuation and Subject Withdrawal

8.2.1.1. Study Drug Discontinuation During Blinded Treatment Period

Unless informed consent is withdrawn*, subjects who permanently discontinue study drug during the Blinded Treatment Period should:

- Attend all subsequent visits within the Blinded Treatment Period
- Complete an EOS Visit in place of Visit 3
- Not continue into the Extension Period

  ** If the subject is not willing to attend all subsequent trial visits within the Blinded Treatment Period, this should be considered a withdrawal of consent and an EOS Visit should be scheduled.*

See Section 10.1.7 for details on End of Study Visit.

8.2.1.2. Study Drug Discontinuation During Extension Period

Subjects who permanently discontinue study drug during the Extension Period should be withdrawn from the trial and an EOS Visit should be scheduled immediately.

See Section 10.1.7 for details on End of Study Visit.

8.3. SUBJECT REPLACEMENT CRITERIA

Subjects who terminate early are not expected to be replaced.

9. TREATMENTS

9.1. INVESTIGATIONAL PRODUCT

TransCon PTH drug product is supplied as a clear solution containing TransCon PTH with a nominal PTH(1-34) content of 0.3 mg/mL in a pre-filled pen intended for SC injection. Excipients include metacresol, mannitol, succinic acid, and NaOH/(HCl). The pens are stored in the refrigerator until first use; the pens are stable at room temperature for 14 days. Refer to the Investigator's Brochure for details on the composition and characteristics of TransCon PTH and the Pharmacy Manual for complete details on storage and handling.

9.1.1. Labeling

All study drug will be labeled according to Good Manufacturing Practice and local regulatory requirements. The labels are trial-specific and carry unique identification pack numbers. Subjects will be provided with dosing and storage instructions.

9.1.2. Accountability, Storage, and Dispensing

Investigator or delegated site staff will be responsible for study drug, ancillary supplies, and associated procedures, exercising accepted medical and pharmaceutical practices.

Study drug must be kept in a locked, temperature-controlled, and temperature-monitored area with access limited to designated trial staff and stored according to its labeling. Investigator or dedicated trial staff must evaluate the storage temperature and inform Ascendis Pharma immediately if study drug has been stored outside the specified conditions on the label.

The trial will use an internet-based interactive web response system (IWRS) as source to capture drug inventory and accountability data, including receipt of drug inventory and supplies by the site, treatment assignment for each subject, distribution to subjects, return to the site from subjects, and return to the Sponsor (or destruction with the Sponsor's approval). The IWRS system complies with all applicable regulatory requirements for record keeping and record retention in clinical trials [21 CFR Part 11 and ICH E6 (R2) GCP].

Investigator or delegated site staff will be responsible for accountability and reconciliation of study drug.

Study drug may be shipped from site or depot to subjects using an Ascendis-approved courier service. In such cases, accountability for study drug remains the responsibility of the principal investigator until subject has confirmed receipt of study drug. Documentation of study drug shipments must be maintained by the site and include, at minimum, the following: date of shipment from site, kit numbers shipped, date of receipt by subject, and temperature monitoring during shipment.

Site staff will provide training on proper storage and study drug administration to each subject at Visit 1. This training will include a review of the Instructions for Use (IFU) and on-site administration of the first dose of study drug by the subject. A copy of the IFU will be provided to the subject for reference at home.

NOTE: Under no circumstances will the investigator allow study drugs to be used other than as directed by this protocol.

See Pharmacy Manual and IFU for further details.

9.2. TREATMENT ADMINISTERED

The TransCon PTH delivery system consists of a multi-use cartridge integrated into a modified Ypsomed Uno Pen Fix using 31G, 5 mm needles. The cartridge contains a liquid formulation of TransCon PTH or placebo for TransCon PTH with a fill volume sufficient for 14 doses.

Each study drug administration is in a volume ≤100 µL and is to be self-administered (following training by study staff) to the upper or lower abdomen or anterior thigh. There are a total of 4 possible injection areas: right abdomen, left abdomen, right anterior thigh, and left anterior thigh. Subjects should be instructed to rotate injection sites. Refer to the IFU for complete instructions on administration.

In the Blinded Treatment Period, both TransCon PTH and placebo for TransCon PTH are provided in the mid-dose pen allowing for doses of 15, 18, and 21 µg/day.

In the Extension Period, three pen presentations are available for the open-label TransCon PTH allowing for an expected dose range of 6-60 µg (6, 9, and 12 µg; 15, 18, and 21 µg; and 24, 27 and 30 µg, respectively).

In addition to the study drug, subjects should continue to take their stable dose of magnesium and vitamin D3, as well as active vitamin D and/or calcium supplements with dose adjustments as per Section 9.7.

9.3. SELECTION OF TRIAL DOSES

TransCon PTH is an inactive prodrug. The Phase 1 clinical trial with TransCon PTH demonstrated that a dose range of 12-20 µg/day was identified as both active and well-tolerated with 20 µg identified as the MTD in healthy volunteers. Although 12 µg daily was the first dose to significantly increase albumin-adjusted calcium in NHVs, as they must first suppress their endogenous PTH, it is possible that somewhat lower doses might be optimal for some patients with HP, explaining the lower doses of 9 and 6 µg in the low-dose pen. Although doses >20 µg daily were not optimally tolerated in healthy adult women with normal calcium levels, it is possible that doses >20 µg daily may be both tolerated and required for some subjects with HP, therefore the dose range for the Blinded Treatment Period will be 15, 18, and 21 µg/day, while during the Extension Period subjects will be individually titrated to an expected optimal dose of 6-60 µg PTH/day in 3 pen presentations (6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively).

9.4. TREATMENT ASSIGNMENT

9.4.1. Treatment Assignment During Blinded Treatment Period

At Visit 1, subjects will be randomized (1:1:1:1) to one of the following:

- TransCon PTH 15 µg/day
- TransCon PTH 18 µg/day
- TransCon PTH 21 µg/day
- Placebo for TransCon PTH (sub-randomized 1:1:1)
  - Mimicking dose of 15 µg/day
  - Mimicking dose of 18 µg/day
  - Mimicking dose of 21 µg/day

9.4.2. Treatment Assignment During Extension Period

At Visit 3, subjects will be assigned to open-label treatment as follows:

- **If taking active vitamin D:** Start TransCon PTH at a dose of 15 µg/day and undergo titration of SOC as performed during the 4-week Blinded Treatment Period.
- **If not taking active vitamin D:** Start TransCon PTH at the same dose of study drug taken during the Blinded Treatment Period. Exception should be made if hypo- or hypercalcemic symptoms are present at Visit 3, in which case TransCon PTH dose may be adjusted by 3 µg/day.

9.5. DOSE ADJUSTMENTS

9.5.1. Screening Period Supplement Dose Adjustments

During the Screening Period, adjustments to doses of HP-related supplements (SOC, magnesium, vitamin D) will be made to achieve the following laboratory levels:

- 25(OH) vitamin D: 30-70 ng/mL
- Magnesium: within the normal range
  - If a subject has a history of inability to be successfully managed within the normal range for magnesium level, a level slightly below the normal range is acceptable with approval of Medical Monitor/ Medical Expert.
- Albumin-adjusted or ionized sCa: within the lower half of the normal range

Supplement doses are adjusted only after initial Screening laboratory results are received. Follow-up laboratory assessment of the above values, with exception of vitamin D level, are performed approximately 3 days after every supplement dose adjustment during the Screening Period. If required, additional supplement dose adjustments, with follow-up laboratory assessments approximately 3 days later, may be performed.

If subjects fail to optimize to the target laboratory ranges within the Screening window, investigators may, with Medical Monitor/Medical Expert approval, extend the Screening Period.

Subjects who appear to already be optimized to the target laboratory ranges based on historical laboratory results within 4 weeks prior to Screening require only a single confirmatory laboratory assessment during the Screening Period.

When laboratory results are within the above optimization ranges, with at least one confirmation laboratory result, and all other entry criteria including the Screening 24-hour urine collection are met, the subject is eligible to move to the Blinded Treatment Period and be randomized following Medical Monitor/Medical Expert or designee confirmation.

9.5.2. Blinded Treatment Period (Visits 1-3; Weeks 0-4) Dose Adjustments

9.5.2.1. Study Drug Dose Adjustments During Blinded Treatment Period

Subjects remain on the same dose of study drug throughout the Blinded Treatment Period.

9.5.2.2. SOC Dose Adjustments During Blinded Treatment Period

Active vitamin D and/or calcium doses will be optimized as per Appendix 1. The investigator may adjust SOC in a different manner than as outlined in Appendix 1with prior Medical Monitor/Medical Expert approval.

SOC adjustments should be made within 48 hours of blood collection at Laboratory Visits. If at Visit 2 SOC dose adjustments are performed, follow-up laboratory assessment approximately 3 days later should be performed via an Unscheduled Laboratory Visit (ULV).

NOTE: If during the Blinded Treatment Period clinical symptoms of hypo- or hypercalcemia occur, an ULV should be scheduled to assess albumin-adjusted or ionized sCa levels to guide calcium and/or active vitamin D dose adjustments. During the Blinded Treatment Period, rescue doses of active vitamin D and/or calcium are allowable, even prior to the ULV.

9.5.3. Extension Period (Visits 3-21; Weeks 4-214) Dose Adjustments

9.5.3.1. Study Drug Dose Adjustments During Extension Period

For subjects taking active vitamin D at Visit 3, the TransCon PTH dose is titrated starting at *Visit 4* as shown in Appendix 2.

For subjects not taking active vitamin D at Visit 3, the TransCon PTH dose is titrated starting at *Visit 3* as shown in Appendix 3.

Starting at Visit 9, all subjects are expected to remain on a stable dose of TransCon PTH. However, dose adjustments should continue as needed based on sCa results and following Appendix 2 and Appendix 3.Dose range for the Extension Period is expected to be 6-360 µg/day in 3 pen presentations (6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively).

NOTE: Rescue doses of active vitamin D and/or calcium are allowable throughout the Extension Period. However, if symptoms of hypo- or hypercalcemia are persistent, the TransCon PTH dose should be adjusted at the following clinic visit (except if prior to Visit 4 for subjects taking active vitamin D at Visit 3). Due to the extended length of time between visits after Visit 9, the TransCon PTH dose may be adjusted between clinic visits. Due to the long half-life of TransCon PTH, the full effect of a dose change cannot be determined until 8 to 10 days after the dose change.

9.5.3.2. SOC Dose Adjustments During Extension Period

For subjects taking active vitamin D at Visit 3, active vitamin D and/or calcium doses will be optimized in the same manner as performed during the Blinded Treatment Period (see Appendix 1) PRIOR to adjustment of TransCon PTH dosing at Visit 4 (see Appendix 2).

Dose adjustments should continue as needed based on sCa results and following Appendix 2 and Appendix 3.

9.6. STUDY DRUG STOPPING OR CHANGE TO ADMINISTRATION

9.6.1. Required Stopping

The investigator, with Sponsor Medical Monitor/Medical Expert notification, **must** stop study drug for an individual subject at any time during the trial in the presence of the following:

- Evidence of a severe hypersensitivity to TransCon PTH
- Confirmed neutralizing anti-PTH antibodies that correlate with reduced PD response

- Suspicion of osteosarcoma (eg, persistent localized pain or occurrence of a new soft tissue mass tender to palpation that could be consistent with osteosarcoma, in association with an elevation of bone-specific alkaline phosphatase)
- Pregnancy

See Section 8.2.1 for further guidance on study drug discontinuation.

9.6.2. Possible Stopping or Change to Administration

The investigator may change the dose, and/or temporarily hold the study drug for an individual subject as per the dose titration appendices (Appendix 2 and Appendix 3).

A discussion between the investigator and medical monitor will occur to determine dose changes and/or study drug holding/stopping for the following situations:

- Persistent hypocalcemia with albumin-corrected serum calcium <8.3 mg/dL[1] for >7 days despite all of the following:
  - increases in doses of (and adherence to) study drug, calcium supplements, and active vitamin D
  - study drug dose ≥30 µg/day
- Persistent severe hypocalcemia with albumin-corrected serum calcium <7.0 mg/dL[2] for >7 days despite:
  - increases in (and adherence to) study drug, calcium supplements, and active vitamin D
  - medical intervention (e.g. intravenous calcium infusions, urgent/emergency care, hospitalization) as needed and at the discretion of the investigator
- Persistent hypercalcemia with albumin-corrected serum calcium >10.6 mg/dL[3] for >7 days despite all of the following:
  - cessation of active vitamin D and calcium supplements
  - study drug dose 6 µg/day
- Persistent severe hypercalcemia with albumin-corrected serum calcium >12.0 mg/dL[4] for >7 days despite:
  - cessation of active vitamin D and calcium supplements
  - decreases in/cessation of study drug
  - oral hydration
  - medication intervention (e.g. intravenous fluids, urgent/emergency care, hospitalization) as at the discretion of the investigator
- Persistent vasodilatory symptoms that cannot be corrected with adjustments to study drug
- Any other study-drug related severe adverse event, or serious adverse event, that warrants holding or discontinuing study drug at the discretion of the investigator and/or medical monitor

  - Thresholds for albumin-corrected serum calcium: <8.3 mg/dL (<2.07 mmol/L), or ionized calcium: <1.16 mmol/L
  - Thresholds for albumin-corrected serum calcium: <7.0 mg/dL (>1.75 mmol/L), or ionized calcium: <0.95 mmol/L
  - Thresholds for albumin-corrected serum calcium: >10.6 mg/dL (>2.64 mmol/L), or ionized calcium: >1.32 mmol/L
  - Thresholds for albumin-corrected serum calcium: >12.0 mg/dL (>3.00 mmol/L), or ionized calcium: >1.50 mmol/L

- "Non-responders" to TransCon PTH may be evaluated for discontinuation of TransCon PTH therapy. A "non-responder" to TransCon PTH is a subject taking the maximum dose of TransCon PTH 60 µg/day for at least 39 weeks, who is unable to reduce standing or as-needed doses of SOC as compared to his/her baseline requirements for conventional therapy (i.e. has symptoms and/or low serum calcium if conventional therapy is reduced below study baseline requirements). If reduction in conventional therapy remains impossible at the end of 39 weeks, the patient may discontinue TransCon PTH. The selection of a 39-week duration recognizes there may be rare instances where subjects temporarily have significantly accelerated clearance of TransCon PTH that is expected to spontaneously resolve by approximately 26-35 weeks (and thus be associated with a reduction in a subject's dose requirement of TransCon PTH).

Persistent severe hypocalcemia and persistent severe hypercalcemia (as defined above) will be reported to the regulatory authorities, based on local requirements (Section 12).

