Endocrinologic and Metabolic Drugs Advisory Committee Meeting

September 12th 2014

FDA Introductory Remarks

BLA 125511

PTH (1-84) for injection, Natpara

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Director

Division of Metabolism and Endocrinology Products (DMEP)

Natpara

Natpara is recombinant human parathyroid hormone (PTH) identical in primary sequence to the full-length human endogenous hormone (i.e., 84 amino acids)

Indication sought:

- *Natpara for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism*

Objectives

- Overview: Regulatory History
- Overview: Hypoparathyroidism and treatment
- Overview: Agenda
- Review: Discussion points and voting question

Regulatory History

- PTH (1-84) was initially developed for the treatment of osteoporosis in post-menopausal women at high risk of bone fracture
- The application for PTH (1-84) seeking the osteoporosis indication was not approved on first cycle of review due to observation of excess events of serious hypercalcemia and because of device reliability issues. In 2011, the applicant officially withdrew the application for osteoporosis
- The investigational new drug application for PTH (1-84) for the treatment of hypoparathyroidism was opened in 2006
- In 2007 the applicant submitted a formal request to designate Natpara for the treatment of hypoparathyroidism an orphan product and Natpara was granted this designation

Hypoparathyroidism

- Parathyroid hormone (PTH) is secreted from the parathyroid glands in response to low circulating calcium levels and plays an important role in calcium homeostasis
- Hypoparathyroidism is characterized by low or normal circulating parathyroid hormone levels in the setting of hypocalcemia
- Hypoparathyroidism most commonly occurs as a result of

  Damage or accidental removal of the parathyroid glands during thyroid surgery

  More rarely it occurs as a result of

  Intentional or accidental removal of the parathyroid glands
  Autoimmune destruction of the parathyroid glands or

  Congenital disorders that affect the development or function of the parathyroid glands

Hypoparathyroidism

- Acute complications of low PTH
  - **Hypocalcemia** and can result in symptoms (numbness, paresthesia, tingling) or if severe enough a threat to life (e.g., tetany, seizures, laryngospasm, cardiac arrhythmias)
- Long-term complications low PTH
  - **Chronic hypocalcemia** can lead to cardiomyopathy,
  - **Chronic hyperphosphatemia** can lead to precipitaion of calcium phosphate in soft tissues
  - **Chronic hypercalciuria** can lead to nephrocalcinosis and progressive renal impairment as well as nephrolithiasis
  - **Low bone turnover** increases bone density may be associated with poor bone quality and increase risk of fractures

Hypoparathyroidism

- Hypoparathyroidism is a rare disease

Reported prevalent complications (retrospective case review)*

	Prevalence in Subgroup of Patients with Available Data
Hypercalciuria on most recent visit (> 300 mg/24 hours)	**26%**
Renal Impairment (eGFR ≤ 60 mL/min/m^2)	**41%**
Renal Calcification on Imaging (stones or nephrocalcinosis)	**44%**
Hypoparathyroidism-related Hospitalizations (symptomatic hypo or hypercalcemia, renal stones)	**33%**

*Journal of Clinical Endocrinology and Metabolism, December 2012, 97(12):4507–4514

Therapeutic Goals

Treatment of hypoparathyroidism with currently available therapies aim to reduce the risk of hypocalcemia while minimizing the risks of renal complication and calcium phosphate deposition in tissues

Therapies

- No PTH (i.e., the deficient hormone) or PTH analogue is approved for the treatment of hypoparathyroidism
- Therapies to treat the complications of hypoparathyroidism include calcium (oral and injectable) and vitamin D (active and inactive forms)
- FDA therapies with an indication for the management of hypocalcemia in hypoparathyroidism include:
  - Ergocalciferol [Drosidol] initially approved in 1941 (NDA 003444)
  - Calcitriol [Rocaltrol] initially approved in 1978 (NDA 018044)
  - Calcium Gluconate Injection
- The dose of oral therapies are adjusted to target the therapeutic goal of preventing hypocalcemia while minimizing specific risks

Therapies

Patients with hypoparathyroidim require calcium multiple times daily and active vitamin D to maintain serum calcium.

Doses of Oral Calcium Active Vitamin D

	Mitchell et al.++ Mean [SD]	Baseline REPLACE trial Median [IQR]
Total Calcium mg per day	**~2000 [±1500]**	**~2000 [1250, 3000]**
Calcitriol* µg per day	**106 [88]**	**75 [50, 100]**

++Journal of Clinical Endocrinology and Metabolism, December 2012, 97(12):4507–4514
*1-α-calcidol converted to calcitriol equivalent dose

Agenda

Day's Proceedings

1. Discussion

Discuss whether the data in the REPLACE trial provide substantial evidence that treatment with Natpara offers a clinically meaningful benefit to patients with hypoparathyroidism regardless of etiology. In your discussion, specifically address this (or these) benefit(s).

2. Discussion

Discuss your level of concern with regard to the risks (acute and chronic) of hypercalcemia and hypocalcemia associated with the use of Natpara. Comment on ways to mitigate these risks in the clinical care setting

3. Discussion

Discuss your level of concern with regard to the risk of osteosarcoma associated with long-term use of Natpara in patients with hypoparathyroidism. In your discussion, specifically address how differences or similarities between a population of patients with osteoporosis and a population of patients with hypoparathyroidism does or does not inform your assessment of this risk.

4. Discussion

Discuss any additional concerns you may have related to risks or benefit not raised above.

1. Voting

In light of the efficacy and safety findings in the Natpara development program, does the overall risk-benefit of Natpara administered at the doses and regimen proposed support approval of Natpara for the long-term treatment of hypoparathyroidism?

a. If voting YES, please provide your rationale and whether you recommend any additional studies post-approval.

b. If voting NO, please provide your rationale and discuss what additional data would be necessary prior to approval to address your concerns.

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
College Park, MD
September 12, 2014

BLA 125511
Natpara®
Clinical Efficacy and Safety Review

Naomi Lowy, M.D.
Medical Officer
Division of Metabolism and Endocrinology Products
Office of New Drugs
CDER

Overview

- Natpara: General Aspects
- Currently Available Treatment for Hypoparathyroidism
- Products Related to Osteosarcoma and Natpara
- Natpara Clinical Development Program
- Pivotal Trial (040)
- Efficacy
  - Primary Efficacy and Related Analyses
  - Secondary Efficacy and Related Analyses
  - Exploratory Efficacy and Related Analyses
  - Efficacy Conclusions
- Summary of Final Doses in Pivotal Trial
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Terminology

- Natpara, NPSP558, and rhPTH(1-84) are used interchangeably.
- Except where specified, “vitamin D” refers to active vitamin D metabolite or vitamin D analog.
- PTH refers to parathyroid hormone.

Natpara® (rhPTH[1-84]) for Injection: General Aspects

- Active ingredient is recombinant human parathyroid hormone (rhPTH)
  - Identical to the full-length human 84-amino acid protein
- Not approved in United States for any indication
- Proposed as replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism

Natpara®: General Aspects

- Biologic-device combination
- Designed for use with a mixing device for product reconstitution and a reusable pen injector for drug delivery
- Supplied in a cartridge in 4 dosage strengths:
  25, 50, 75, and 100 µg

Natpara®: General Aspects

- Applicant recommends a starting dose of 50 µg
  - Based on calcemic response, titrate at 2- to 4-week intervals upward to a maximum of 100 µg
  - Downward titration to 25 µg at any time
  - Subcutaneous (SC) injection into alternating thighs

Currently Available Treatment for Hypoparathyroidism

- Natpara: General Aspects
- **Currently Available Treatment for Hypoparathyroidism**
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Currently Available Treatment for Hypoparathyroidism

- There are no formal guidelines for the management of hypoparathyroidism.
- Vitamin D metabolites and analogues are essential to the management of hypoparathyroidism
  - Suggested that calcitriol is preferred (over vitamin D_2 or D_3) because of its potency and rapid onset and offset of action[1]
- Hormone replacement therapy does not currently play a role

[1]Shoback D. Clinical Practice: Hypoparathyroidism. N Engl J Med 2008; 359:391-403

Goals of Currently Available Therapy[1]

Control symptoms of hypocalcemia without causing hypercalciuria

1) A serum albumin-corrected total calcium level at the lower end of the normal range (approximately 8.0 to 8.5 mg/dL)
2) A 24-hour urinary calcium level well below 300 mg
3) A calcium–phosphate product below 55 mg^2/dL^2

[1]Shoback D. Clinical Practice: Hypoparathyroidism. N Engl J Med 2008; 359:391-403

Complications from Over-treatment: Etiologies

- High filtered load of calcium
  - Nephrocalcinosis
  - Kidney stones
- High calcium-phosphate products can lead to precipitation of calcium–phosphate salts in soft tissues
  - Kidney
  - Lens
  - Basal ganglia

Other Limitations of Currently Available Treatment

- Bone turnover is dramatically reduced in hypoparathyroidism
  - Calcium and vitamin D do not correct the defective bone metabolism resulting from PTH deficiency

Horwitz M and Stewart M. Hyoparathyroidism: Is it Time for Replacement Therapy? Journal of Clinical Endocrinology and Metabolism. September 2008.