If study drug is permanently discontinued, see Section 8.2.1.

NOTE: Reinstitution of TransCon PTH treatment following any of the above events requires prior approval by the Sponsor Medical Monitor/Medical Expert.

9.7. TREATMENT COMPLIANCE

Compliance of both study drug and HP-related supplements (SOC, magnesium, vitamin D) will be assessed based on review of the daily diary and returned pens at every clinic visit.

9.8. PRIOR AND CONCOMITANT THERAPIES

Prior and concomitant therapies include all prescription or over-the-counter medications, vitamins and herbal/nutritional supplements taken within 26 weeks prior to Visit 1 and through the end of the trial.

9.8.1. Required HP Therapies

Prior to Screening, subjects must be taking stable doses of the following SOC HP treatments for at least 12 weeks:

- ≥0.25 µg BID of calcitriol (active vitamin D) or ≥0.5 µg BID or ≥1.0 µg daily of alfacalcidol (active vitamin D) **and**
- ≥400 mg BID calcium citrate or carbonate

With approval of the Medical Monitor/Medical Expert, subjects may be on doses less than those above if there is a history of hypercalcemia on such doses.

Subjects may also be on cholecalciferol (vitamin D3) and magnesium supplements as part of their HP treatment, as long as doses are expected to remain stable throughout the trial. Subjects are to be instructed to take their HP-related supplements at approximately the same times every day throughout the trial. Subjects taking a thiazide diuretic should discontinue at least 4 weeks prior to Screening activities, including supplement dose optimization and Screening 24-hour urine collection.

9.8.2. Prohibited Therapies

The following therapies are prohibited throughout the trial:

- PTH therapies other than TransCon PTH
- Thiazide or loop diuretics
- Phosphate binders (other than calcium carbonate/calcium citrate)
- Digoxin, lithium, methotrexate
- Systemic corticosteroids (other than as replacement therapy)
- Bisphosphonates
- Denosumab

In case of any questions regarding current medication or prior therapy(ies), Sponsor Medical Monitor/Medical Expert should be contacted.

If the administration of a prohibited concomitant medication becomes necessary, participation in the trial may be discontinued prematurely for that subject, based on a decision made jointly by the Investigator and Sponsor Medical Monitor/Medical Expert.

See Section 8.1.2 Exclusion Criteria for prohibited *prior* therapies.

10. TRIAL PROCEDURES

10.1. TRIAL DURATION

Each subject's participation is expected to last up to 214 weeks plus a screening period of up to approximately 4 weeks.

- **Screening Period (supplement optimization):** Up to approximately 4 weeks
- **Blinded Treatment Period (study drug stable with 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 196 weeks of individualized dosing

10.1.1. Trial Periods and Visits

See Appendix 4 for Schedule of Events.

Following the Screening Period, each subject attends:

- Blinded Treatment Period
  - Visit 1 (Week 0, Day 1)
  - Laboratory Visit 1 (Week 0, Day 3, +1 day)
  - Laboratory Visit 2 (Week 0, Day 6, +1 day)
  - Laboratory Visit 3 (Week 1, Day 9, +1 day)
  - Visit 2 (Week 2, Day 14, ±2 days)
  - Visit 3 (Week 4, Day 28, ±2 days)
- Extension Period
  - Laboratory Visit 4 (Week 4, 3 Days Post-Visit 3, +1 day)*
  - Laboratory Visit 5 (Week 4, 6 Days Post-Visit 3, +1 day)*
  - Laboratory Visit 6 (Week 5, 9 Days Post-Visit 3, +1 day)*
  - Visit 4 (Week 6, Day 42, ±2 days)
  - Visit 5 (Week 8, Day 56, ±2 days)
  - Visit 6 (Week 10, Day 70, ±2 days)
  - Visit 7 (Week 12, Day 84, ±2 days)
  - Visit 8 (Week 14, Day 98, ±2 days)
  - Visit 9 (Week 18, Day 126, ±3 days)
  - Visit 10 (Week 22, Day 154, ±3 days)
  - Visit 11 (Week 26, Day 182, ±3 days)
  - Visit 12 (Week 34, Day 238, ±7 days)
  - Visit 13 (Week 42, Day 294, ±7 days)
  - Visit 14 (Week 50, Day 350, ±7 days)
  - Visit 15 (Week 58, Day 406, ±7 days)
  - Visit 15A (Week 66, Day 462, ±7 days)
  - Laboratory Visit 7 (Week 71, Day 497, ±14 days)
  - Visit 15B (Week 74, Day 518, ±7 days)
  - Visit 16 (Week 84, Day 588, ±14 days)
  - Visit 16A (Week 92, Day 644, ±7 days)

- Laboratory Visit 8 (Week 97, Day 679, ±14 days)
- Visit 16B (Week 100, Day 700, ±7 days)
- Visit 17 (Week 110, Day 770, ±14 days)
- Visit 17A (Week 118, Day 826, ±7 days)
- Laboratory Visit 9 (Week 123, Day 861, ±14 days)
- Visit 17B (Week 126, Day 882, ±7 days)
- Visit 18 (Week 136, Day 952, ±14 days)
- Visit 18A (Week 144, Day 1008, ±7 days)
- Laboratory Visit 10 (Week 149, Day 1043, ±14 days)
- Visit 18B (Week 152, Day 1064, ±7 days)
- Visit 19 (Week 162, Day 1134, ±14 days)
- Visit 19A (Week 170, Day 1190, ±7 days)
- Laboratory Visit 11 (Week 175, Day 1225, ±14 days)
- Visit 19B (Week 178, Day 1246, ±7 days)
- Visit 20 (Week 188, Day 1316, ±14 days)
- Visit 20A (Week 196, Day 1372, ±7 days)
- Laboratory Visit 12 (Week 201, Day 1407, ±14 days)
- Visit 20B (Week 204, Day 1428, ±7 days)
- Visit 21 (Week 214, Day 1498, ±14 days)

** Only for subjects taking active vitamin D at Visit 3*

10.1.2. Screening Period (Week -4 to -1, Day -28 to -7)

The Screening Period will last up to approximately 4 weeks during which clinical data will be collected and Screening procedures will be performed to determine eligibility and optimize subjects on their HP-related supplements prior to enrollment.

Prior to any protocol related activities, Screening procedures, or assignment of a Subject Number, informed consent will be obtained from each potential subject in accordance with GCP and regional regulatory requirements. The format and content of the ICF must be approved by the appropriate institutional review board/independent ethics committee/human research ethics committee (IRB/ERC) prior to implementation.

The following must be performed during the Screening period prior to enrollment/randomization:

1. HPES validation battery
2. Demographics review
3. Height and weight measurements
4. Vital sign measurements
5. Medical history review
6. Prior and concomitant medication review
7. Physical examination
8. 12-lead electrocardiogram (ECG)
9. Dual-energy X-ray absorptiometry (DXA) and trabecular bone score (TBS)
   - Canada Only: TBS scoring will not be performed for subjects 18 to 20 years of age
10. *Only for subjects ≤25 years old as of Visit 1:* X-ray of non-dominant wrist and hand with evidence of epiphyseal closure
11. *Only for females of childbearing potential:* Urine collection for local hCG
12. Blood collection for local laboratory assessments
13. Blood and urine collection for central laboratory assessments
14. Dietary calcium questionnaire and counseling based on results
15. Dispensing and training on daily diary
16. Optimization of vitamin D3, magnesium, active vitamin D, and/or calcium to establish target laboratory values prior to randomization (See Section 9.5.1):
    a. 25(OH) vitamin D: 30-70 ng/mL (75-175 nmol/L)
    b. Magnesium: within the normal range
       – If a subject has a history of inability to be successfully managed within the normal range for magnesium level, a level slightly below the normal range is acceptable with approval of Medical Monitor/ Medical Expert
    c. Albumin-adjusted or ionized sCa: within the lower half of the normal range*
       * *For the purpose of this trial, the normal range for albumin-adjusted sCa is 8.3-10.6 mg/dL (2.07-2.64 mmol/L) and the normal range for ionized sCa is 1.16-1.32 mmol/L*
17. 24-hour urine collection (within the week prior to Visit 1 following investigator confirmation of eligibility)

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 lower half of the normal range, as well as normalize the serum magnesium and vitamin D level. Once the laboratory results are within the above optimization ranges, a set of confirmation laboratory results should be obtained 2-7 days following previous laboratory assessment.

When confirmation laboratory results are obtained, and all other entry criteria are met, the subject is eligible to move to the Blinded Treatment Period and be randomized following Medical Monitor/Medical Expert or designee confirmation.

Subjects who fail to optimize to the target laboratory ranges within the Screening window, may, with Medical Monitor/Medical Expert approval, extend the Screening Period.

Subjects who appear to already be optimized to the target laboratory ranges based on historical laboratory results within 4 weeks prior to Screening require only a single confirmatory laboratory assessment and a 24-hour urine collection during the Screening Period.

See Section 11 for further details on procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

Subjects who sign the informed consent form but do not meet one or more eligibility criteria (including withdrawing of consent) prior to first study drug dosing will be considered screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography and screen failure details (eligibility criteria).

The decision to rescreen will be made on a case by case basis after discussion with Sponsor Medical Monitor/Medical Expert, including which screening procedures may not need repeating. Rescreened subjects should receive a new Subject Number. Documentation for rescreening must include date and reason for initial exclusion.

10.1.3. Blinded Treatment Period (Week 0 to Week 4)

During the Blinded Treatment Period, subjects are randomized into 4 treatment groups (1:1:1:1):

- TransCon PTH 15 µg/day*
- TransCon PTH 18 µg/day
- TransCon PTH 21 µg/day
- Placebo for TransCon PTH (excipients solution)

  ** Dose of TransCon PTH refers to dose of PTH(1-34) administered*

To maintain blinding, the placebo group will be sub-randomized into 3 groups (1:1:1) to mimic doses of 15, 18, and 21 µg/day.

NOTE: Subjects remain on the same dose of study drug throughout the Blinded Treatment Period, however active vitamin D and/or calcium doses will be optimized (See Section 9.5.2).

Vitamin D3 and magnesium dosing are expected to remain stable throughout the remainder of the trial.

10.1.3.1. Visit 1 (Week 0, Day 1) Procedures

The following procedures are performed at this *morning* visit:

1. Subset of HPES validation battery
2. Vital sign measurements, including 30-minute post-dose orthostatic measurements
3. Daily diary review
4. Concomitant medication review, including SOC
5. Adverse event review
6. *Only for women of childbearing potential:* Urine collection for local hCG (results must confirm subject is not pregnant prior to first study drug dose administration)
7. Blood and urine collection for central laboratory assessments
8. Dietary calcium questionnaire and counseling based on results
9. Blinded treatment assignment
10. Daily diary dispensing
11. Study drug dispensing and training via Instructions For Use (IFU)
    - Reminder to dose every *morning* up to (but NOT including) the day of Visit 2
12. Study drug administration by subject
13. Local tolerability assessment by site staff
14. SOC dose adjustment (See Section 9.5.2.2)
15. Device usability questionnaire

See Section 11 for further details on procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.3.2. Laboratory Visits 1-3 (LV1-LV3; Weeks 0-1, Days 3, 6, 9 +1 day) Procedures

The following is performed at these *morning* visits:

1. Blood collection for local laboratory assessments
2. SOC dose adjustment (See Section 9.5.2.2)

See Section 11 for further details on procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.3.3. Visit 2 (Week 2, Day 14 ±2 days) Procedures

The following will be performed at this *morning* visit:

1. Blood collection for local laboratory assessments
2. Blood and urine collection for central laboratory assessments
3. Vital sign measurements
4. Daily diary review
5. Study drug receipt and compliance review
6. Concomitant medication review, including SOC
7. Adverse event review
8. Dietary calcium questionnaire and counseling based on results
9. Device usability questionnaire
10. SOC dose adjustment (See Section 9.5.2.2)
11. Daily diary dispensing
12. Study drug dispensing
    - Reminder to begin to evening dosing [ideally every night at bedtime (qHS) in bed]

Multiple local laboratory assessments between Visits 2 and 3 may be necessary to guide SOC dose adjustment.

See Section 11 for further details on procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.3.4. Visit 3 (Week 4, Day 28 ±2 days) Procedures

The following will be performed at this *morning* visit:

1. Subset of HPES validation battery
2. Device usability questionnaire
3. Blood collection for local laboratory assessments
4. Blood and urine collection for central laboratory assessments
5. Vital sign measurements
6. Daily diary review
7. Study drug receipt and compliance review
8. Concomitant medication review, including SOC
9. Adverse event review
10. Dietary calcium questionnaire and counseling based on results
11. Daily diary dispensing

12. Open-label treatment assignment
13. Titration of TransCon PTH and/or SOC dose adjustment (See Section 9.5.3)
14. Study drug dispensing
    - For subjects on active vitamin D only: Reminder to dose every morning up to (but NOT including) the day of Visit 4
    - For subjects on active vitamin D only: Study drug administration by subject
    - For subjects on active vitamin D only: Local tolerability assessment by site staff
    - For subjects on active vitamin D only: 30-minute post-dose orthostatic measurements

See Section 11 for further details on procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.4. Extension Period (Week 4 – 214)

During the Extension Period, all subjects begin treatment with open-label TransCon PTH with the availability of 3 pen presentations (6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively), allowing for an expanded dose range.

For subjects taking active vitamin D at Visit 3, the TransCon PTH dose is titrated starting at *Visit 4* as shown in Appendix 2.

For subjects not taking active vitamin D at Visit 3, the TransCon PTH dose is titrated starting at *Visit 3* as shown in Appendix 3.

Starting at Visit 9, all subjects are expected to remain on a stable dose of TransCon PTH. However, dose adjustments should continue as needed based on sCa results and following Appendix 2 and Appendix 3.

NOTE: Rescue doses of active vitamin D and/or calcium are allowable throughout the Extension Period. However, if symptoms of hypo- or hypercalcemia are persistent, the TransCon PTH dose should be adjusted at the following clinic visit (except if prior to Visit 4 for subjects taking active vitamin D at Visit 3). Due to the extended length of time between visits after Visit 9, the TransCon PTH dose may be adjusted between clinic visits.

10.1.4.1. Laboratory Visits* 4-6 (LV4-LV6) Procedures

If Visit 3 occurs on Day 26: LV4-LV6 occur on Day 29, 32, 35 +1 day

If Visit 3 occurs on Day 27: LV4-LV6 occur on Day 30, 33, 36 +1 day

If Visit 3 occurs on Day 28: LV4-LV6 occur on Day 31, 34, 37 +1 day

If Visit 3 occurs on Day 29: LV4-LV6 occur on Day 32, 35, 38 +1 day

If Visit 3 occurs on Day 30: LV4-LV6 occur on Day 33, 36, 39 +1 day

*Only for subjects who are still taking active vitamin D at Visit 3

The following will be performed at these morning visits:

1. Blood collection for local laboratory assessments

2. SOC dose adjustment (See Section 9.5.3.2)

See Section 11 for further details of procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.4.2. Visits 4-8 (Weeks 6-14; Days 42, 56, 70, 84, 98 ±2 days) Procedures

The following will be performed at these *morning* visits:

1. Subset of HPES validation battery (only Visits 4, 5, and 7)
2. *Only for women of childbearing potential:* Urine collection for local hCG (only at Visits 6 and 8)
3. Blood collection for local laboratory assessments
4. Blood collection for central laboratory assessments (only Visits 4, 5, and 7)
5. Urine collection for central laboratory assessments (only Visit 5)
6. Vital sign measurements
7. Daily diary review
8. TransCon PTH receipt and compliance review
9. Concomitant medication review, including active vitamin D and calcium
10. Adverse event review
11. Daily diary dispensing (only Visits 4-7)
12. Titration of TransCon PTH and/or SOC dose adjustment (See Section 9.5.3)
13. TransCon PTH dispensing
    - Only for subjects on active vitamin D at Visit 3: Reminder to begin evening dosing (ideally qHS in bed) (only Visit 4)

See Section 11 for further details of procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.4.3. Visits 9-11 (Weeks 18-26; Day 126-182 ±3 days) Procedures

The following will be performed at these *morning* visits:

1. HPES validation battery (only at Visit 11)
2. *Only for women of childbearing potential:* Urine collection for local hCG (only at Visit 10)
3. Blood collection for central laboratory assessments (only at Visits 9 and 11)
4. Urine collection for central laboratory assessments (only at Visits 9 and 11)
5. 24-hour urine collection (only within a week of Visit 11)
6. Vital sign measurements
7. TransCon PTH receipt and compliance review

8. Concomitant medication review, including rescue doses of SOC
9. Adverse event review
10. DXA and TBS (only within a week of Visit 11)
    a. *Canada Only:* TBS scoring will not be performed for subjects 18 to 20 years of age
11. Titration of TransCon PTH and/or SOC dose adjustment, if needed (See Section 9.5.3)
12. TransCon PTH dispensing

See Section 11 for further details of procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.4.4. Visits 12-15 (Weeks 34-58; Day 238-406 ±7 days) Procedures

The following will be performed at these *morning* visits:

1. HPES validation battery (only at Visit 15)
2. *Only for women of childbearing potential:* Urine collection for local hCG (only at Visits 12 and 14)
3. Blood collection for central laboratory assessments (only at Visits 13 and 15)
4. Urine collection for central laboratory assessments (only at Visit 15)
5. 24-hour urine collection (only within a week of Visit 15)
6. Vital sign measurements
7. TransCon PTH receipt and compliance review
8. Concomitant medication review, including rescue doses of SOC
9. Adverse event review
10. DXA and TBS (only within a week of Visit 15)
    a. *Canada Only:* TBS scoring will not be performed for subjects 18 to 20 years of age
11. TransCon PTH dispensing

See Section 11 for further details of procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.4.5. Laboratory Visits 7-12 (LV7-LV12; Weeks 71-201; Day 497-201 ±14 days) Procedures

The following will be performed at these *morning* visits:

1. Blood collection for local laboratory assessments
2. *Only for women of childbearing potential:* Urine collection for local hCG

Correspondence (eg, phone call, email) with the subject within 3 days following receipt of abnormal sCa result or within 5 days following receipt of normal sCa result is required to perform the following:

1. Concomitant medication review, including rescue doses of SOC
2. Adverse event review

See Section 11 for further details of procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.4.6. Visits 16-21 (Weeks 84-214; Day 588-1498 ±14 days) Procedures

The following will be performed at these *morning* visits:

1. Subset of HPES validation battery (only Visits 17, 19, and 21)
2. *Only for women of childbearing potential:* Urine collection for local hCG
3. Blood and urine collection for central laboratory assessments
4. 24-hour urine collection (within a week of Visits 16-20, and within the week prior to Visit 21)
5. Vital sign measurements
6. TransCon PTH receipt and compliance review
7. Concomitant medication review, including rescue doses of SOC
8. Physical exam
9. Adverse event review
10. DXA and TBS (only within a week of Visits 17 and 19, and within the week prior to Visit 21
    a. *Canada Only:* TBS scoring will not be performed for subjects 18 to 20 years of age
11. TransCon PTH dispensing (except for Visit 21)

Additional TransCon PTH dispensing will occur 8 and 16 weeks (±7 days) after Visits 15-20. These Visits will be labelled as Visits A and B (e.g. Visit 15A is 8 weeks after Visit 15 and Visit 15B is 16 weeks after Visit 15).

Correspondence (eg, phone call, email) with the subject 2 weeks (+7 days) after Visit 21 is required to evaluate the subject for any further AEs during the 2 weeks since last study drug administration.

See Section 11 for further details of procedures listed above.

See Appendix 5 for further details on laboratory assessments to be performed.

10.1.5. Unscheduled Visits (UV)

Unscheduled Visits are those visits that occur *at the clinic* between regularly scheduled visits at investigator discretion to assess a potential AE, manage an already documented AE, and/or confirm an abnormal laboratory value requiring Central Laboratory testing. Only focused assessments (guided by the reason for the visit) will occur at these visits. Unscheduled local laboratory visits (ULVs) do not constitute UVs.

10.1.6. Unscheduled Laboratory Visits (ULV)

Unscheduled Laboratory Visits are those visits that occur *at the local laboratory* between regularly scheduled visits at subject or investigator discretion to assess a potential AE, follow-up on an already documented AE, confirm an abnormal laboratory value requiring Local Laboratory testing. This inludes assessment of albumin-adjusted or ionized sCa levels if clinical symptoms of hypo- or hypercalcemia occur at any time during the trial.

10.1.7. End of Study (EOS) Visits

End of Study (EOS) Visits are performed for any withdrawal of a subject from this clinical trial.

If EOS Visits occur *prior* to Visit 3, the structure and assessments of the EOS Visit should be as similar as possible to Visit 3.

If EOS Visits occur *after* Visit 3, the structure and assessments of the EOS Visit should be as similar as possible to Visit 15. If prior to Visit 8, diary review should also be included in the EOS Visit.

Additionally, correspondence (eg, phone call, email) with the subject 2 weeks (+7 days) after last study drug administration is required to evaluate the subject for any further AEs during the 2 weeks since last study drug administration.

See Section 8.2 for details on Premature Subject Withdrawal.

11. ASSESSMENTS

11.1. VITAL SIGN MEASUREMENTS

Subjects should rest for at least 5 minutes before vital sign measurement. The following vital signs should be measured:

- Respiratory Rate
- Body Temperature
- Orthostatic Blood Pressure & Heart Rate
  Blood pressure and heart rate are measured while subject is sitting. Subject is then asked to stand up and, within 3 minutes of doing so, blood pressure and heart rate are measured again.

11.1.1. Post-Dose Orthostatic Measurements

At Visit 1, a set of orthostatic blood pressure and heart rate should be taken 30 minutes after study drug administration.

At Visit 3, a set of orthostatic blood pressure and heart rate should be taken 30 minutes after study drug administration for subjects on active vitamin D at Visit 3.

11.2. PRIOR AND CONCOMITANT MEDICATION REVIEW

Prior and concomitant therapies include all prescription or over-the-counter medications, vitamins and herbal/nutritional supplements taken within 26 weeks prior to Visit 1 and through the end of the trial, which should be documented with the name of the medication/supplement, dosage information including dose, route, and frequency, dates of administration including start and end dates, and reason for use.

11.3. ELECTROCARDIOGRAM (ECG)

An ECG must be performed and read locally prior to Visit 1. Standard 12-lead ECG will be recorded when the subject is in a resting state, prior to blood collection if performed at the same visit. A historical ECG performed within the 12 weeks prior to Visit 1 is acceptable if the report includes QT interval (or QTcF) and Heart Rate.

11.4. X-RAY OF NON-DOMINANT WRIST AND HAND

To confirm epiphyseal closure, an x-ray of the non-dominant wrist and hand must be performed and read locally prior to Visit 1 for subjects 25 years old or younger (as of Visit 1). A historical x-ray showing epiphyseal closure is acceptable.

11.5. DUAL-ENERGY X-RAY ABSORPTIOMETRY (DXA) AND TRABECULAR BONE SCORE (TBS)

To evaluate bone density and quality, a DXA scan of the spine, hip, and forearm, as well as TBS scoring must be performed *Canada Only.* TBS scoring will not be performed for subjects 18 to 20 years of age.

See the DXA Manual for complete details. The same DXA machine should be used throughout the trial. The sponsor must be notified if a change in scanner occurs.

A historical DXA performed within the 12 weeks prior to Visit 1 is acceptable for Screening purposes if the same DXA machine will be used throughout the trial and meets the requirements outlined in the DXA Manual. If the historical DXA did not include TBS, TBS analysis should be performed (*Canada Only:* unless subject is 18 to 20 years of age).

11.6. DIETARY CALCIUM QUESTIONNAIRE

Dietary Calcium Questionnaire is a subject-completed assessment of the subject's daily dietary calcium intake. After the questionnaire is completed, site will enter data into the International Osteoporosis Foundation's Dietary Calcium Calculator (http://www.iofbonehealth.org/calcium-calculator) and print out the calculated results as source documentation to be entered into the electronic data capture (EDC) system by the site staff. Based on the results, site staff will also review and counsel subject to maintain a reasonably stable dietary calcium intake during the trial, as well as avoiding unhealthy intake of sodium that can contribute to hypercalciuria.

11.7. HYPOPARATHYROIDISM PATIENT EXPERIENCE SCALE VALIDATION BATTERY

The Hypoparathyroidism Patient Experience Scale (HPES) is the disease-specific subject-completed Patient-Reported Outcome (PRO) measure being developed by the Sponsor to assess relevant patient-reported symptom and disease impacts. The HPES takes approximately 5 minutes to complete. The measure assesses both the key HP-related symptoms from the patient perspective and the key impacts of these symptoms on patient functioning and well-being.

The concept elicitation phase of the measure development has been completed based on semi-structured interviews with 43 patients and 5 clinical experts. To continue the measure development process and validate these measures, data will be collected in this trial for use in the psychometric analyses necessary to finalize the measures. The data collected in the trial will be combined with similar data collected via a web-study conducted independently of this study. A separate Psychometric Analysis Plan based on the data collected from the two studies will be prepared independently of the SAP for this trial.

The Validation Battery consists of the following Clinical Outcome Assessments (COAs): the HPES, other PROs, and a clinician-reported outcome measure needed for the psychometric testing. It is expected that completion of the Validation Battery takes approximately 30-45 minutes. Data from the validation battery, and a subset thereof at various time points, will be used to assess the measurement properties of the HPES such as the factor structure and scoring algorithm. The Validation Battery, or a subset, will also be completed later in the trial for exploratory purposes. In addition, one of the PROs will also be used for resource utilization evaluation.

If suicidal ideation is spontaneously reported during PRO assessments or at any other time during the trial, study staff should follow their site-specific suicide safety plan.

NOTE: All PROs must be completed by the subject without assistance and prior to conducting any clinical assessments.

11.8. DEVICE USABILITY QUESTIONNAIRE

The Device Usability Questionaire will be used to assess the usability of the pre-filled injection pen, including any malfunction.

NOTE: This questionnaire should be completed by the subject without assistance.

11.9. DAILY DIARY

Subjects are trained on the daily diary during Screening and instructed to return the diary at every visit for site staff review as part of concomitant medication review, AE review and study drug compliance.

Diary completion during the Screening Period assists in tracking HP-related supplement optimization. The minimum 7 days between the Screening Period and Visit 1 should be used as an opportunity for subjects who are already optimized on HP-related supplements prior to Screening to become acquainted with the daily diary prior to enrollment/randomization.

11.10. 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 erythema is not considered an ISR.

At Visit 1, assessment of local tolerability is performed by trial staff using the Local Tolerability Scale at the time of the first 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.

11.11. ADVERSE EVENT REVIEW

At each visit, the subject should be asked about the following to assess for any potential AEs:

- General well-being
- Any changes to health or medications since the previous visit
- Hypo- or hypercalcemic symptoms since the previous visit
- Emergency/urgent care visits or hospitalizations since the previous visit

At applicable visits, site staff will review daily diary with the subject and any data related to changes in health or medications should be further assessed for potential AEs.

Additionally, at applicable visits, changes from baseline noted during a physical examination should be assessed for potential AEs.

At the investigator's discretion, additional assessments, including an examination of injection sites, a physical examination, or additional laboratory assessment, may be performed even if not required at the specific study visit or if an UV or ULV must be scheduled.

See Section 12 for details on reporting AEs.

11.12. LABORATORY ASSESSMENTS

Samples will be obtained at a minimum for both central and local laboratory tests to be performed as outlined in Section 11.12.1 and Appendix 5.

NOTE:

- **Blood and urine collection must occur prior to on-site study drug administration, when applicable**
- **On the day of lab assessments, subjects should avoid exercise prior to blood collection**
- **On the day of lab assessments, subjects should be instructed to take their SOC (as applicable) and eat their usual breakfast prior to blood collection**
- **Blood and urine collection for central laboratory testing should occur within 1 hour of each other**

Investigators must be able to receive local laboratory results within a time frame sufficent to allow instructions to subjects on dose adjustments within 48 hours of blood collection. All local laboratory results will be entered into the EDC system by the site staff.

11.12.1. Laboratory Assessments by Visit

See Appendix 5 for the Schedule of Laboratory Assessments.

11.12.1.1. Screening Period Laboratory Assessments

The following laboratory assessments are performed locally during the Screening Period to guide optimization of HP-related supplements (vitamin D3, active vitamin D, calcium, and/or magnesium) prior to dosing (See Section 9.5.1). Multiple laboratory assessments may be performed as needed, including **at least one set of confirmation laboratory assessments once the laboratory results are within the optimization ranges**.