Osteosarcoma and Related Products

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Osteosarcoma

- Osteosarcoma is a primary malignancy of bone
- Rare, with an estimated incidence ranging from 1.7 to 4.4 per million depending on age[1]
- Peak incidence is in male adolescents
  - Extremities are the most common anatomic site
- Secondary incidence peak in the elderly
  - Axial locations more common
  - Cases often secondary neoplasms (e.g., transformation of Paget's disease of bone)
  - Previous irradiation a risk factor

[1]Mirabello L, et al. Osteosarcoma incidence and survival rates from 1973 to 2004: Data from the Surveillance, Epidemiology, and End Results Program. *Cancer*. 2009: 115, 1531-1543.

rhPTH: Regulatory History

- Forteo® (rhPTH[1-34])
  - Recombinant, truncated version consisting of first 34 amino acids
  - Initial US approval 2002
  - Indicated for the treatment of osteoporosis in specific populations
  - Use beyond 2 years of a patient's lifetime not recommended
- Preotact® (rhPTH[1-84])
  - Was approved in the European Union for the treatment of post-menopausal osteoporosis who are at high risk of fractures
  - Daily dose of 100 µg
  - Withdrawn from market in 2014 for business reasons

[1]Forteo Full Prescribing Information, Revised 3/2012

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Forteo®: Potential Risk of Osteosarcoma

- Package Insert includes a boxed warning:

WARNING: POTENTIAL RISK OF OSTEOSARCOMA

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) ***[see Warnings and Precautions (5.1), Adverse Reactions (6.2), and Nonclinical Toxicology (13.1)]*****.**

- Use for more than 2 years of a patient‘s lifetime not recommended
- Risk Evaluation and Mitigation Strategy (REMS) in place

Forteo®: Post-Marketing Requirements

- PMR 1: Teriparatide Post-Approval Osteosarcoma Surveillance Study
  - Ongoing 15-year surveillance study
  - Objective to identify 1/3 of the incident cases of osteosarcoma annually (patients ≥ 40 years) and assess for a history of Forteo exposure
  - Interim data (7 years): no cases of incident osteosarcoma with a prior history of Forteo exposure[1]
  - Final report submission is expected in 2019
- PMR 2: Forteo User Registry Study
  - Ongoing prospective cohort study with voluntary registration of users
  - Data from registered patients linked with participating cancer registries to ascertain any new cases of osteosarcoma in Forteo-exposed patients
  - Final report submission is expected in 2022

[1]Andrews E, et al. The US Postmarketing Surveillance Study of Adult Osteosarcoma and Teriparatide: Study Design and Findings from the First 7 Years. *JBMR*. 2012: 27, 2429-2437.

Forteo®: Post-Marketing Data for Osteosarcoma

- FDA Adverse Event Reporting System (FAERS)
  - Over 9 million adverse event reports associated with approved products
  - Includes both domestic and foreign reports; reporting both voluntary (healthcare providers, consumers) and mandatory (manufacturers)
  - Report quality varies; FDA unable to verify or validate data
- FAERS search strategy
  - Reports with one or more preferred terms from the Bone Sarcomas HLT
  - Forteo, teriparatide, or teriparatide acetate as a suspect drug
  - No date restrictions

Forteo®: Post-Marketing Data for Osteosarcoma

- Osteosarcoma FAERS cases for Forteo
  - 9 cases of osteosarcoma identified; 6 domestic
  - 43-90 years; 6 female/3 male
  - 8 cases with a history of Forteo prior to initial osteosarcoma diagnosis
    - Duration of therapy (5 of the 8 cases): 3-24 months
    - Pathology consistent with osteosarcoma: 4 of 8 cases
    - Prior history of radiation therapy: 2 of 8 cases
- Prescribing Information:

  Section 6.2 Postmarketing Experience

  "Osteosarcoma: Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to Forteo use is unclear."

Forteo®: Potential Risk of Osteosarcoma

- The non-clinical findings regarding osteosarcoma in rats in the Forteo program are comparable to those observed in the Preos/Natpara nonclinical program.

Natpara Clinical Development Program

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Natpara Clinical Development Program: Efficacy and Safety Studies in Hypoparathyroidism

Study	Objectives	Design/ Control	Dose	# Subjects	Duration
CL1-11-040 (REPLACE)	Efficacy and safety	Randomized, double-blind, placebo-controlled	50, 75, and 100 µg (flexible doses) or placebo	Natpara, 90; placebo, 44	24 weeks
PAR-C10-008 (RACE)	Safety and tolerability	Open-label	25, 50, 75, and 100 µg (flexible doses)	53	52 weeks + extension ONGOING
PAR-C10-007 (RELAY)	Efficacy and tolerability	Randomized, dose-blinded	25 or 50 µg (fixed doses)	25 µg, 23; 50 µg, 24	8 weeks
PAR-C10-009 (REPEAT)	Safety and tolerability	Open-label	50, 75, and 100 µg (flexible doses)	24	24 weeks

Pivotal Trial (040)

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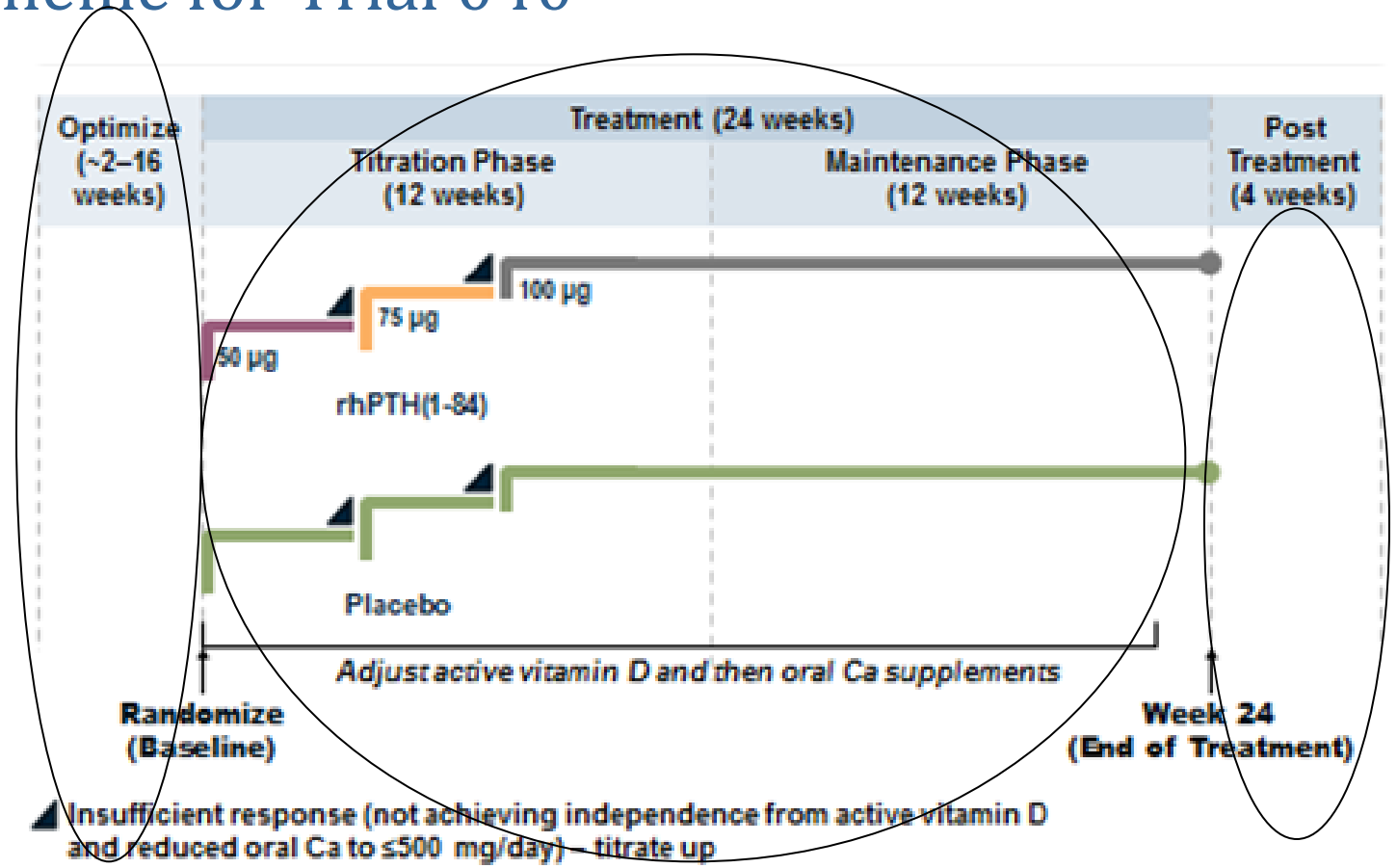
Trial 040: General Aspects