1. 25(OH) vitamin D
2. Calcium and albumin (or ionized calcium)
3. Magnesium

The following laboratory assessments are performed locally once during the Screening Period to ensure eligibility prior to Visit 1:

1. Urine Human chorionic gonadotropin (hCG; pregnancy test)
   Only for females of childbearing potential defined as NOT surgically sterile or postmenopausal (≥45 years old as of Screening, without menses for at least 52 weeks prior to Screening without an alternative medical cause, and FSH > 20 IU/L)
2. Serum Follicle Stimulating Hormone (FSH)
   Only for females ≥45 years old as of Screening, without menses for at least 52 weeks prior to Screening without an alternative medical cause (eg, surgically sterile) to determine if postmenopausal status

The following laboratory assessments will be performed centrally on blood and urine collected once during the Screening period to ensure eligibility or to provide another baseline prior to Visit 1:

1. 25(OH) vitamin D
2. $1,25(OH)_2$ vitamin D
3. PTH(1-84)
4. Chemistry panel including serum calcium, albumin, and creatinine
5. Hematology panel
6. Urine calcium and creatinine
7. Bone turnover markers
8. TSH

After the investigator confirms the subject is eligible to move into the Blinded Treatment Period, a 24-hour urine collection will be performed by the subject at home within the week prior to Visit 1 to provide baseline values. The laboratory assessments associated with the 24-hour urine collection will be performed centrally.

11.12.1.2. Visit 1 (V1) Laboratory Assessments

The following laboratory assessment is performed locally at Visit 1 to ensure eligibility prior to study drug dosing:

1. Urine Human chorionic gonadotropin (hCG; pregnancy test)
   Only for females of childbearing potential defined as NOT surgically sterile or postmenopausal (≥45 years old as of Screening, without menses for at least 52 weeks prior to Screening without an alternative medical cause, and FSH > 20 IU/L)

The following laboratory assessments will be performed centrally on blood and urine collected at Visit 1 to provide a baseline for each subject:

1. 25(OH) vitamin D
2. $1,25(OH)_2$ vitamin D
3. Total PTH (corresponding to TransCon PTH) and mPEG
4. Antibodies against PTH and PEG
   a. These data will be used to support evaluation of post-dose antibody detection
   b. Banked blood samples may be used for additional exploratory characterization of anti-drug antibody responses
5. Chemistry panel including serum calcium, albumin, and creatinine
6. Hematology panel
7. Urine calcium and creatinine
8. Bone turnover markers
9. *Only for female subjects of child-bearing potential:* serum hCG

For a cohort of approximately 24 subjects at selected sites, an additional assessment of Free PTH [PTH(1-34) and PTH(1-33)] will be performed centrally.

11.12.1.3. Laboratory Visits 1-3 (LV1-LV3) Laboratory Assessments

The following laboratory assessments will be performed locally at Laboratory Visits 1-3 to guide *SOC dose adjustment between Visits 1 & 2* (see Section 9.5.2.2):

1. Calcium and albumin (or ionized calcium)

If, at selected sites where the Free PTH assessment will be performed at Visit 1, subjects return to the site's own local laboratory for LV1-LV3, an additional assessment of Free PTH [PTH(1-34) and PTH(1-33)] will be performed centrally.

11.12.1.4. Visit 2 (V2) Laboratory Assessments

The following laboratory assessments will be performed locally at Visit 2 to guide *SOC dose adjustments* while the subject is *still in the clinic* (see Section 9.5.2.2):

1. Calcium and albumin (or ionized calcium)

The following laboratory assessments will be performed centrally on blood and urine collected at Visit 2:

1. $1,25(OH)_2$ vitamin D
2. Total PTH (corresponding to TransCon PTH) and mPEG
3. Antibodies against PTH and PEG
    a. Banked blood samples may be used for additional exploratory characterization of anti-drug antibody responses
4. Chemistry panel including serum calcium, albumin, and creatinine
5. Urine calcium and creatinine
6. Bone turnover markers
7. *Only for female subjects of child-bearing potential:* serum hCG

For a cohort of approximately 24 subjects at selected sites, an additional assessment of Free PTH [PTH(1-34) and PTH(1-33)] will be performed centrally.

11.12.1.5. Visit 3 (V3) Laboratory Assessments

The following laboratory assessments will be performed locally at Visit 3 to guide *TransCon PTH and/or SOC dose adjustment* while the subject is *still in the clinic* (see Section 9.5.3):

1. Calcium and albumin (or ionized calcium)

The following laboratory assessments will be performed centrally on blood and urine collected at Visit 3:

1. 25(OH) vitamin D
2. $1,25(OH)_2$ vitamin D
3. Total PTH (corresponding to TransCon PTH) and mPEG
4. Antibodies against PTH and PEG
    a. Banked blood samples may be used for additional exploratory characterization of anti-drug antibody responses
5. Chemistry panel including serum calcium, albumin, and creatinine
6. Hematology panel
7. Urine calcium and creatinine
8. Bone turnover markers
9. Only for female subjects of child-bearing potential: serum hCG

For a cohort of approximately 24 subjects at selected sites, an additional assessment of Free PTH [PTH(1-34) and PTH(1-33)] will be performed centrally.

11.12.1.6. Laboratory Visits 4-6 (LV4-LV6) Laboratory Assessments

The following laboratory assessments will be performed locally at Laboratory Visits 4-6 to guide *SOC dose adjustments* **only for subjects taking active vitamin D at Visit 3** *between Visits 3 & 4* (see Section 9.5.3.2):

1. Calcium and albumin (or ionized calcium)

11.12.1.7. Visits 4-8 (V4-V8) Laboratory Assessments

The following laboratory assessments will be performed locally at Visits 4-8 to guide *SOC and/or TransCon PTH dose adjustments* while the subject is *still in the clinic* (see Section 9.5.3):

1. Calcium and albumin (or ionized calcium)
2. Only for women of child-bearing potential: urine hCG (only at Visits 6 and 8)

The following laboratory assessments will be performed centrally on blood and urine collected at Visits 4-8 (Visits 6 and 8 do not have central laboratory assessments):

1. 25(OH) vitamin D (only at Visit 5)
2. $1,25(OH)_2$ vitamin D (only at Visit 5)
3. Total PTH, corresponding to TransCon PTH and mPEG (only at Visits 4, 5 and 7)
4. Antibodies against PTH and PEG (only at Visits 4, 5 and 7)
    a. Banked blood samples may be used for additional exploratory characterization of anti-drug antibody responses
5. Chemistry panel including serum calcium, albumin, and creatinine (only at Visit 5)
6. Hematology panel (only at Visit 5)
7. Urine calcium and creatinine (only at Visit 5)
8. Bone turnover markers (only at Visits 5 and 7)
9. *For female subjects of child-bearing potential only:* serum hCG (only at Visits 4, 5 and 7)

For a cohort of approximately 24 subjects at selected sites, an additional assessment of Free PTH [PTH(1-34) and PTH(1-33)] will be performed centrally only at Visits 4, 5, and 7.

11.12.1.8. Visit 9-21 (V9-V21) Laboratory Assessments

The following laboratory assessments will be performed locally on urine collected at Visits 10, 12, and 14:

1. Only for women of child-bearing potential: urine hCG

The following laboratory assessments will be performed centrally on blood and urine collected at Visits 9, 11, 13, 15, and 16-21-:

1. 25(OH) Vitamin D
2. $1,25(OH)_2$ vitamin D
3. Total PTH (corresponding to TransCon PTH) and mPEG

4. Antibodies against PTH and PEG
    a. Banked blood samples may be used for additional exploratory characterization of anti-drug antibody responses
5. Chemistry panel including serum calcium, albumin, and creatinine
6. Hematology panel
7. Urine calcium and creatinine (only at Visits 9, 11, 15, and 16-21)
8. Bone turnover markers (only at Visits 11,15, 17, 19, and 21)
9. *Only for women of child-bearing potential:* serum hCG

Additionally, a 24-hour urine collection will be performed by the subject at home within a week of Visits 11, 15, 16-20, and within the week prior to Visit 21. The laboratory assessments associated with the 24-hour urine collection will be performed centrally.

For Selected Countries:

A PD-PK sub-set study will be performed in approximately 8 subjects on any day from Week 58 (visit 15) and prior to 31 Aug 2021. The PD-PK sub-set study requires 24-hour admission in a research unit and frequent lab draws to assess the serum calcium and Free PTH. Please refer to Appendix 9 for further details.

11.12.1.9. Laboratory Visits 7-12 (LV7-LV12) Laboratory Assessments

The following laboratory assessments will be performed locally at all Laboratory Visits starting at Laboratory Visit 7:

1. Calcium and albumin (or ionized calcium)
2. Serum calcium (only if ionized calcium is collected)
3. Serum phosphate
4. *Only for women of child-bearing potential:* urine hCG

11.13. LIFESTYLE MODIFICATION

11.13.1. Dietary Modifications

Subjects should be advised to consume approximately the same amount of calcium from their diet every day to minimize the effect of dietary calcium on fluctuation in sCa level. The Investigator or site staff will counsel the subjects about their dietary calcium intake based on the dietary calcium questionnaire and counseled to avoid excessive sodium intake.

11.13.2. Exercise Modifications

Subjects should be advised to avoid exercise prior to visits which include blood collection.

11.13.3. Contraception

Male and female fertility and embryofetal developmental studies have been conducted in rats. TransCon PTH did not induce adverse effects on fertility or on embryofetal development in pregnant rats when administered through gestation day 17. The highest dose tested had an approximate 20-fold exposure margin to the Phase 1 SAD dose of 20 µg PTH(1-34)/day.

Irrespectively, highly effective contraception during the trial and for 2 weeks after the last dose of study drug is required for women of childbearing potential if sexually active, and pregnancy testing for women of childbearing potential will be performed throughout the trial. See Appendix 7 for further guidance on highly effective contraception.

See Appendix 5 for further details on pregnancy testing schedule.

11.13.4. Study Drug Administration

11.13.4.1. Blinded Treatment Period Administration

The first dose of study drug will be administered by the subject in the clinic, and the subject will be observed for at least 30 minutes for local tolerability assessment and adverse reactions, including orthostatic hypotension and light-headedness. Subjects will inject subsequent doses of study drug daily at home.

During the first two weeks of the Blinded Treatment Period, dosing remains in the morning. Subjects should continue to be careful of orthostatic changes/light-headedness.

Starting at Visit 2, study drug dosing changes to evening dosing (ideally qHS in bed), with the last morning dose taken the day BEFORE Visit 2.

11.13.4.2. Extension Period Administration

For subjects on active vitamin D at Visit 3, the first dose of open-label TransCon PTH is administered by the subject in the clinic, and the subjects will be observed for at least 30 minutes for local tolerability assessment and adverse reactions, including orthostatic hypotension and light-headedness. During the first two weeks of the Extension Period, dosing for these subjects remains in the morning. Starting at Visit 4, dosing changes to evening dosing (ideally qHS in bed), with the last morning dose taken the day before Visit 4.

For subjects not on active vitamin D at Visit 3, the first dose of open-label TransCon PTH is administered at home in the evening (ideally qHS in bed) following the clinic visit, with all subsequent administrations also in the evening.

11.13.5. Hypo- or Hypercalcemia Symptom Management

Most HP subjects are able to recognize their symptoms of hypocalcemia, and many can recognize symptoms of hypercalcemia. Just as in normal management of patients with HP, if hypo- or hypercalcemic symptoms develops any time in-between study visits, subjects should contact the site and visit the local laboratory (ie, ULV) to assess albumin-adjusted or ionized sCa.

Additionally, as in normal management of patients with HP, all subjects will be permitted to take extra active vitamin D and/or calcium supplements as rescue medications to resolve symptoms of hypocalcemia, and reduce calcium and/or active vitamin D supplements (or hold/reduce their dose of Transcon PTH if off SOC) to resolve acute symptoms of hypercalcemia. Subjects should be encouraged to visit the local laboratory for assessment of serum calcium and albumin, or ionized calcium, levels for symptoms of hypercalcemia.

11.13.6. Daily Diary

Subjects will be required to complete a daily diary to capture the following:

- HP-related supplements (name, dose, and administration date and time), including rescue doses
- Study drug, starting at Visit 1 (dose, administration date and time)
- Changes to health and concomitant medications

See Section 11.9 for details regarding training and site review of the daily diary.

12. ADVERSE EVENT ASSESSMENT AND REPORTING

12.1. DEFINITION

12.1.1. Adverse Event

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with hypoparathyroidism that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

12.1.2. Serious Adverse Events

- An AE should be classified as an SAE if any of the following criteria are met:
- It results in death (i.e., the AE cause or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form or was allowed to continue, might have caused death).

- It requires or prolongs inpatient hospitalization (see Section 12.4.3.6).
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe; see Section 12.3.1; the event itself may be of relatively minor medical significance (such as severe headache without any further findings.

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious AEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 12.5.2 for reporting instructions).

12.1.3. Adverse Events of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and potential medical concern specific to the product, for which ongoing monitoring and reported by the Investigator within 24 hours to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g. Regulatory Authorities) may also be warranted.

12.1.4. TransCon PTH Adverse Events of Special Interest

AEs of special interest for this study include the following:

- Vasodilatory signs and symptoms which may include orthostatic dizziness, lightheadedness, weakness, blurring of vision, pre-syncope, syncope, headache, orthostatic hypotension, orthostatic tachycardia/palpitations. Such symptoms are usually transient in nature and can be managed by dosing at bedtime, while reclining. PTH is known to have vasodilatory effects (*Rambausek 1982*)
- Persistent severe hypocalcemia (as defined in Section 9.6.2)
- Persistent severe hypercalcemia (as defined in Section 9.6.2)

12.1.5. Special Situation

Special situations are non-standard medical conditions that provide valuable information (e.g. clinical, safety) about a medicinal product, even when they do not occur in association with an AE or medical condition. Examples of special situations include and should all be captured in the eCRF:

- Pregnancy
- Breastfeeding

- Overdose
- Drug abuse
- Misuse
- Off label use
- Occupational exposure
- Lack of therapeutic efficacy
- Medication error

The Medical Monitor will review all safety information on an ongoing basis.

12.2. METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs, AESIs and SAEs that are observed or reported during the study are collected and reported to Ascendis Pharma, in accordance with FDA CFR 312.32 (IND Safety Reports) and ICH E6.

12.3. ADVERSE EVENT REPORTING PERIOD

The Adverse Event Reporting Period is the period requiring reporting of AEs, AESIs and SAEs for any subjects exposed to IMP product and or any study related procedures. Reporting period begins from the time when the informed consent is obtained and ends 2 weeks following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment Severity, Causality, and Outcome Assessment.

12.3.1. Assessment of Severity of Adverse Events

The World Health Organization (WHO) toxicity grading scale will be used for assessing AE severity. Table 2 will be used for assessing severity for AEs that are not specifically listed in the WHO toxicity grading scale.

Table 2: Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious AE (see Section 12.1.2).

12.3.1.1. Causality Rating

All AEs, AESIs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means must be reported appropriately.

Each reported AE, AESIs or SAE must be described by its duration (i.e., start and end dates), seriousness criteria if applicable, suspected relationship to the TransCon PTH (see following guidance), and actions taken. To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Related (Yes) – There is a plausible temporal relationship between the onset of the AE and administration of TransCon PTH. The AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. The AE follows a known pattern of response to TransCon PTH or with similar treatments. And/or the AE abates or resolves upon discontinuation of TransCon PTH or dose reduction and, if applicable, reappears upon re-challenge.

Not Related (No) – Evidence exists that the AE has an etiology other than the TransCon PTH (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication). The AE has no plausible temporal relationship to TransCon PTH administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the current Investigator Brochure (IB)

Unexpected AEs are those not listed in the current IB or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the IB.

12.3.1.2. Outcome Assessment

Subjects will be followed until AEs have either resolved, subjects have returned to their baseline status, or subjects are deemed stable or commensurate with ongoing disease processes. One of five outcomes listed below must be recorded:

- Recovered/Resolved – The event has stopped. The stop date of the event must be recorded.
- Recovering/Resolving – The subject is clearly recovering from an event. The event is not yet completely resolved.
- Not Recovered/Not Resolved – The event is still ongoing. (Could include stable and commensurate with ongoing disease processes).
- Recovered/Resolved with sequelae – The event has reached a state where no further changes are expected, and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.
- The stop date of the event must be recorded. In case of SAE, the sequelae should be specified.
- Fatal – The subject has died as a consequent of the event. Date of death is recorded as stop date for the AE.
- Unknown – Unknown to investigator, e.g. subject lost to follow up.

12.4. PROCEDURES FOR ELICITING, RECORDING AND REPORTING ADVERSE EVENTS

12.4.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

12.4.2. Recording Procedures for All Adverse Events

All AEs will be documented in response to question about the subject's well-being and whether any possible changes in well-being have occurred since the previous visit.

AEs, including AESIs and SAEs, will be documented through the end of the subject's participation in the trial or Early Termination Visit. All AEs must be recorded on the appropriate eCRF. AEs either observed by the investigator or reported by the subject must be recorded regardless of causality. The following attributes must be documented for each reported AE:

- Subject ID
- Description
- Onset date (if AE was present on Day 1, include whether onset was prior to or after the first dose of the study drug)
- Resolution date, if applicable
- Severity
- Causality (relationship to the study drug)
- Outcome
- Action taken
- Determination of "seriousness criteria" (whether serious or not serious)

Any medical history condition, signs, symptoms, and illnesses active during the Screening Period will be captured as baseline (preexisting) events, if appropriate, to assure that any change(s) in these experiences during the trial also are recorded as an AE and a complete safety profile is obtained. An event that occurs after signing of ICF but prior to the first study drug administration will be documented as medical history unless the event is trial procedure–related, in which case it will be reported as a non–treatment-emergent AE. Any new or worsening pretreatment event that occurs from the time of the first study drug administration until the EOT Visit will be recorded as an AE.

Routine titration of chronic, concomitant medications will not be considered to meet the criteria for AEs.

Investigators should use correct medical terminology/concepts when reporting AEs, AESIs or SAEs. Avoid colloquialisms and abbreviation (e.g., hypertension for elevated BP that persists and requires chronic treatment and follow-up, or increased blood pressure for elevated blood pressure that occurs for a limited time and does not persist or require ongoing treatment).

An accidental overdose is not an AE if there are no signs or symptoms. Any undesirable medical occurrence resulting from an accidental overdose is an AE and should be recorded and reported on the appropriate eCRF. Regardless of classification as an AE or not, *all* overdoses should be documented, and the subject(s) monitored. Since accidental overdoses with the study drug could have serious clinical consequences and/or represent a compliance issue, they should be reported to the Medical Monitor immediately and evaluated by the Sponsor.

12.4.3. Specific Instructions for Recording Adverse Events

12.4.3.1. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification or titration, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

12.4.3.2. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

12.4.3.3. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only hypercalcemia rather than abdominal pain, nausea, polyuria, and high serum calcium). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available as separate AEs. If a diagnosis is subsequently established, it should be reported as follow-up information.

12.4.3.4. Injection Related Reaction

Each sign or symptoms will be recorded as a separate AE on the AE eCRF.

Local reaction at the site of injection administration should be captured as unified diagnosis rather than as individual signs and symptoms on the Adverse Event eCRF (e.g. adverse event reporting as an injection site reaction rather than capturing injection site bleeding or injection site induration as separate adverse events).

12.4.3.5. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

12.4.3.6. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

12.4.3.7. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

12.4.3.8. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within two weeks after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within two weeks, a Pregnancy report should be completed and expeditiously submitted to Ascendis Pharma. Follow-up to obtain the outcome of the pregnancy should also occur and the outcome reported to Ascendis Pharma. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be expeditiously reported as an SAE.

12.4.3.9. Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

In this study, the TransCon PTH delivery system consists of a multi-use cartridge integrated into a device to constitute a pre-filled injection pen which is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should follow the guidance in the Pharmacy Manual for reporting product complaints and forward the information to the Sponsor immediately. If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 12.5.2.

12.5. SERIOUS ADVERSE EVENTS (SAE) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR)

12.5.1. Non-Serious Adverse Events Leading to Discontinuation

If situation permits, non-serious events (including laboratory abnormalities and pregnancies) that may require permanent discontinuation of study drug should be discussed with the Medical Monitor prior to making any final decision.

12.5.2. Reporting

All initial and follow-up information regarding SAEs, AESIs, and Special Situations reporting must be reported by the investigator to the Sponsor or its representatives within 24 hours of discovery/awareness, including those related to protocol-mandated procedures and regardless of suspected causality.

For each AE recorded on the AE eCRF, the investigator will make an assessment of seriousness (see Section 12.1.2 for seriousness criteria), severity (Section 12.3.1), and causality (see Section 12.3.1.1).

Reporting must not be delayed by waiting for additional information. The minimum information required for reporting an SAE, AESIs, and Special Situations are the AE term (diagnosis), patient, study drug, reporter, and the investigator's initial causality assessment. Additional information must be reported to the Sponsor or its representatives as a follow-up report. All SAEs, AESIs, and Special Situations (including follow-up information) must be reported to:

[redacted]

OR

[redacted]

SAEs, AESIs, and Special Situations information is collected and reported via SAE Forms provided by the Sponsor or its representative. Pregnancy information is collected and reported via Pregnancy Forms provided by the Sponsor or its representative. The Sponsor (or its representatives) is responsible for reporting within the time frame required by applicable regulations all SAEs qualifying as SUSARs to:

- Investigators.
- Central IRBs/HRECs/IECs (if applicable).
- National ethics committees (if applicable).
- Appropriate regulatory authorities.

It is the investigators' responsibility to comply with the requirements of their local IRB/HREC/IEC for reporting SUSARs, other SAEs, and any new and/or relevant safety information provided by the Sponsor or its representatives. At minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

13. SAFETY MONITORING

The Sponsor will conduct an ongoing review of all trial data, with particular attention given to laboratory findings (in particular related to albumin adjusted serum calcium, ionized calcium), AEs, and concomitant medications. Any important safety trends or other findings considered related to the study drug will be reported to the investigators and to regulatory authorities. In particular, the Sponsor will notify investigators and regulatory authorities of AEs that:

- Fulfill the criteria for SUSARs.
- Occur at a meaningfully greater frequency than described in the current Investigator's Brochure or Reference Safety Information.

- Any AE that occurs during the clinical trial must be monitored and followed up until:
- It has resolved or receded
- Pathology laboratory findings have returned to normal
- Steady-state has been achieved
- It has been shown to be unrelated to the study drug and/or trial related procedure

Details will be described in the Safety Management Plan.

14. STATISTICS

14.1. GENERAL

Details of applicable statistical methods will be provided in a statistical analysis plan (SAP) which will be finalized before trial unblinding and database lock of the Blinded Treatment Period. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record.

Data from clinical assessments will be summarized using descriptive statistics. Numerical variables will be summarized by mean, median, standard deviation, standard error, minimum, and maximum while categorical variables will be summarized by counts and proportions. In general subjects on placebo for TransCon PTH at different doses will be pooled as a control group to compare with each of the active dose groups.

14.2. ENDPOINTS

14.2.1. Efficacy Endpoints

14.2.1.1. 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

14.2.1.2. Secondary Efficacy Endpoints

14.2.1.2.1. 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

14.2.1.2.2. Other Secondary Efficacy Endpoints

Primary and key secondary efficacy endpoints measured at predefined timepoints over the Extension Period. For the analysis of these endpoints in the Extension Period, the 24-hour urine calcium excretion will be used.

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

At predefined timepoints over the Extension Period:

- 24-hour urine calcium excretion

14.2.2. 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, AESI, and serious adverse events (SAEs)
- 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, including vital signs

14.2.3. Exploratory Endpoints

At 4 weeks of treatment, assessment of the following:

- Clinical Outcome Assessments (COAs)
- Bone turnover markers (serum P1NP and CTx)
- Device usability questionnaire

Throughout the Extension Period, assessment of the following:

- BMD and TBS by DXA at 26, 58, 110, 162, and 214 weeks
- 24-hour urine calcium excretion at 26,58, 84, 110, 136, 162, 188, and 214 weeks
- COAs at 6, 8, 12, and 26, 58, 110, 162, and 214 weeks
- Bone turnover markers (serum P1NP and CTx) at 8, 12, 26, 58, 110, 162, and 214 weeks
- Albumin-adjusted sCa, magnesium, phosphate, and sCA x sP product at 8, 18, 26, 42, 58, 84, 110, 136, 162, 188, and 214 weeks

14.3. STATISTICAL ANALYSIS

14.3.1. Baseline Characteristics and Analysis Population

Safety data will be analyzed on all randomized subjects who receive at least one dose of study drug. Efficacy data will be analyzed on all randomized subjects who receive at least one dose of study drug and have any follow-up data that comprises the primary endpoint

Baseline and demographic data will be summarized to characterize the trial population. Subgroups of interest, such as prior exposure to PTH and age categories will be determined and corresponding subgroup analyses for safety and efficacy will be performed as appropriate.

14.3.2. Efficacy Analysis

Pairwise comparison between each of the active TransCon PTH dose groups and the pooled placebo group will be conducted for the primary endpoint and key secondary endpoints using the Fisher's exact test based on all intent-to-treat (ITT) subjects. A significant treatment effect is defined as adjusted $P < 0.05$ (2-sided).

14.3.3. Pharmacokinetic Analysis

All subjects who will receive the study drug and for whom the primary PK data are considered sufficient and interpretable will be analyzed in the PK analysis. The primary PK analysis of interest is the Free PTH [PTH(1-34) and PTH(1-33)], which represents the unmodified PTH released from the prodrug and which showed the strongest correlation with PD in the Phase 1 study. Free PTH will be assessed in a cohort of approximately 24 subjects only due the burden on sites to acidify and freeze the sample quickly to stop the release of Free PTH by the TransCon pro-drug in the sample. The PK parameters and their statistical evaluation will be included in the Clinical Study Report or as an appendix. Based on the well-understood PK/PD relationship of PTH in general, and PTH(1-34) in particular, and data showing that continuous SC infusion of PTH(1-34) provides optimal treatment of both adults and children with HP, the PK data will primarily be used to describe the time to steady-state and the presence or lack of accumulation once steady-state is achieved. Potential impact of any anti-PTH and anti-PEG antibodies detected will be included in the evaluation.

14.3.4. Safety Analysis

The reporting of the safety data is descriptive and will include all subjects receiving at least one dose of study drug. Descriptive analysis will include the incidence and type of adverse events, and changes in laboratory and vital signs parameters and treatment-emergent anti-PTH and anti-PEG antibodies from pre-dosing to listed post-dose time points. Listings of abnormal laboratory data by treatment group will be presented. Incidence of abnormal vital signs over time will be summarized by treatment/dose group. All AEs will be coded using Medical Dictionary for Regulatory Authorities (MedDRA) and tabulated by system, organ, and class. Individual events within each system will be presented in descending frequency. AEs will also be tabulated by severity and relationship to the trial drug and will be presented by dosage. SAEs will be summarized separately.

14.3.5. Interim Analysis

The analysis of the Blinded Treatment Period will be conducted after database lock of the Blinded Treatment Period, which will occur prior to database lock of the Extension Period. No interim analysis prior to database lock of the Blinded Treatment Period is planned.

14.4. POWER CALCULATION

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, 66% of subjects with continuous infusion of PTH will have normal sCa. The phase 1 study 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 3.

Table 3: 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%
80%	1%	94.7%	97.3%

14.5. SIGNIFICANCE

Statistical significance is defined as P <0.05 (2-sided).

14.6. ACCOUNTABILITY

Subjects with missing data, including missed assessments and early discontinuation will be summarized.

14.7. DEVIATION REPORTING

Major protocol deviations will be summarized.

14.8. UNBLINDING PROCEDURES

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 (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.

15. TRIAL CONDUCT

15.1. SITE INITIATION

Prior to participation, investigational sites and investigators will be evaluated for appropriate qualifications and ability to execute the trial. Each investigational site must undergo appropriate training on the trial protocol and ancillary trial procedures and documents through participation in a Site Initiation Visit (SIV) or Investigator Meeting (IM). Protocol and GCP training must take place before any subjects are enrolled at a site. SIVs and IMs will include, but may not be limited to, study drug preparation and administration procedures, data collection requirements, and subject eligibility requirements.

15.2. DATA HANDLING AND RECORD KEEPING

15.2.1. Collection of Data

Data will be collected in the eCRF. The eCRF is an integral part of the trial and subsequent reports. It must be used to capture trial-specific data collected and must be kept current to reflect subject status during the course of the trial. Only a Subject Identification Number will be used to identify the subject. The investigator must keep a separate Subject Identification Code List with subject names and medical record numbers or other personal identifier(s).

The trial will use an Internet-based remote data entry system to collect clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 (R2) GCP. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The system is configured based on the requirements from the Sponsor. Source documents are to be retained to enable a reconstruction and evaluation of the trial. Source documents include the site files and trial worksheets provided by the Sponsor. Data will be recorded in the trial worksheets as appropriate to complete and/or clarify the source data.

The design of the computerized system complies with all the applicable regulatory requirements for record keeping and record retention in clinical trials [21 CFR Part 11 and ICH E6 (R2) GCP] to the same degree of confidence as is provided with paper systems. Clinical investigators must retain either the original or a certified copy of all source documents, including query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly provides a means to locate and read the prior information. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

15.2.2. Coding Dictionaries

Prior and concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

15.2.3. Data Handling

eCRFs should be completed in a timely manner to enable the sponsor or designee to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock, the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or sponsor, who routinely review the data for completeness, correctness, and consistency. The site is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and by providing the reason for the update (eg, data entry error). At the conclusion of the trial, Sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 15.2.1.