- "Pivotal" trial
- Phase 3, Randomized, double-blind, placebo-controlled international trial
- 24-week treatment period of Natpara compared to standard of care
- Overall goal of trial was to reduce calcium and vitamin D supplementation while maintaining calcium within the normal reference range
- Subjects randomized 2:1 to Natpara or placebo
- Studied doses of 50, 75, and 100 µg

Scheme for Trial 040



From Applicant's CSR

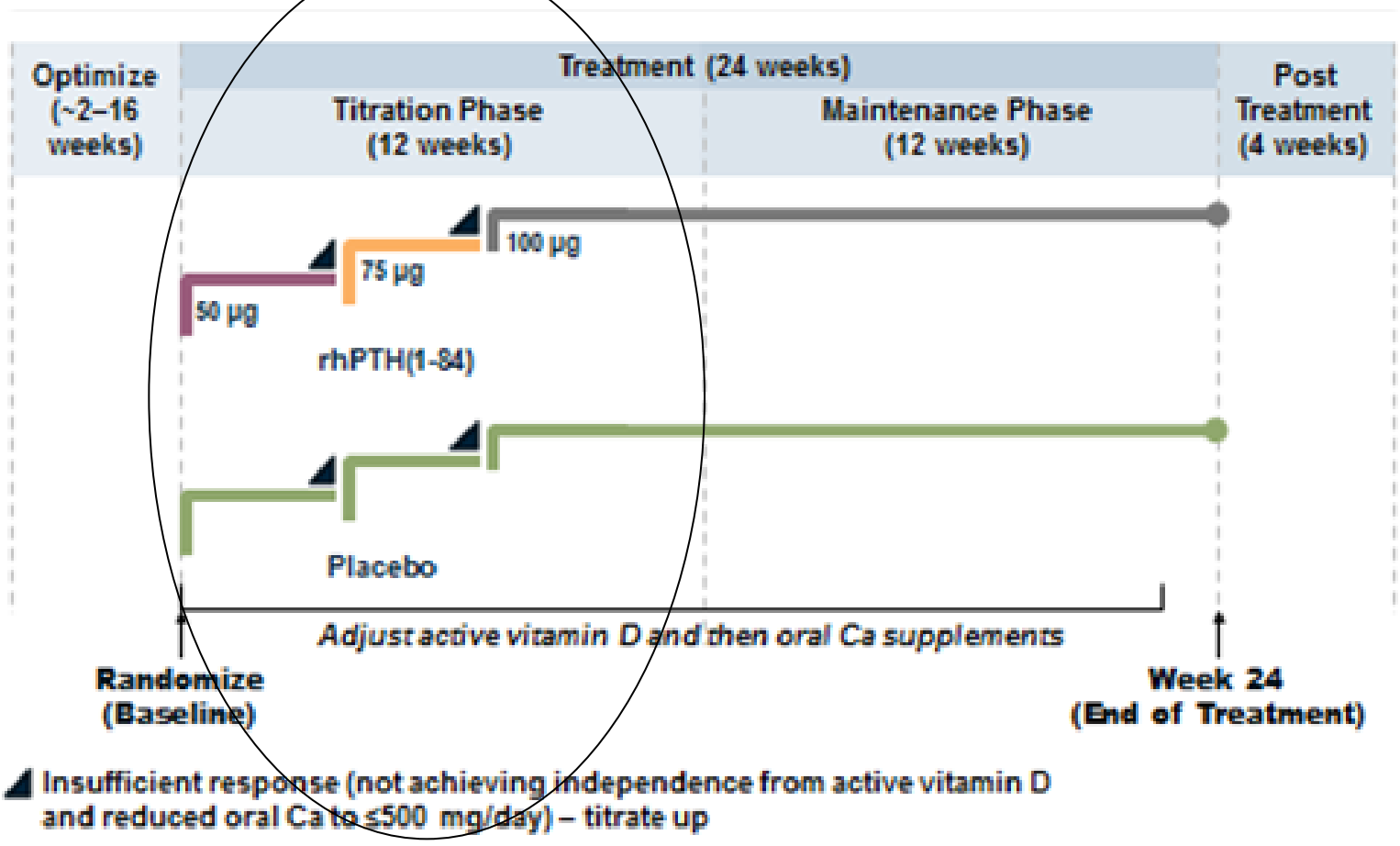
Optimization Phase: Goals

- Oral calcium and active vitamin D metabolite/analog doses were adjusted to a total serum calcium concentration within an 8-9 mg/dL target range.
- Subjects with low levels of 25-hydroxyvitamin D were supplemented with vitamin D_3 until the levels returned to the normal range.
- Subjects were optimized on calcium citrate and either calcitriol or alphacalcidol.
- Subjects who were taking other forms of calcium before the trial were converted to Applicant-sponsored supplements.

Optimization Phase: Goals

- Subjects received dietary advice
- Subjects taking thiazide diuretics for the treatment of hypertension were changed to and stabilized on an alternate antihypertensive agent that was neutral in its effects on calcium metabolism.
- Subjects were ready for randomization when:
  - They were on **stable** doses of calcium citrate of 1,000 mg or greater and daily dose of calcitriol was 0.25 µg or greater, or the daily alfacalcidol dose was 0.50 µg or greater (relative potency of calcitriol thought to be approximately double compared to alfacalcidol);
  - The albumin-corrected total serum calcium concentration was between 7.5 mg/dL and the ULN.

Titration Phase



Principles of Titration

- Following randomization to Natpara 50 µg or placebo, subjects underwent staged reductions in calcium and vitamin D metabolite/analog while maintaining serum calcium with a goal of 8-9 mg/dL
  - Algorithm provided
  - Investigator discretion
  - Initial 50% reduction in vitamin D metabolite/analog with initiation of study drug

Titration of Natpara

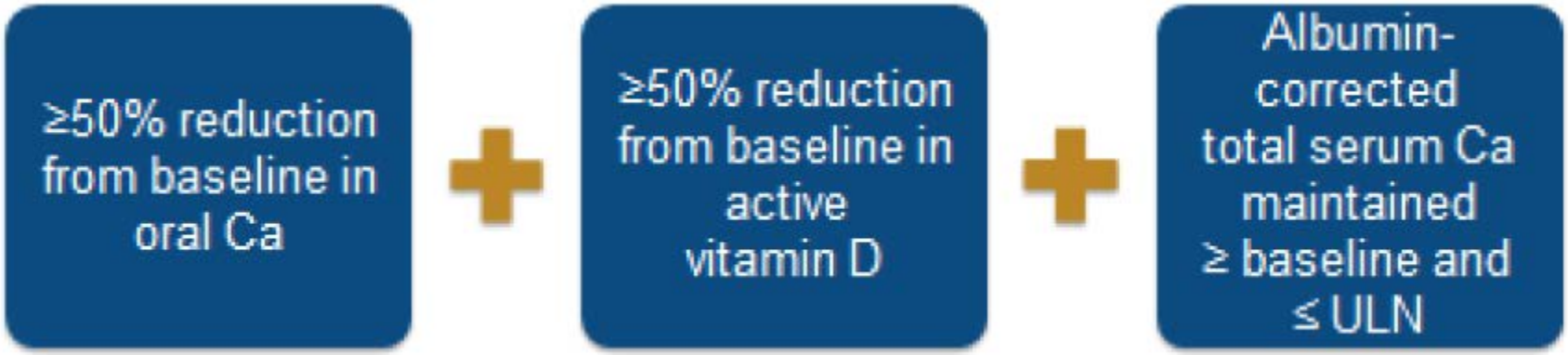
- Overall goal was to maintain serum calcium in the 8-9 mg/dL range
- Up-titration of Natpara to 75 µg at Week 2 and then 100 µg at Week 4
- Up-titration of Natpara was done in conjunction with frequent measurements of serum calcium
- Down-titration back to 50 µg could occur at any time if needed

Pivotal Trial (040): Primary Objective

- To demonstrate that once-daily SC dosing with NPSP558 across a dose range of 50 µg, 75 µg or 100 µg is a safe and effective hormone replacement therapy for the treatment of subjects with hypoparathyroidism

Primary Efficacy Endpoint: Pivotal Trial (040)

- Percentage of responders at Week 24, based on investigator-prescribed data relating to a composite endpoint of 3 components. A subject was considered a responder if he/she achieved:



7.5-10.6 mg/dL

Primary Efficacy Endpoint: Serum Calcium Goal vs Criteria for Response

- Goal during trial to maintain each subject's total serum calcium in the 8-9 mg/dL range,

  however

- To be considered a responder, a subject's serum calcium could span 7.5-10.6 mg/dL at Week 24.

Secondary Efficacy Endpoints: Pivotal Trial (040)

- Percent reduction in calcium supplementation dose at Week 24
- Proportion of subjects who achieved independence from supplemental active vitamin D metabolite/analog usage and a calcium supplementation dose of ≤500 mg/day by Week 24
- Frequency of clinical symptoms of hypocalcemia (including paresthesia, muscle cramping, tetany, seizures) during Week 16 to Week 24
  - List of terms was generated *post hoc*
  - Arbitrarily limited to second half of maintenance period

Exploratory Endpoints: Pivotal Trial (040)

- Change from baseline in 24-hour urine calcium excretion at Week 24
- Change in bone turnover markers at Week 24
- Change in bone mineral density (BMD) as measured by DXA at Week 24
- Proportion of patients that maintain a calcium–phosphate product in the normal range of 35-55 mg^2/dL^2 at Week 24 in the NPSP558 treatment group vs placebo

Key Inclusion Criteria: Pivotal Trial

- Adults with a history of hypoparathyroidism for ≥18 months
- Vitamin D metabolite/analog therapy with either calcitriol ≥0.25 µg per day or alfacalcidol ≥0.50 µg per day
- Supplemental oral calcium treatment ≥1000 mg per day over and above normal dietary calcium intake

Key Exclusion Criteria: Pivotal Trial

- Known history of hypoparathyroidism resulting from an activating mutation in the *CaSR* gene or impaired responsiveness to PTH (pseudohypoparathyroidism)
- Any disease that may affect calcium metabolism or calcium-phosphate homeostasis
- Use of other drugs known to influence calcium and/or bone metabolism
- Clinical history of renal stones within the past 12 months

Issue Related to Protocol Amendment

- At least a 50% reduction from the baseline oral calcium supplementation dose and
- At least a 50% reduction from the baseline active vitamin D metabolite/analog dose and
- An albumin-corrected total serum calcium concentration that as maintained or normalized compared to the baseline value (≥7.5 mg/dL) and did not exceed the upper limit of normal (10.6 mg/dL)

Original Protocol	**Protocol Amendment**
8.4-10.6 mg/dL	7.5- 10.6 mg/dL

Issues Related to Good Clinical Practices (GCPs)

- Routine inspection of three clinical sites was completed
- One site had multiple, serious violations of GCPs
  - Site involved in multiple trials in this program
  - Data originating from this site considered unreliable
- At the request of the Division, the Applicant excluded all data coming from this site for all relevant trials.

Issues Related to Good Clinical Practices (GCPs)

- For the pivotal trial, this led to the exclusion of 4 placebo-treated subjects and 6 Natpara-treated subjects.
- All data and analyses presented exclude data from the problematic site.
- Results of the primary endpoint analysis remained significant even after exclusion of data.

Efficacy

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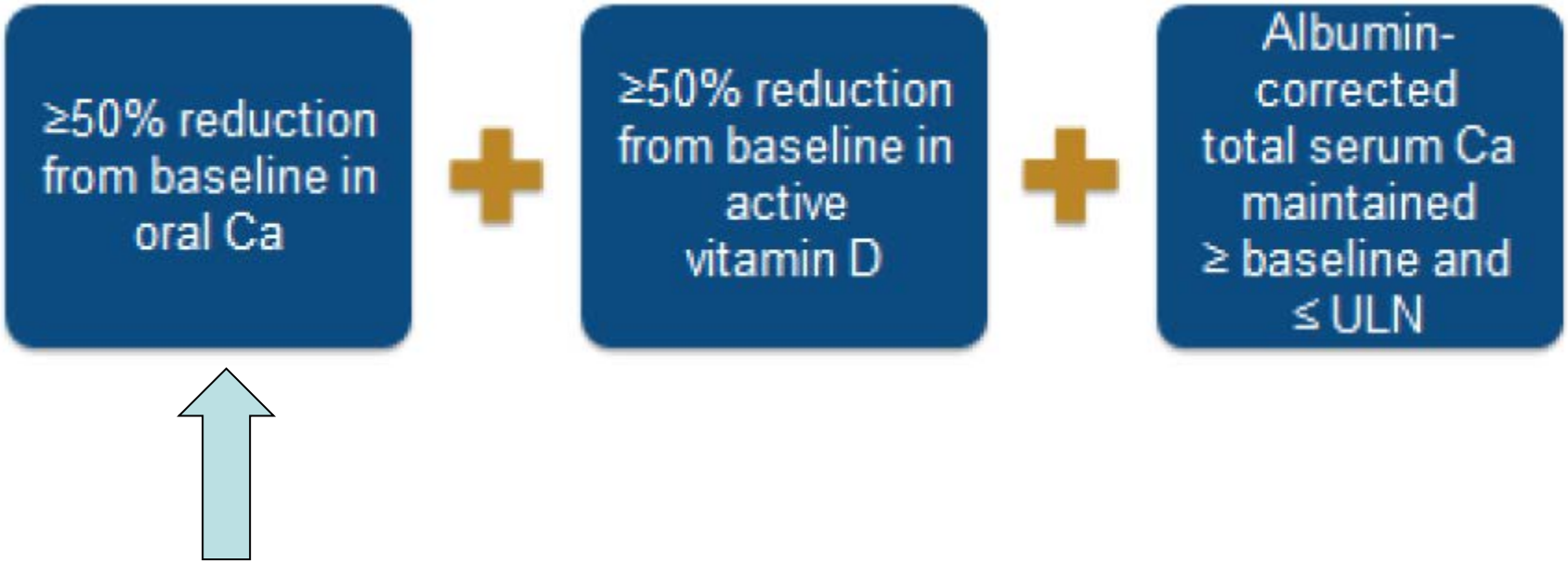
Primary Efficacy Analysis—ITT Population

Status	Placebo N=40		NPSP558 N=84		Treatment Difference	p-value
	n (%)	95% CI	n (%)	95% CI	% (95% CI)	
Responder	1 (2.5)	0.1, 13.2	46 (54.8)	43.5, 65.7	52.3 (40.6, 64)	<0.001

Alternate Analysis of Primary Efficacy Endpoint: 8.4-10.6 mg/dL

Status	Placebo N=40		NPSP558 N=84		Treatment Difference	p-value
	n (%)	95% CI	n (%)	95% CI	% (95% CI)	
Responder	2 (5)	0.6, 16.9	29 (34.5)	24.5, 45.7	29.5 (17.3, 41.7)	<0.001

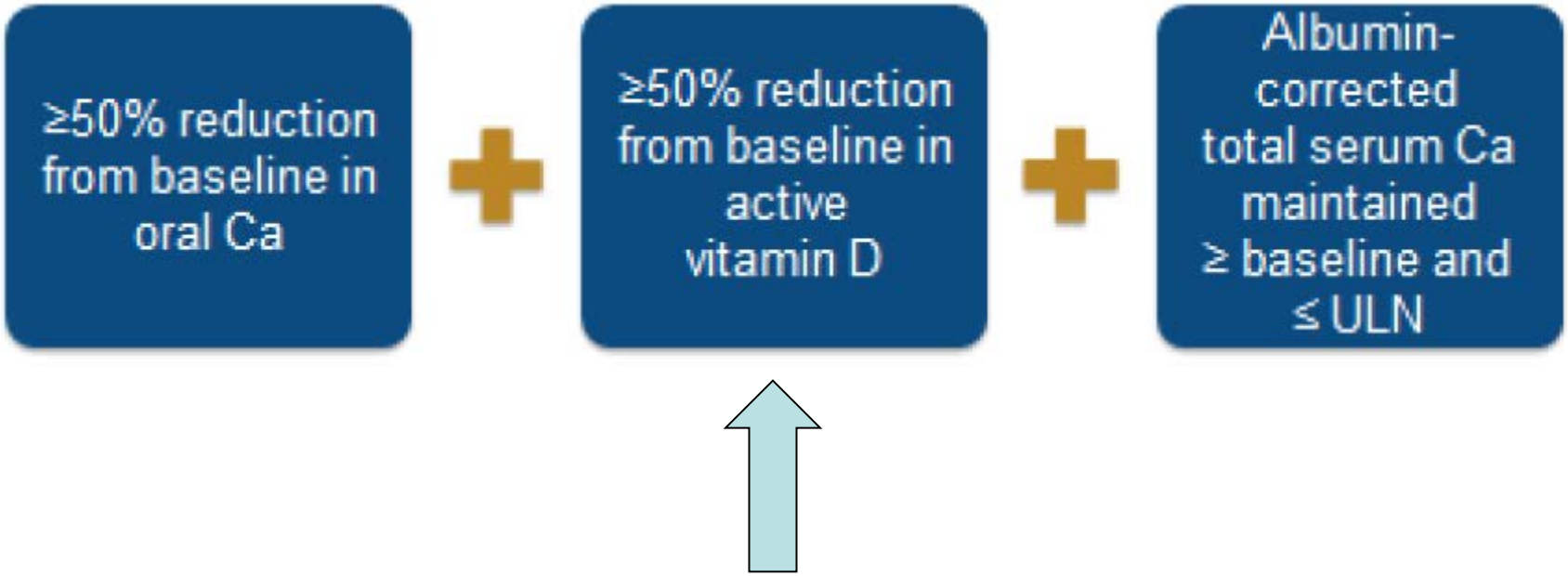
Individual Components of the Primary Endpoint