15.2.4. Direct Access to Source Data/Documents

The investigator/trial site is to provide direct access to source data/documents for trial-related monitoring, audits, IRB/ERC review, and regulatory inspection.

15.2.5. Record Keeping

The investigator is responsible for maintaining adequate records to fully document the conduct of the trial consistent with that noted in ICH E6 (R2), including but not limited to the following:

- All versions of the Investigator's Brochure
- Signed Protocol and Amendments in effect during the conduct of the trial
- Signed ICFs
- Source documents, including adequate case histories, questionnaires, and subject diaries
- Signed, dated, and completed eCRFs and documentation of data corrections
- Notification of SAEs and related reports
- Dated and documented IRB/ERC approvals and approval by regulatory authorities, as required
- Normal laboratory values
- Laboratory certifications
- Curricula Vitae of all clinical investigators
- Completed Forms FDA 1572, as applicable
- SIV documentation
- Delegation of Authority Log
- Subject Screening & Enrollment Log(s)
- Subject Identification Code List
- Study drug accountability documentation
- Signed agreements between involved parties
- Relevant communication, including that related to monitor site visits (eg, letters, meeting notes, notes from telephone calls)
- Interim, annual, or final reports to IRBs/ERCs and regulatory authorities, as required
- Audit certificate(s), if applicable

15.3. DATA QUALITY CONTROL

15.3.1. Monitoring Procedures

The Sponsor and/or its representative may make periodic visits to the investigational site to assess compliance with trial procedures and regulatory requirements; to ensure that the safety, welfare, and privacy of subjects are being protected; and to verify the accuracy and integrity of the trial data. In addition, independent Quality Assurance site audits may be conducted as verification of the quality and compliance of trial conduct.

The Sponsor and/or its representative will periodically review the trial data to ensure that data are being appropriately collected and reported. Queries and corrections will be made as needed.

15.3.2. Data Management

Sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and CRO's standard operating procedures (SOPs). A comprehensive data management plan will be developed including a data management overview, database development, validation and maintenance, data entry and processing, external data transfer, data validation and archive, and medical coding processes. Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

15.4. AUDITING PROCEDURES

In addition to the routine monitoring procedures, a GCP Quality Assurance audit may be initiated by the Sponsor. The investigator has to ensure that subjects/parents/legal guardians are aware of and consent to personal information being reviewed during the data verification process as a part of monitoring/auditing/inspection by the Sponsor, properly authorized agents of the Sponsor, or competent authorities. In addition, participation and personal information is treated as strictly confidential to the extent that applicable law permits and to which it is not publicly available. The purpose of audits and inspections is to evaluate compliance with the principles of GCP, international and local regulatory requirements, and the trial protocol. The audit or inspection may include, for example, a review of all source documents, drug records, original clinic medical notes, and some or all of the facilities used in the trial.

The audits may be conducted by the Sponsor or Sponsor's selected agent in accordance with Sponsor's SOP or SOPs of the selected and properly authorized agent. A competent authority may also wish to conduct an inspection during the trial or after its completion. If an inspection is requested by a competent authority, the investigator must inform the Sponsor immediately that this request has been made. The investigator and his/her institution will permit all monitoring, audits, and regulatory inspections, providing direct access to source data.

15.5. LABORATORY QUALITY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local and central laboratories. Some blood samples may be used for laboratory test validation.

The laboratories must provide a list of reference ranges for applicable analyses. The methods employed for each assay should be available on request. Any change in the laboratory procedures, reference values, etc., during the trial must promptly be communicated to the Sponsor. The laboratories may also be audited by the Sponsor or by competent authorities.

15.6. TRIAL TERMINATION OR COMPLETION

The investigator should notify the IRB/ERC in writing of the completion or early termination of the trial. End of trial is defined as last subject last visit.

Upon trial completion or termination, applicable regulatory reporting requirements will be followed. The Sponsor reserves the right to terminate the trial at any time for any reason including insufficient efficacy and unanticipated safety concerns.

The Sponsor may stop this trial at a particular site for any of the following reasons:

- The site cannot enroll an adequate number of subjects
- Serious and/or persistent non-compliance with the protocol or clinical trial conduct
- Careless or premeditated false documentation in the electronic case report form (eCRF)
- Inadequate cooperation with the investigator
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation

15.7. CHANGES TO THE PROTOCOL

Changes in any portion of this protocol must be documented in the form of an amendment from the Sponsor and must be approved by the investigational site's IRB/ERC and regulatory authorities, as required, before the amendment is implemented. However, in the event of apparent immediate hazard to a subject, a deviation from the protocol is allowed to eliminate the hazard. In this case, the deviation and the reason for it must be promptly reported as required by regional regulations to the applicable IRB/ERC and regulatory authorities, along with a proposed protocol amendment if appropriate.

Protocol amendments may only be made with prior written approval of the Sponsor and/or its representative and documented approval or favorable opinion from applicable regulatory authorities or regional IRB/ERC, as required. The investigator must send a copy of the documented approval to the Sponsor and/or its representative.

15.8. OTHER CHANGES IN TRIAL CONDUCT

Changes in trial conduct are not permitted. Any unforeseen changes in trial conduct will be recorded in the clinical study report.

15.9. USE OF INFORMATION AND PUBLICATION

The data and information generated in this trial are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required prior to disclosing any information related to this trial. Publication of the results will be based on appropriate analyses and review of the complete data. Authorship will be determined based on enrollment of eligible subjects or contribution to the design, conduct, or interpretation of the trial. Publication of any data of this trial without prior Sponsor approval is not permitted.

16. ETHICAL AND LEGAL CONSIDERATIONS

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- GCPs as outlined in ICH E6 (R2) and regional regulations
- Declaration of Helsinki

- Regional required subject data protection laws and regulations
- Applicable regional regulations
- US Federal Regulations, as applicable

16.1. DATA MONITORING SAFETY BOARD/INDEPENDENT SAFETY COMMITTEE

Independent oversight of this trial may be provided by a DSMB/ISC, if deemed appropriate despite the relatively short duration of the pivotal trial.

16.2. INFORMED CONSENT

The draft ICF must be reviewed by the Sponsor and/or its representative prior to submission to a regional IRB/ERC for approval. A copy of the ICF approved by the review board must be forwarded to the Sponsor and/or its representative.

The ICF (and Subject Information Sheet, if applicable) documents the trial-specific information the investigator provides to the subject and the subject's agreement to participate. The investigator or designee will fully explain in layman's terms the nature of the trial along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The ICF and Subject Information Sheet must be appropriately signed and dated before the subject undergoes any trial-related procedure. The original and any amended signed and dated ICFs and subject information sheets must be retained at the trial site with a copy of each provided to the subject.

16.3. IRB/ERC APPROVALS

The Principal Investigator at each site is responsible for obtaining approval from the appropriate regional IRB/ERC for the final protocol, Sponsor-approved ICF and subject information sheet (if applicable), and any advertisements to recruit subjects. Written approval of these documents must be obtained from the committee before any subject is enrolled at a trial site. The IRB/ERC must comply with all applicable US FDA regulations, as applicable.

The Principal Investigator is also responsible for the following interactions with the regional IRB/ERC:

1. Obtaining review board approval for any protocol amendments and ICF revisions before implementing the changes
2. Providing the review board with any required information before or during the trial
3. Submitting progress reports to the review board as required during the conduct of the trial, requesting continuing review and approval of the trial as needed and providing copies of all review board re-approvals and relevant communication to the Sponsor and/or its representative
4. Notifying the review board of all serious and unexpected AEs related to the study drug reported by the Sponsor and/or its representative, as required
5. Notifying the review board of the end of trial participation, in accordance with regional guidelines and regulations

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18. SIGNATURE OF AGREEMENT

In signing this protocol, the investigator agrees to:

1. Conduct the trial in accordance with the relevant, current protocol and make changes only after notifying the Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human subjects
2. Comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice plus appropriate regional regulatory laws and requirements, including US Federal Regulations, as applicable
3. Personally conduct or supervise the described investigation
4. Inform any subjects or persons used as controls that the study drugs are being used for investigational purposes
5. Ensure requirements relating to obtaining informed consent and regional ethical or institutional review board approval have been met
6. Report to the Sponsor or its representative any AEs that occur in the course of the investigations, as specified in Section 12
7. Read and understand the Investigator's Brochure, including potential risks and side effects of the study drug
8. Ensure all associates, colleagues, and employees assisting in the conduct of the trial are informed of their obligations in meeting their commitments
9. Maintain adequate and accurate records and make these available for inspection by the Sponsor and/or its representative or any regulatory agency authorized by law
10. Promptly report to the regional ethical or institutional review board all changes in research activity and all unanticipated problems involving risks to human subjects or others
11. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements
12. Administer study drug only to subjects who meet trial entry criteria and are enrolled in the trial and only according to the guidelines set forth in this protocol
13. Sign a Form 1572, as applicable

SIGNATURE OF AGREEMENT

I have read and understand the information in this clinical trial protocol, including the potential risks and side effects of the study drug, and agree to personally conduct or supervise the described investigation(s) in accordance with the relevant, current protocol(s) and will not deviate from the protocol, except when necessary to protect the safety, rights, or welfare of subjects. I agree to inform all subjects that the study drug is being used for experimental purposes, and I will ensure that the requirements related to obtaining informed consent are met. I agree to report to the Sponsor any adverse events that occur in the course of the investigation(s).

1. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments.
2. I will not make any changes in the research without IRB/ERC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
3. I agree to maintain all information in this document and regarding the stud(ies) as confidential and to use it only for the purpose of conducting the stud(ies). I agree not to forward this document to any other party without the prior written authorization of the Sponsor.

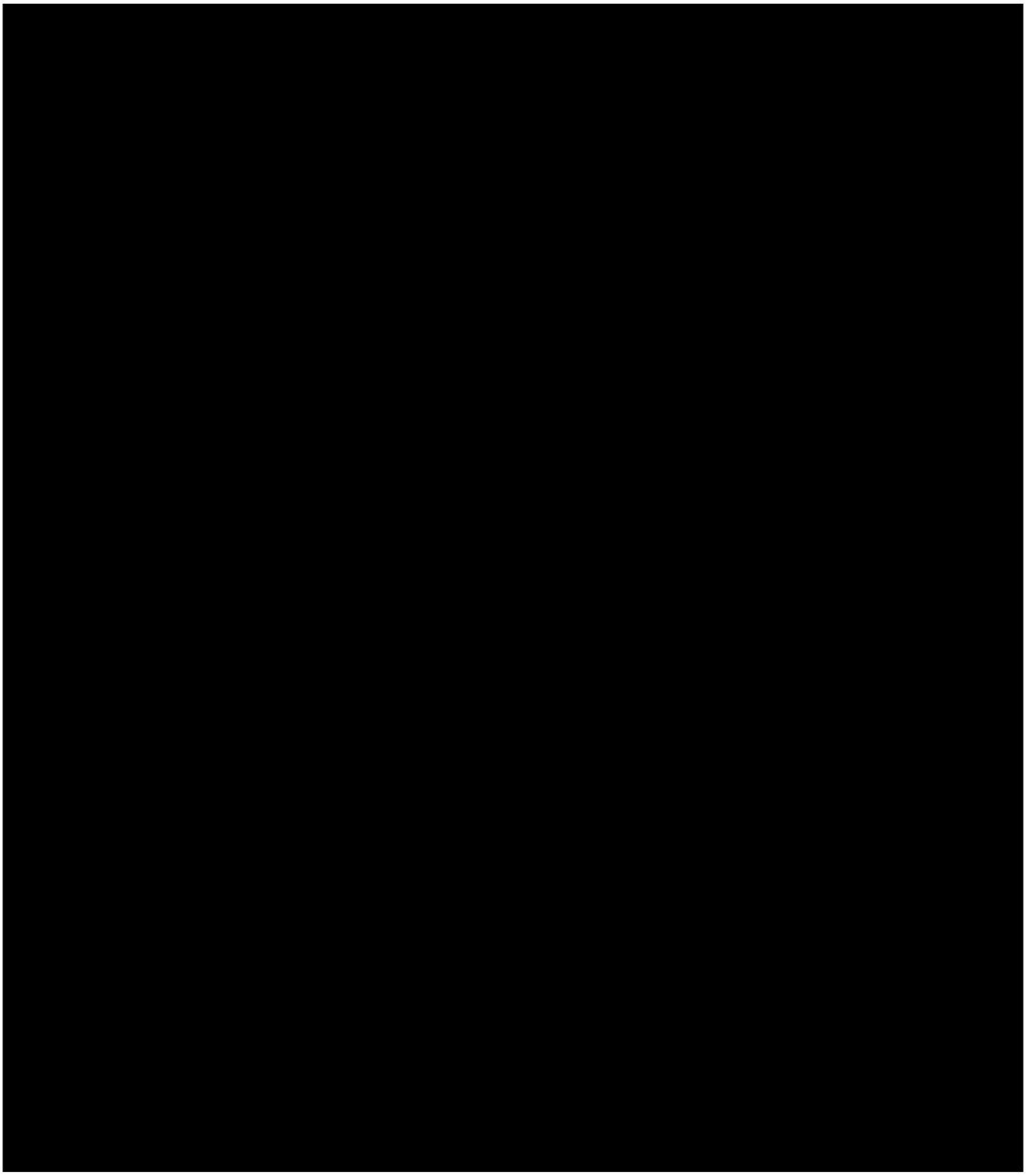
Investigator:

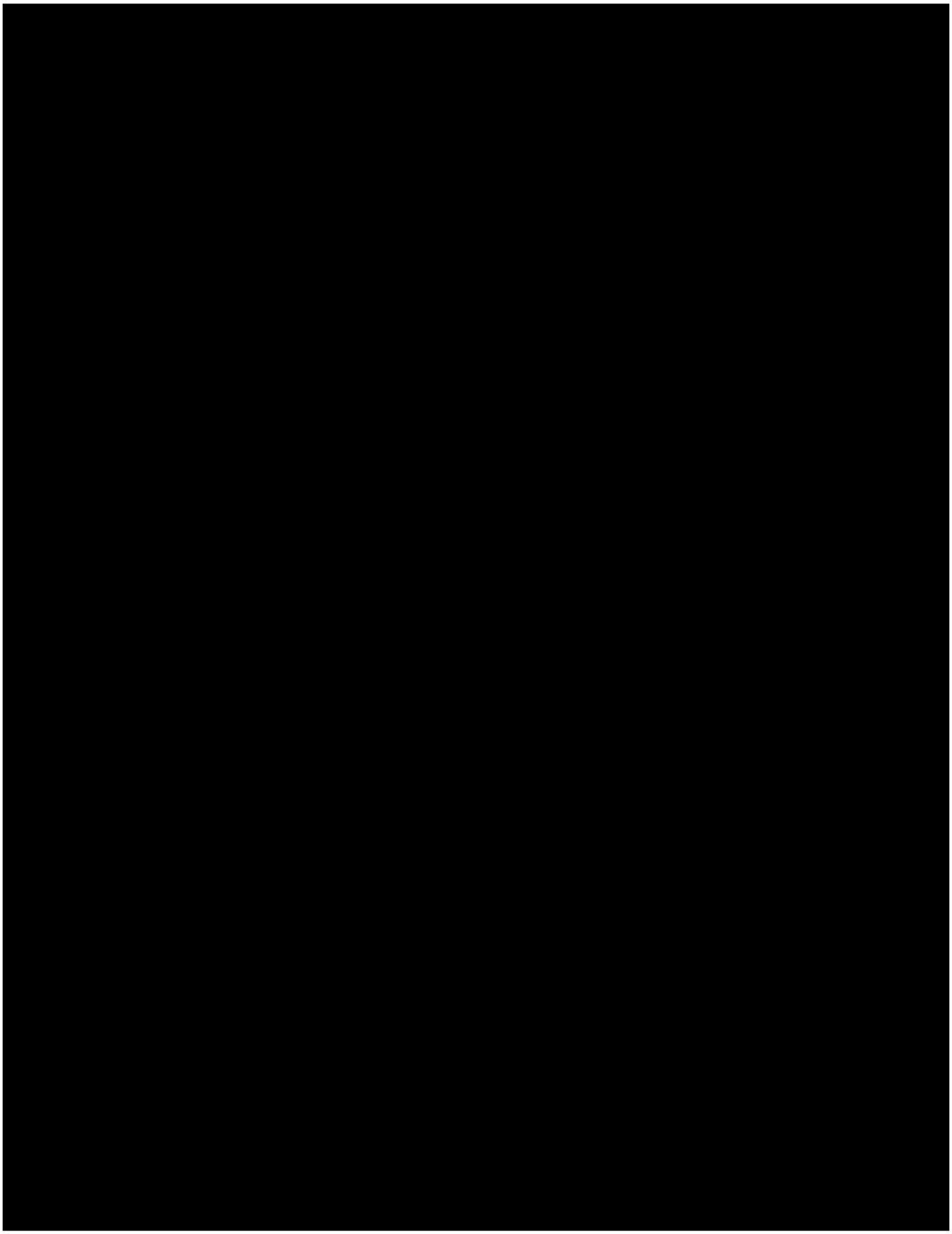
Printed Name and Title: _____

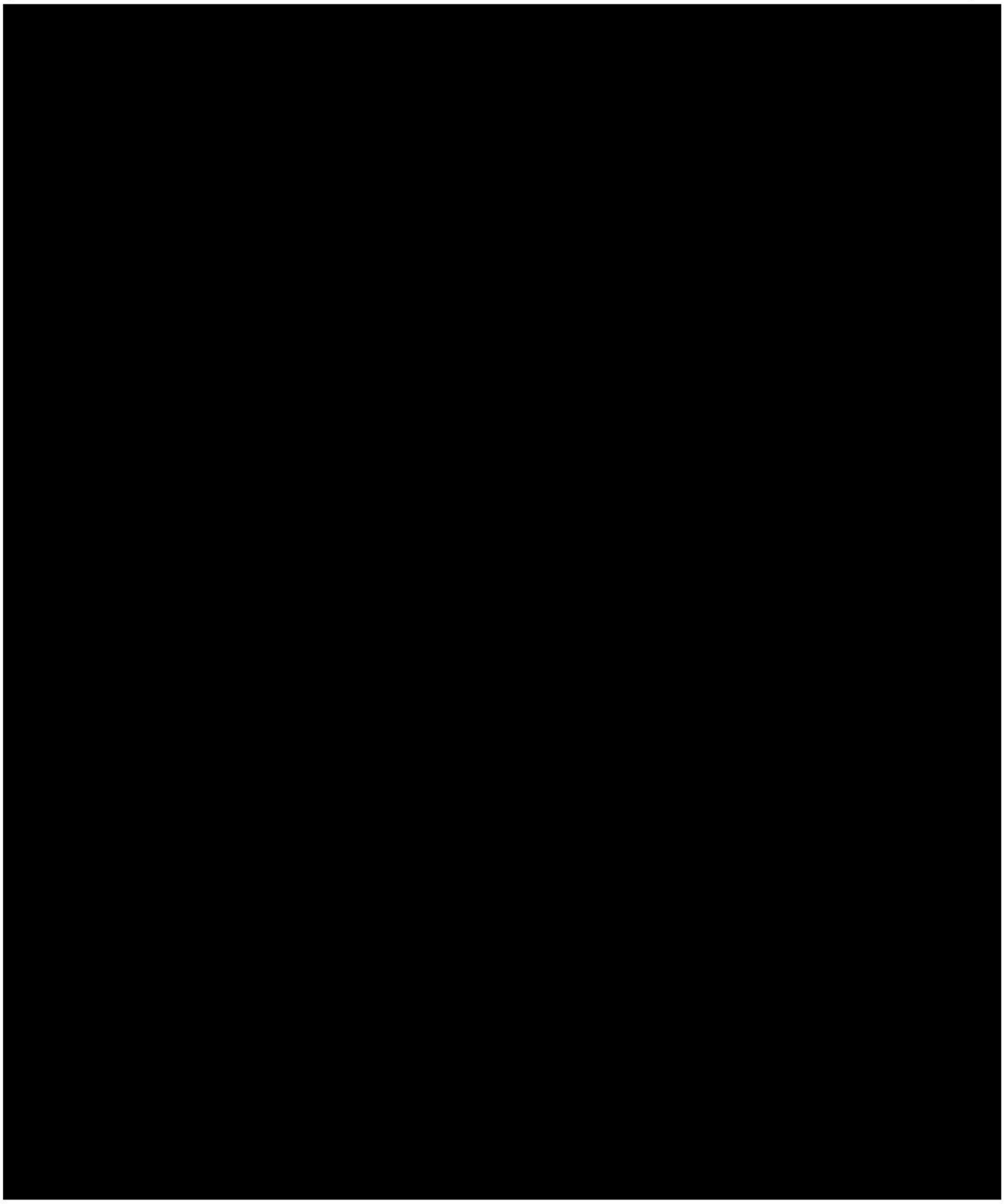
Signature: _____

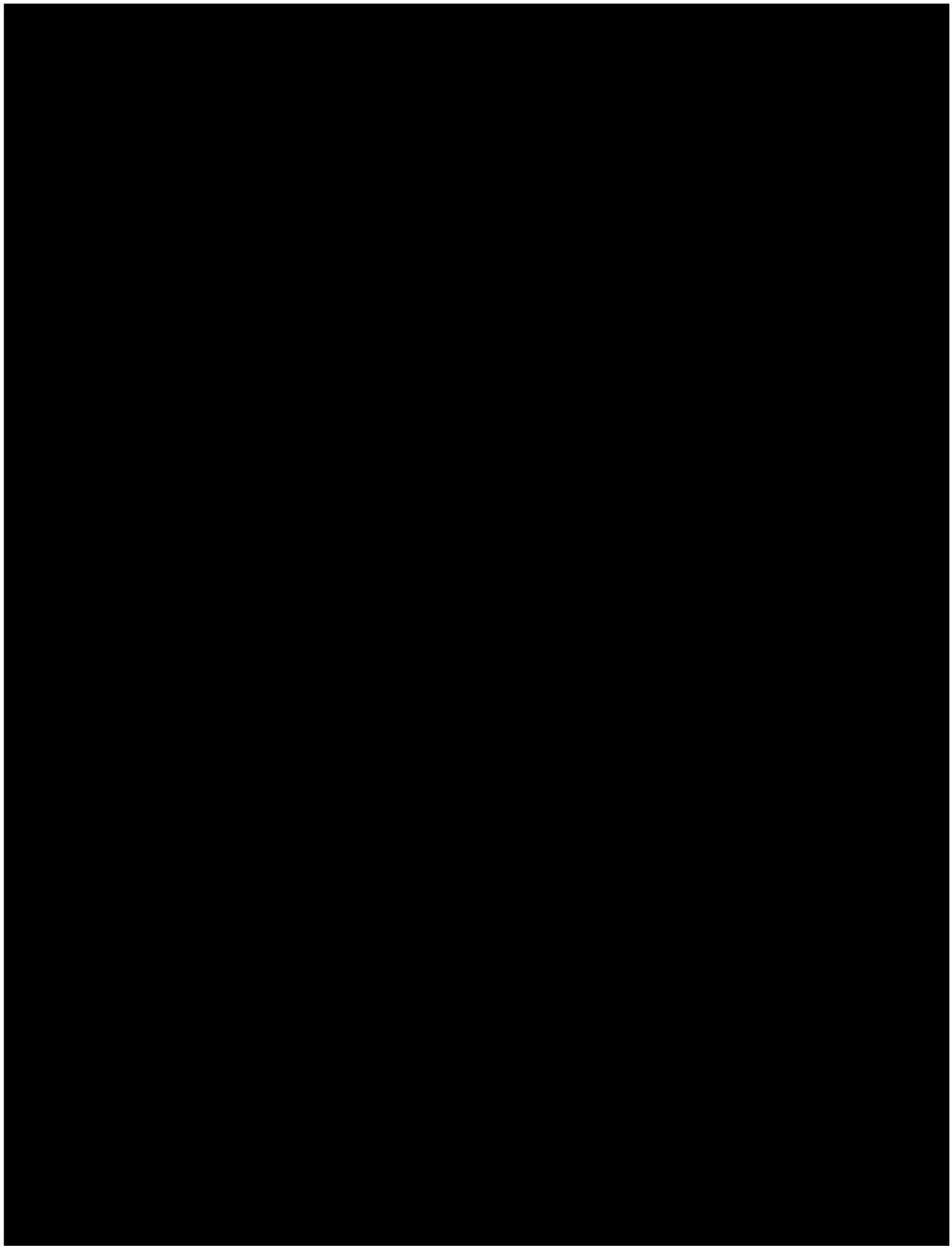
Date: _____

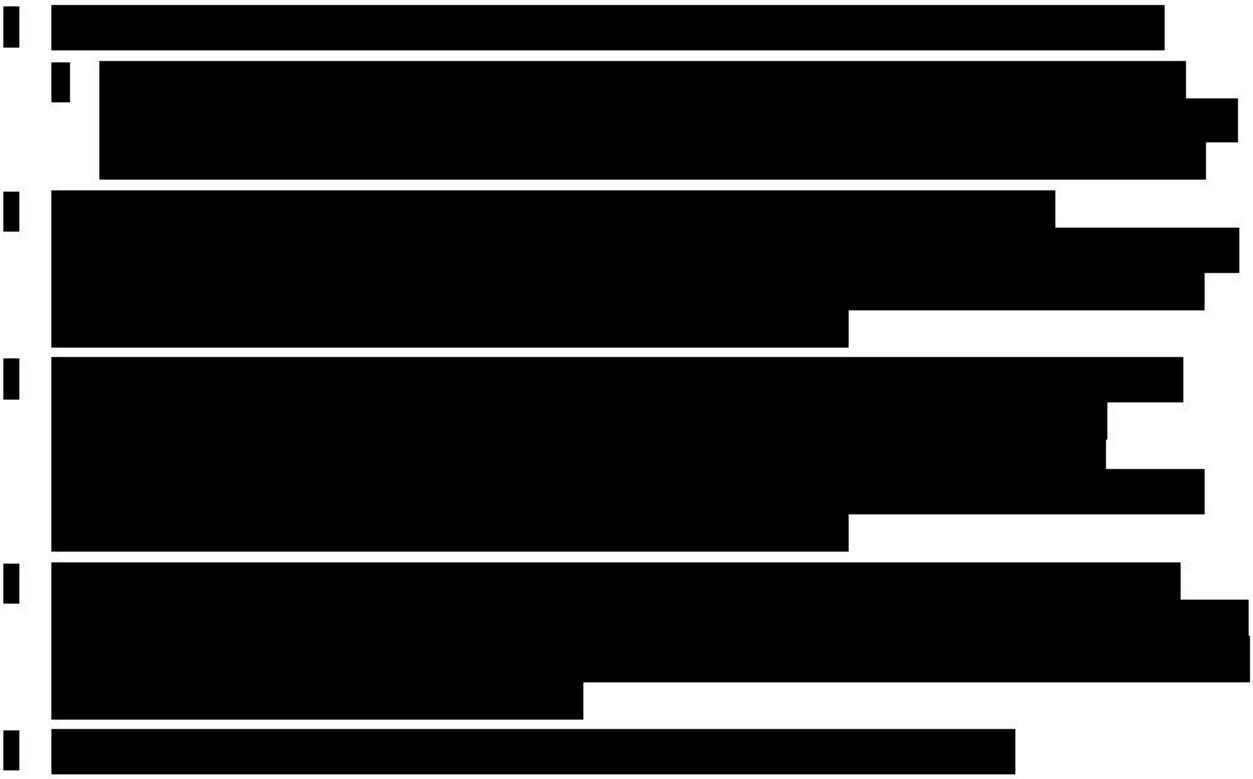
19. APPENDICES











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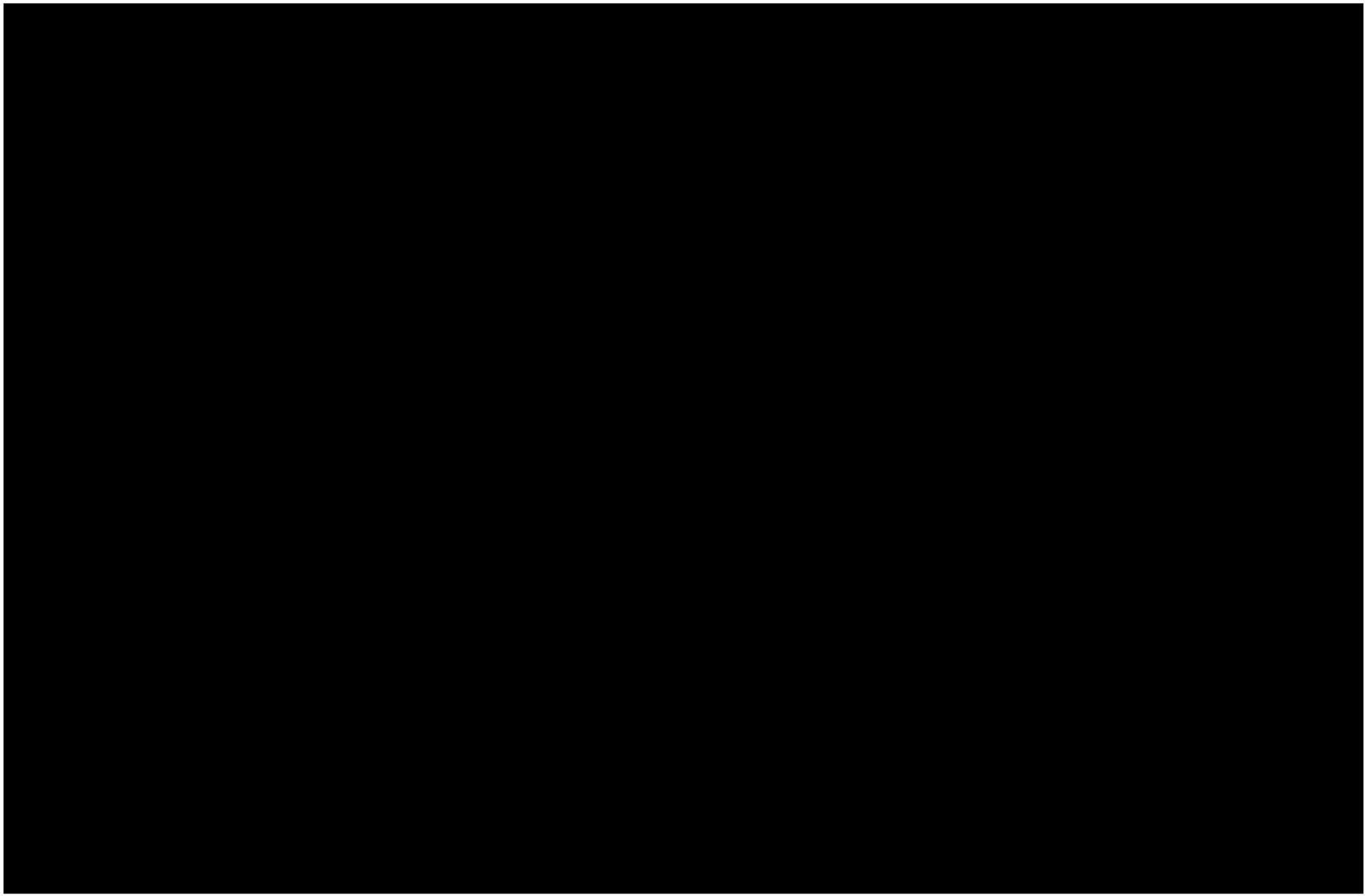