Component 1:
Percentage of Subjects who Achieved ≥50% Reduction from Baseline Oral Calcium

	Placebo N=40 n (%)	**NPSP558 N=84 n (%)**
Achieved	3 (7.5)	58 (69)
Not Achieved	37 (92.5)	26 (31)

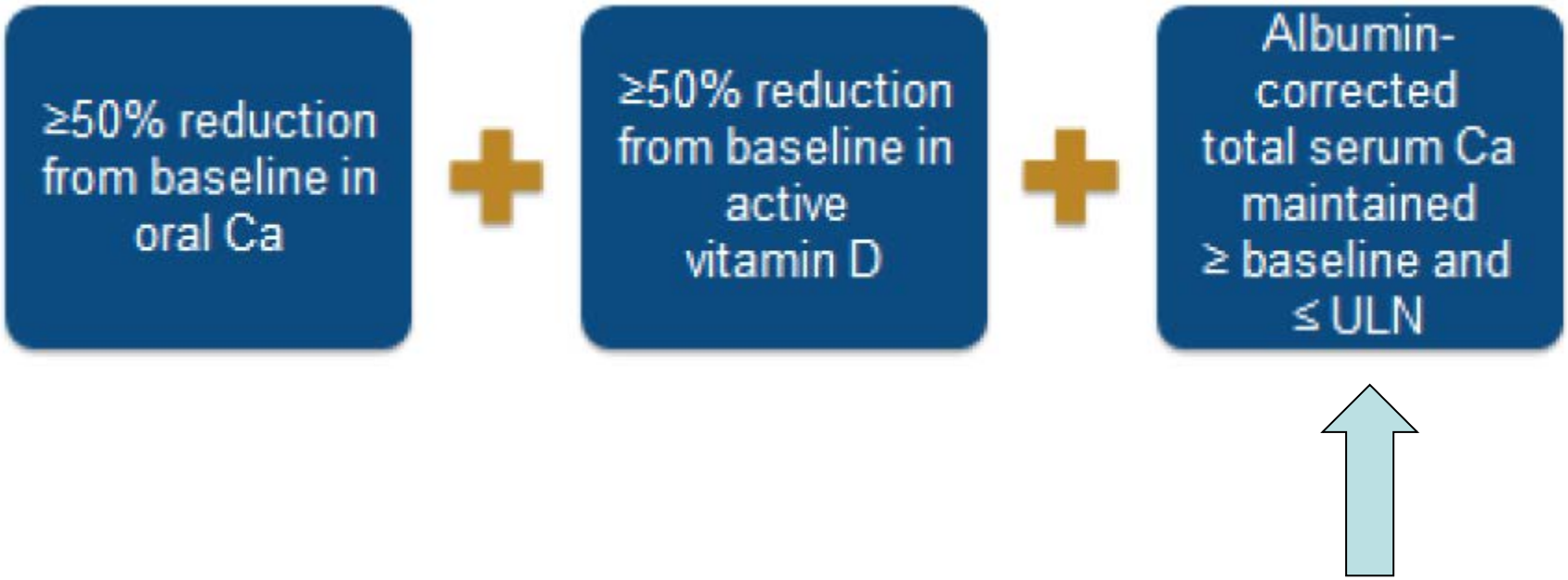
Responder Criteria



Component 2: Percentage of Subjects who Achieved ≥50% Reduction from Baseline Vitamin D Metabolite/Analog

	Placebo N=40 n (%)	**NPSP558 N=84 n (%)**
Achieved	18 (45)	73 (87)
Not Achieved	22 (55)	11 (13)

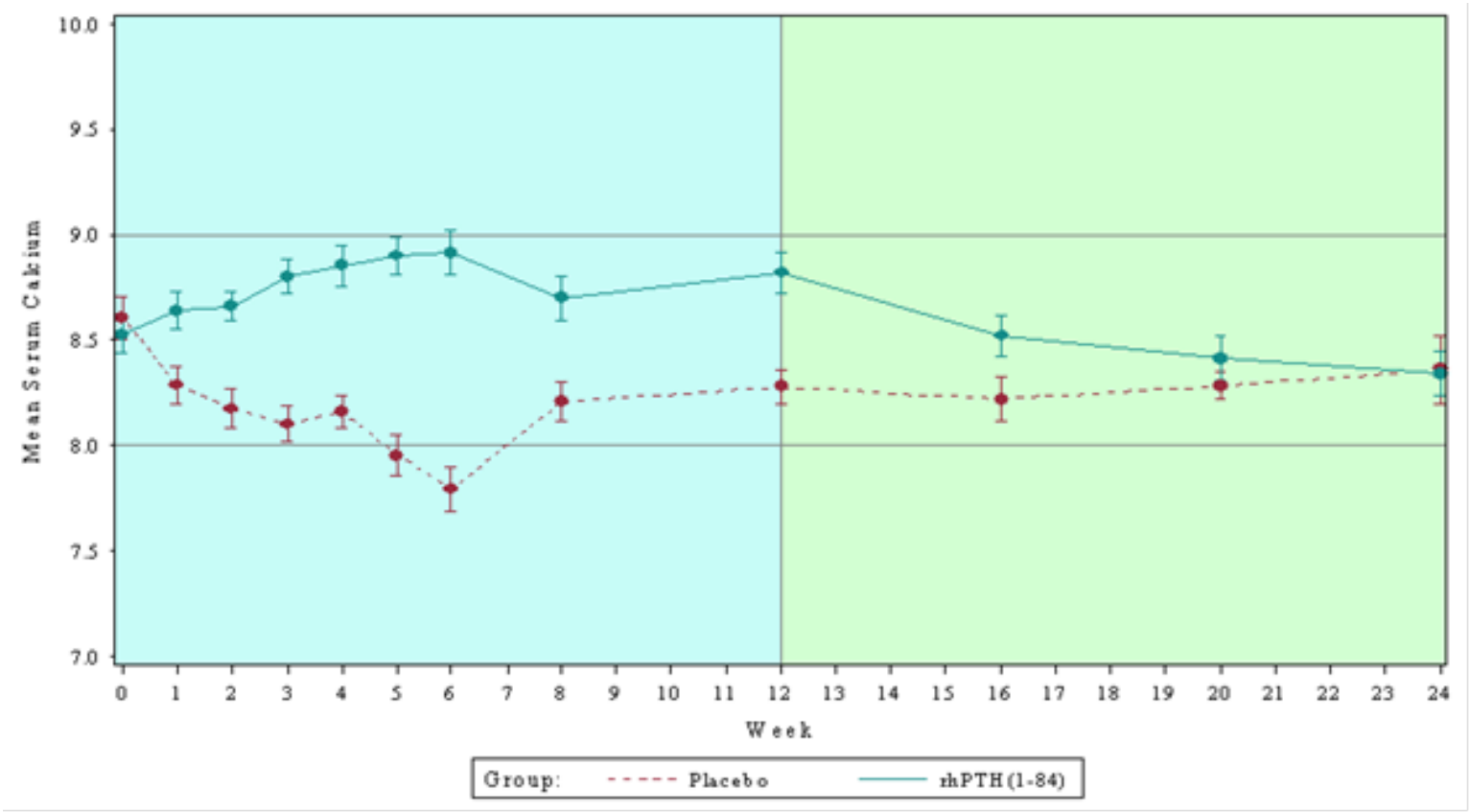
Responder Criteria



Component 3:
Percentage of Subjects who Achieved Serum Calcium 7.5 to 10.6 mg/dL

	Placebo N=40 n (%)	**NPSP558 N=84 n (%)**
Achieved	35 (88)	74 (88)
Not Achieved	5 (13)	10 (12)

Mean (±SE) of Albumin-corrected Total Serum Calcium –Observed



Applicant's Submission dated May 30, 2014, Figure 1-b

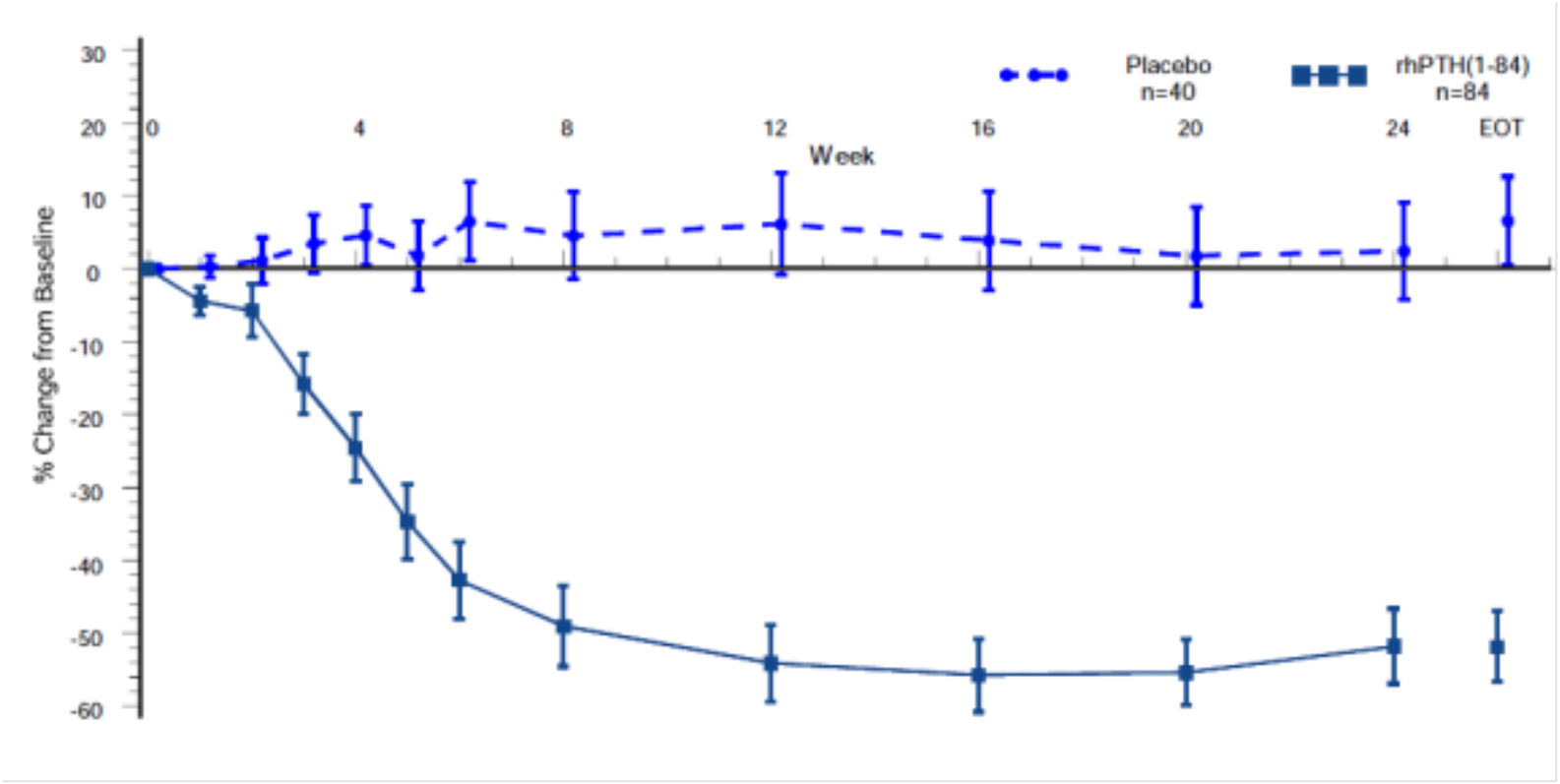
ULN=10.6 mg/dL and lower limit of normal=8.4 mg/dL

Mean (SD) Albumin-corrected Total Serum Calcium (mg/dL)

Time Point	Placebo N=40	Natpara N=84
Baseline	8.6 (0.6)	8.5 (0.8)
Week 4	8.2 (0.5)	8.9 (0.9)
Week 6	7.8 (0.6)	8.9 (0.9)
Week 8	8.2 (0.6)	8.7 (0.9)
Week 16	8.2 (0.6)	8.5 (0.8)
Week 24	8.4 (0.9)	8.3 (0.9)

ULN=10.6 mg/dL and lower limit of normal=8.4 mg/dL

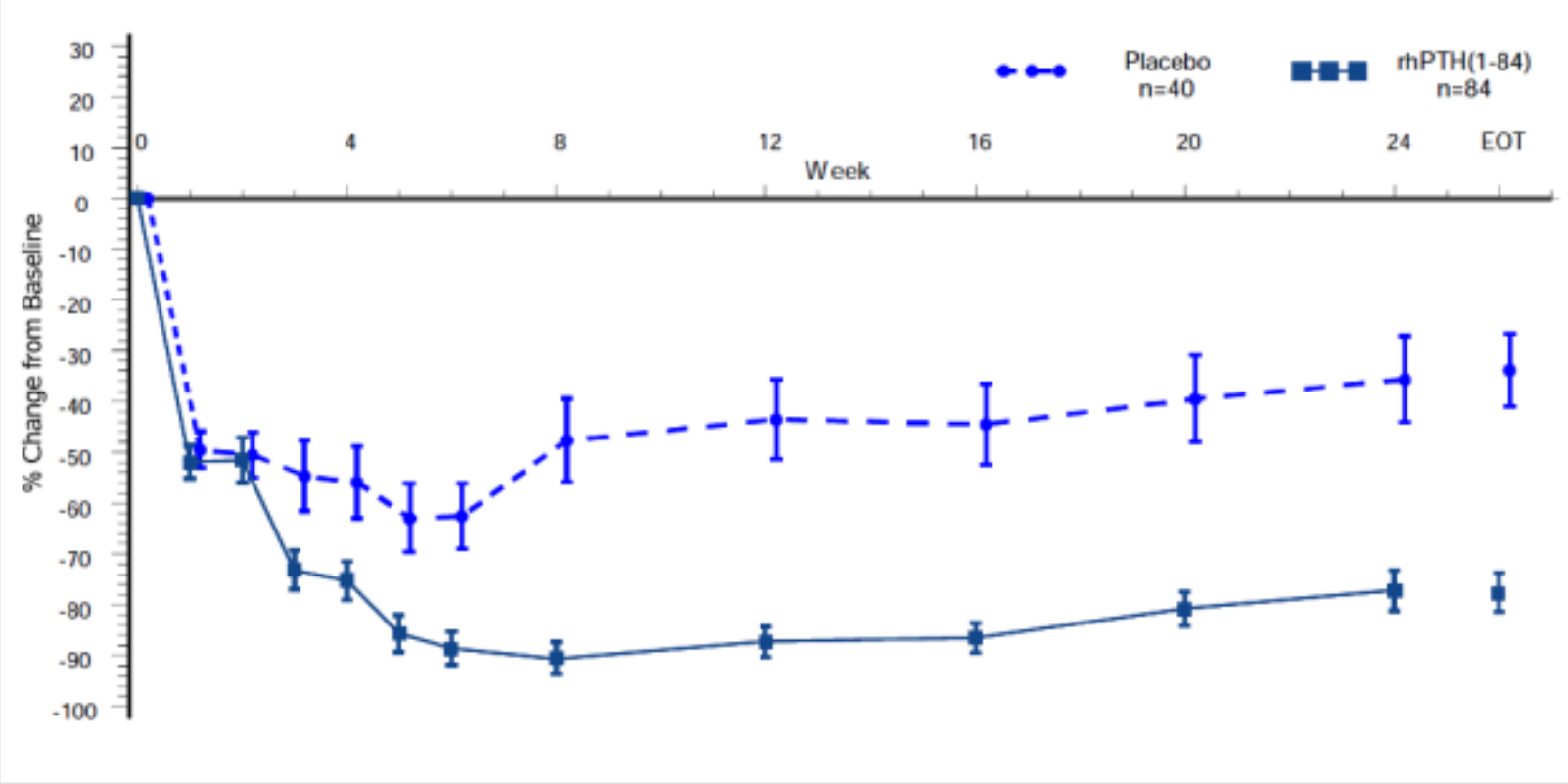
Secondary Efficacy Endpoint: Percent Change (Mean ±SE) from Baseline Dose of Calcium—ITT Population



Median (Interquartile Range) of Daily Oral Calcium Doses (mg) Over Time--Observed

Time Point	Placebo N=40	Natpara N=84
Baseline	1875 (1250, 2250)	2000 (1250, 3000)
Week 4	2000 (1375, 2750)	1250 (937, 2000)
Week 8	2000 (1500, 3000)	750 (0, 1500)
Week 12	2000 (1500, 2500)	562 (0, 1500)
Week 16	2000 (1375, 2650)	500 (0, 1250)
Week 20	2000 (1250, 3000)	625 (250, 1250)
Week 24	2000 (1250, 2750)	750 (250, 1500)