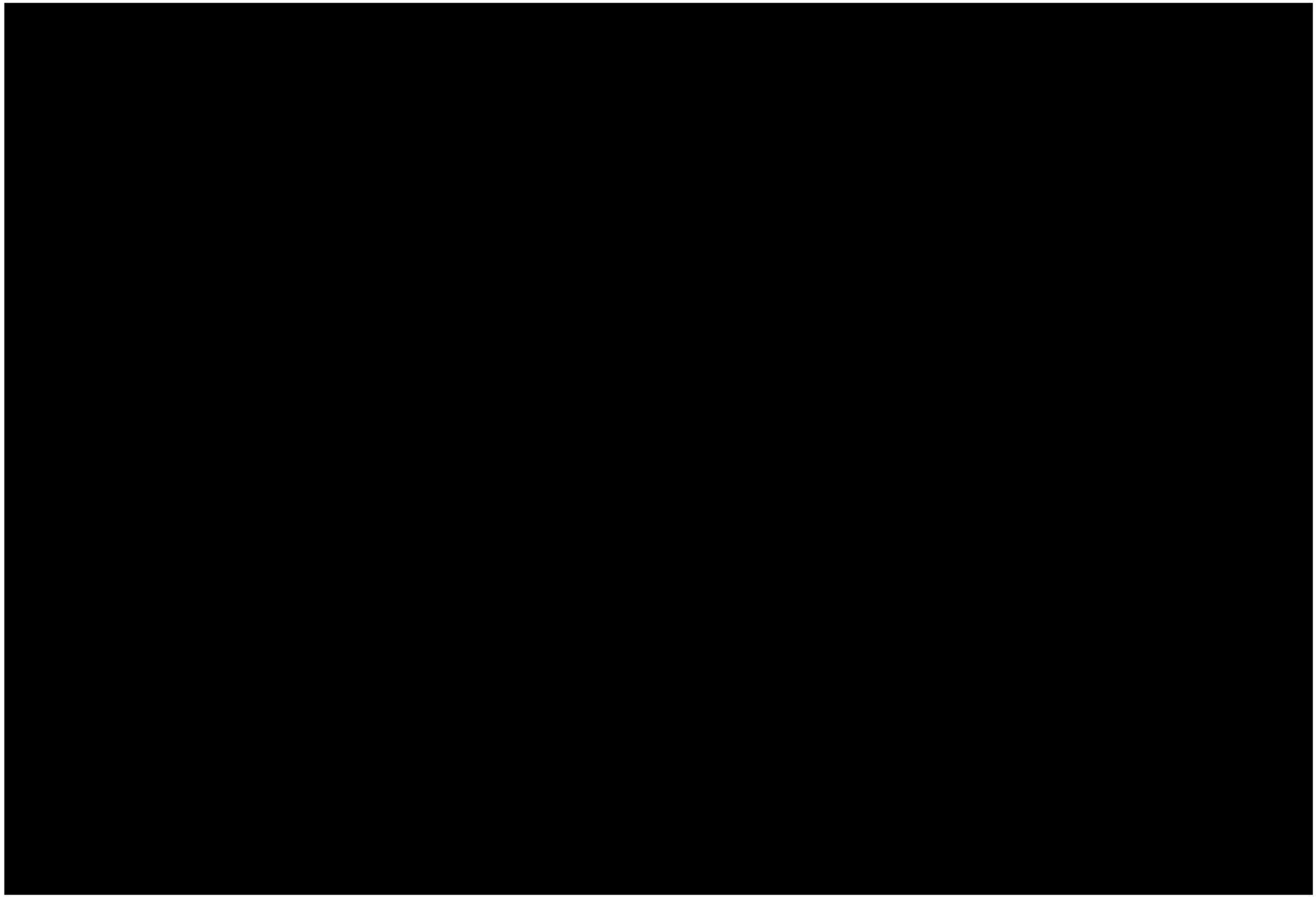

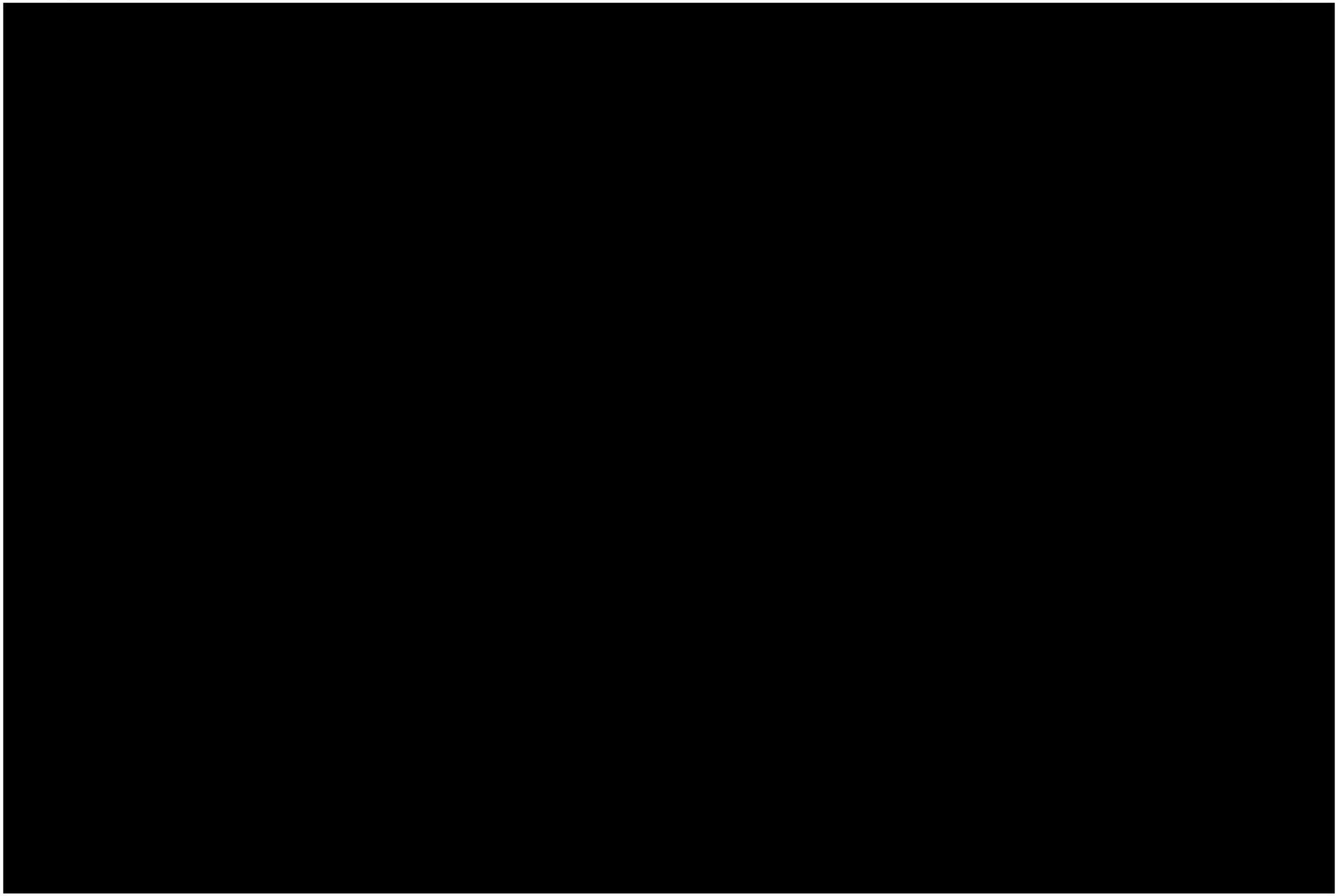

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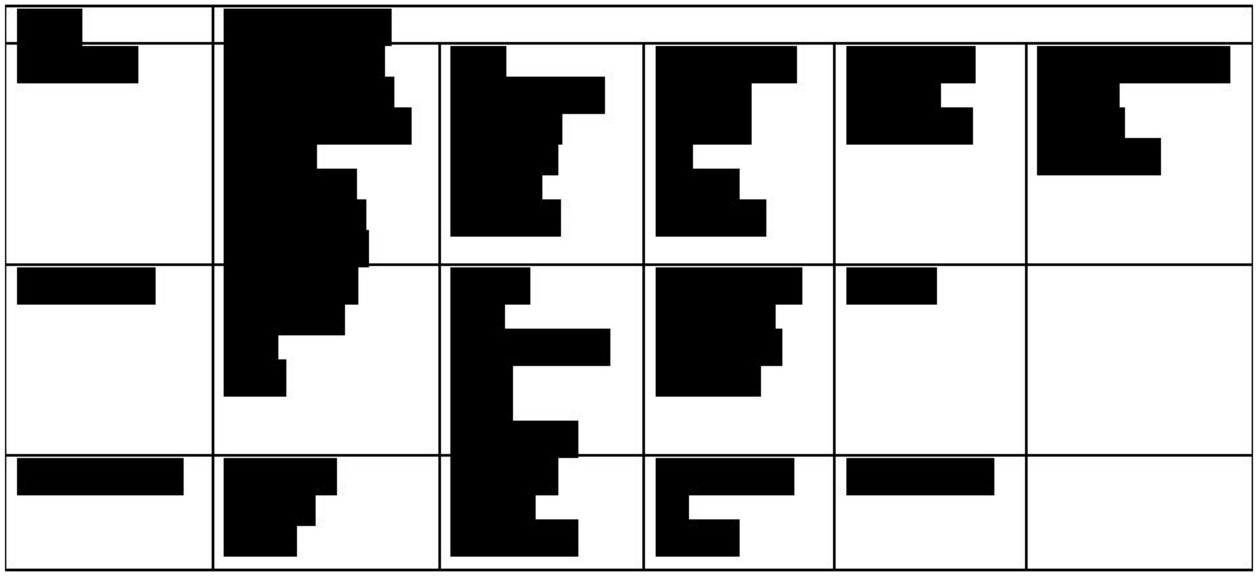

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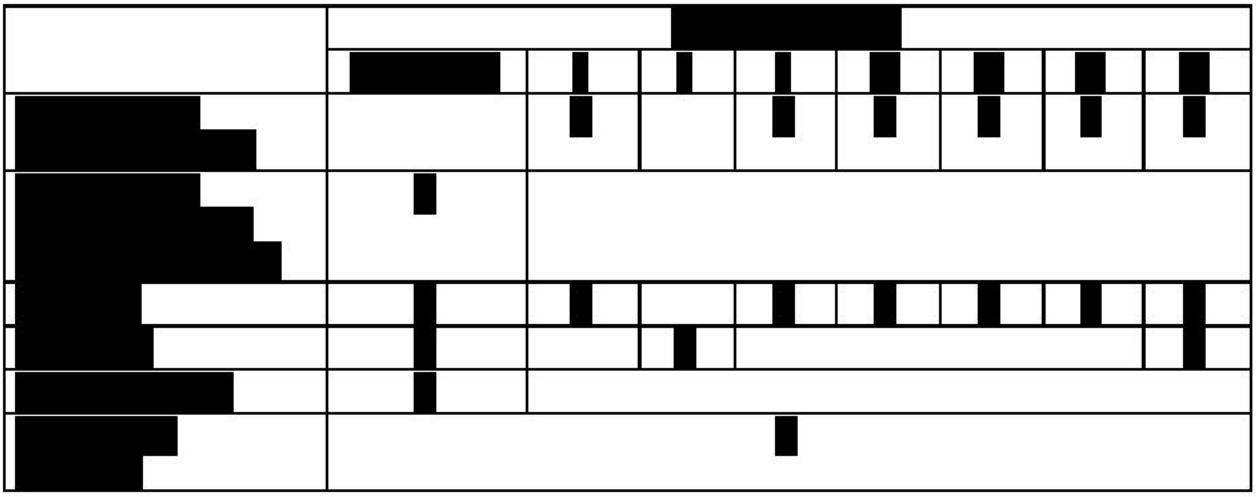

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