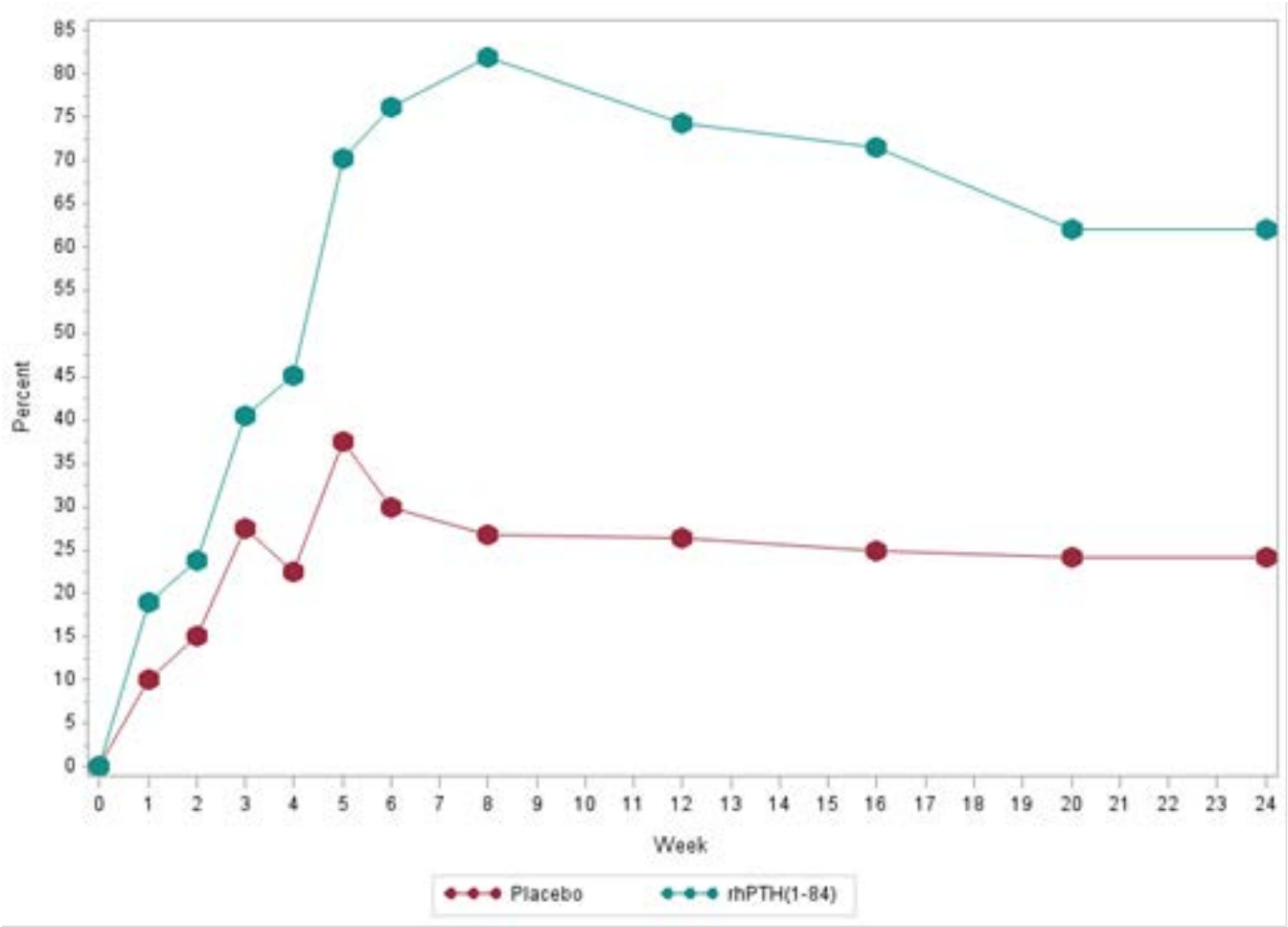
Mean (±SE) of Percent Change from Baseline in Dose of Active Vitamin Metabolite/Analog—ITT Population



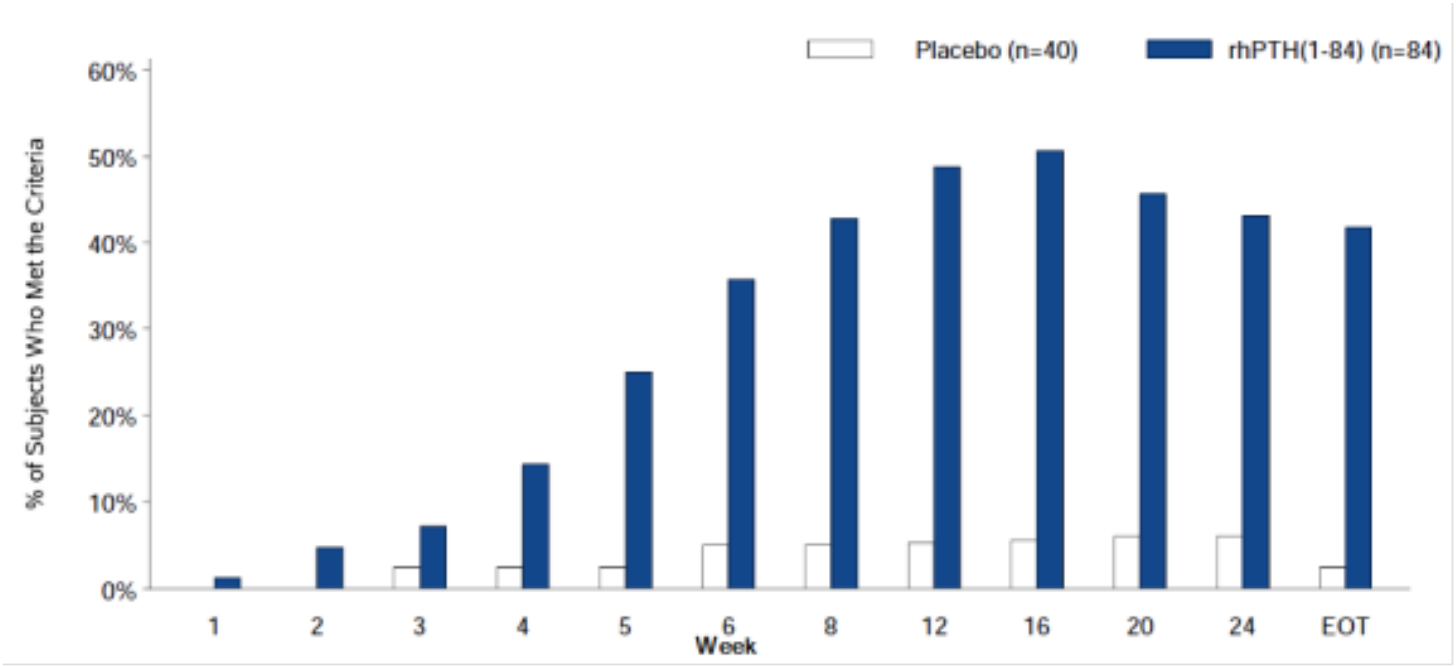
Median (Interquartile Range) of Vitamin D Metabolite/Analog Doses (µg) Over Time--Observed

	Placebo N=40	**Natpara N=84**
Baseline	0.75 (0.5, 1)	0.75 (0.5, 1)
Week 4	0.25 (0.16, 0.5)	0.22 (0, 0.25)
Week 8	0.5 (0, 0.75)	0 (0, 0)
Week 12	0.5 (0, 0.75)	0 (0, 0.25)
Week 16	0.5 (0.06, 0.75)	0 (0, 0.25)
Week 20	0.5 (0.13, 1)	0 (0, 0.25)
Week 24	0.5 (0.25, 1)	0 (0, 0.25)

Percentage of Subjects Independent of Vitamin D metabolite/analog Over Time--ITT



Secondary Efficacy Endpoint: Proportion of Subjects Who Achieved Independence from Active Vitamin D Metabolite/Analog Usage and a Calcium Supplementation Dose of ≤500 mg/day



Summary Observations Regarding Calcium Levels and Doses of Supplements

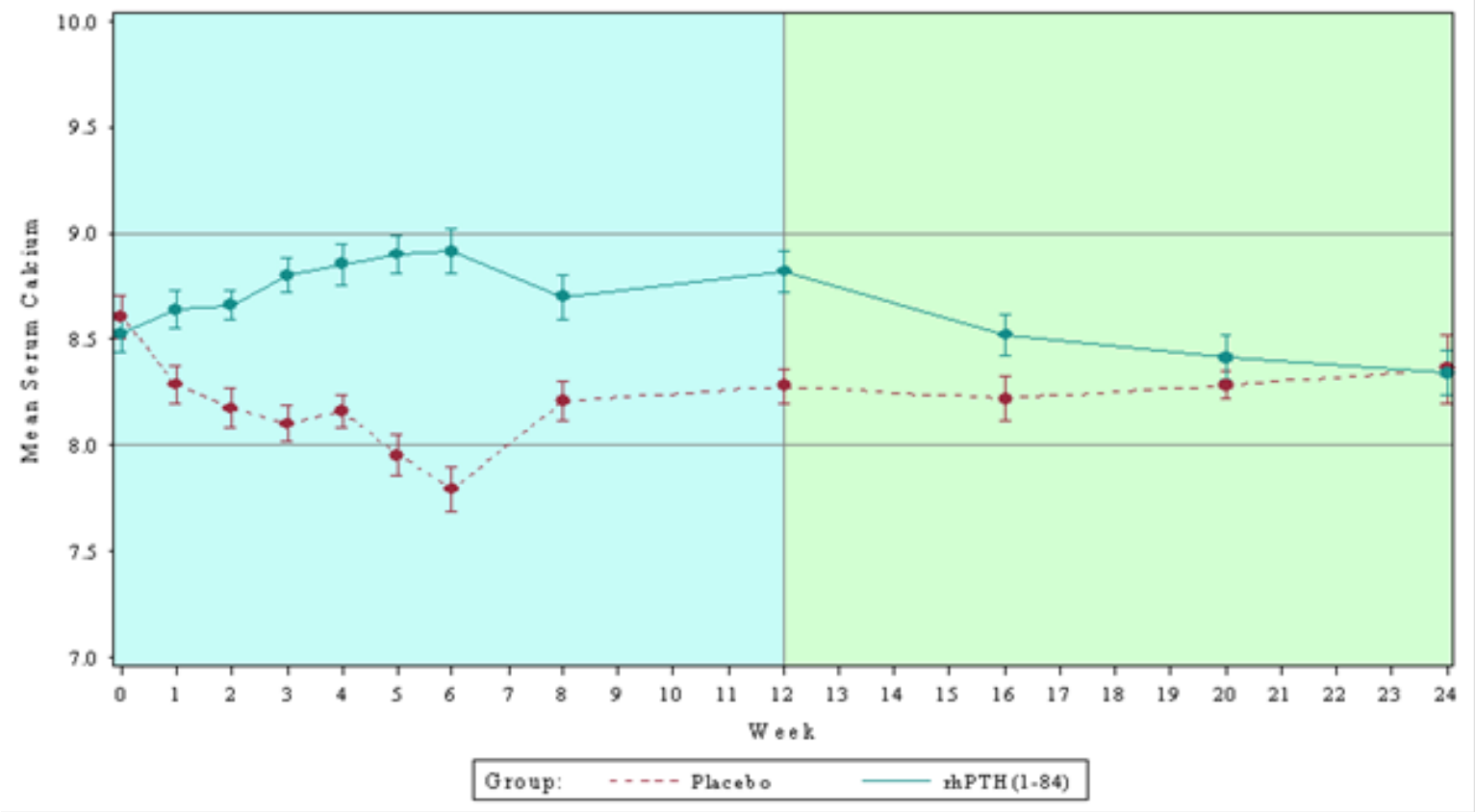
- The median daily dose of calcium in the Natpara group decreased from 2000 mg to 750 mg
  - No decrease in placebo
- The median daily dose of vitamin D metabolite/analog in the Natpara group decreased to 0 mg
  - Smaller decrease in placebo group
- There were 43% of Natpara subjects who achieved independence from vitamin D metabolite/analog in addition to achieving an oral calcium dose of 500 mg/day or less, compared to 6% of placebo subjects.

Exploratory Endpoints in Pivotal Trial

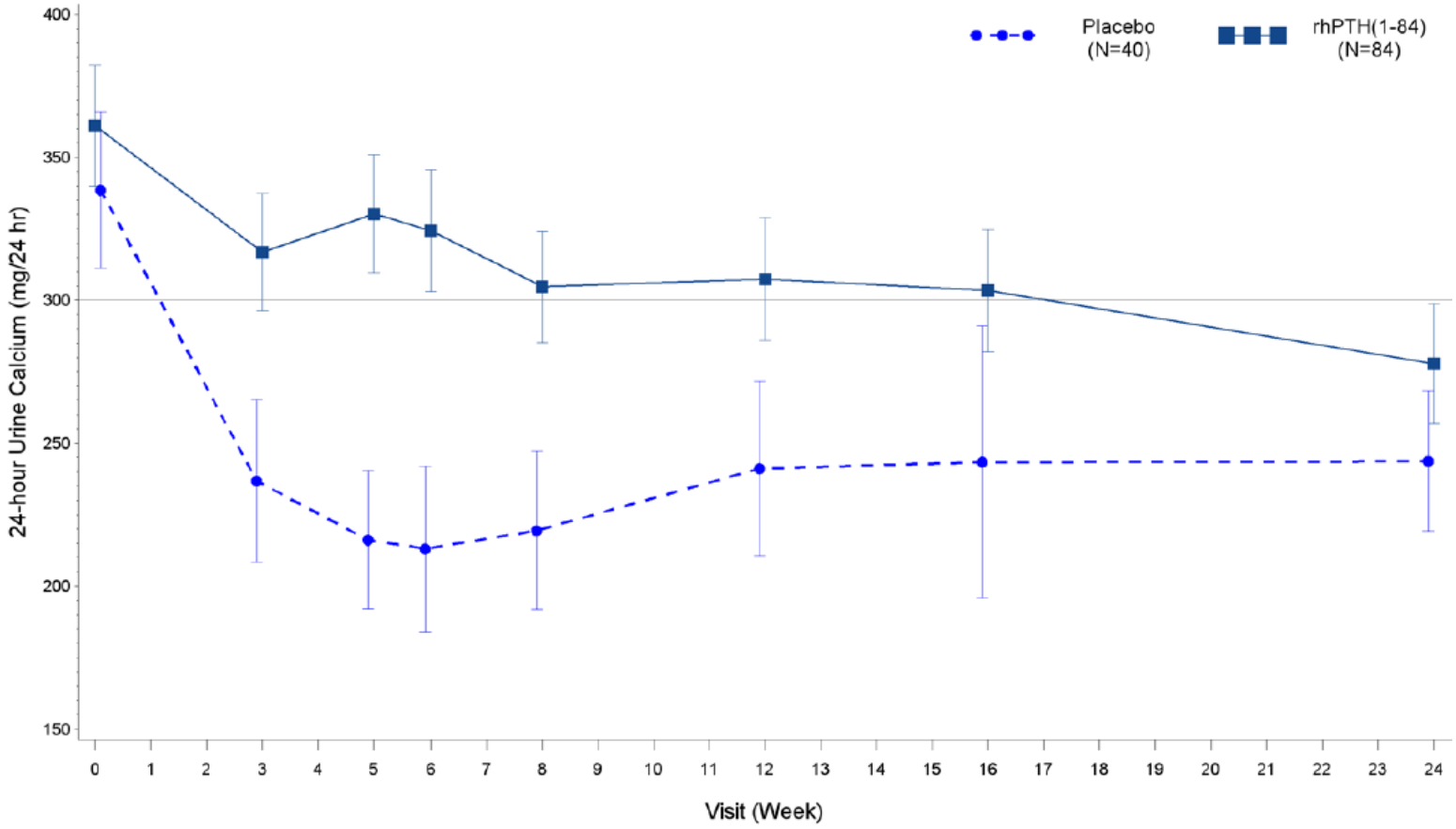
- Change from baseline in 24-hour urine calcium excretion at Week 24
- Change in bone turnover markers at Week 24
- Change in bone mineral density (BMD) as measured by DXA at Week 24
- Proportion of patients that maintain a calcium–phosphate product in the normal range of 35-55 mg^2/dL^2 at Week 24 in the NPSP558 treatment group vs placebo

Changes in 24-hour Urinary Calcium

Mean Serum Calcium (mg/dL) During the Pivotal Trial



Mean (±SD) 24-hour Urinary Calcium by Trial Week



Mean 24-hour Urinary Calcium (mg/24 hrs)During the Pivotal Trial

	Placebo N=40	**Natpara N=84**
Baseline		
n	40	84
Mean (SD)	339 (172)	361 (193)
Median	306	339
Min, Max	49, 770	26, 973
Week 24		
n	33	74
Mean (SD)	244 (141)	276 (178)
Median	232	231
Min, Max	32, 612	26, 915
Change from Baseline (SD)	-91 (171)	-79 (194)

Percentage of Subjects with Abnormal Urinary Calcium During the Pivotal Trial

	m	Placebo (>300 mg/24 hrs) n (%)	m	Natpara (>300 mg/24 hrs) n (%)
Baseline	40	21 (53)	84	48 (57)
Week 3	21	4 (19)	61	25 (41)
Week 5	21	3 (14)	58	33 (57)
Week 6	27	7 (26)	63	26 (41)
Week 8	38	11 (29)	80	39 (49)
Week 12	32	10 (31)	77	36 (47)
Week 16	33	10 (30)	72	34 (47)
Week 24	33	13 (39)	74	25 (34)

m=number of subjects with 24-hour urine calcium data at specified time point

Summary: Changes in Urinary Calcium

- Exploratory endpoint
- Fewer data points
- Mean decreases from baseline in 24 hour urinary calcium were observed in both placebo and Natpara groups throughout the trial
- During the maintenance period, elevated urinary calcium remained an issue in both groups
  - At Week 16, hypercalciuria was observed in 30% of the placebo group and 47% of the Natpara group
  - At Week 24, hypercalciuria was observed in 39% of the placebo group and 34% of the Natpara group

Changes in Bone Markers and Bone Mineral Density

Bone in Hypoparathyroidism

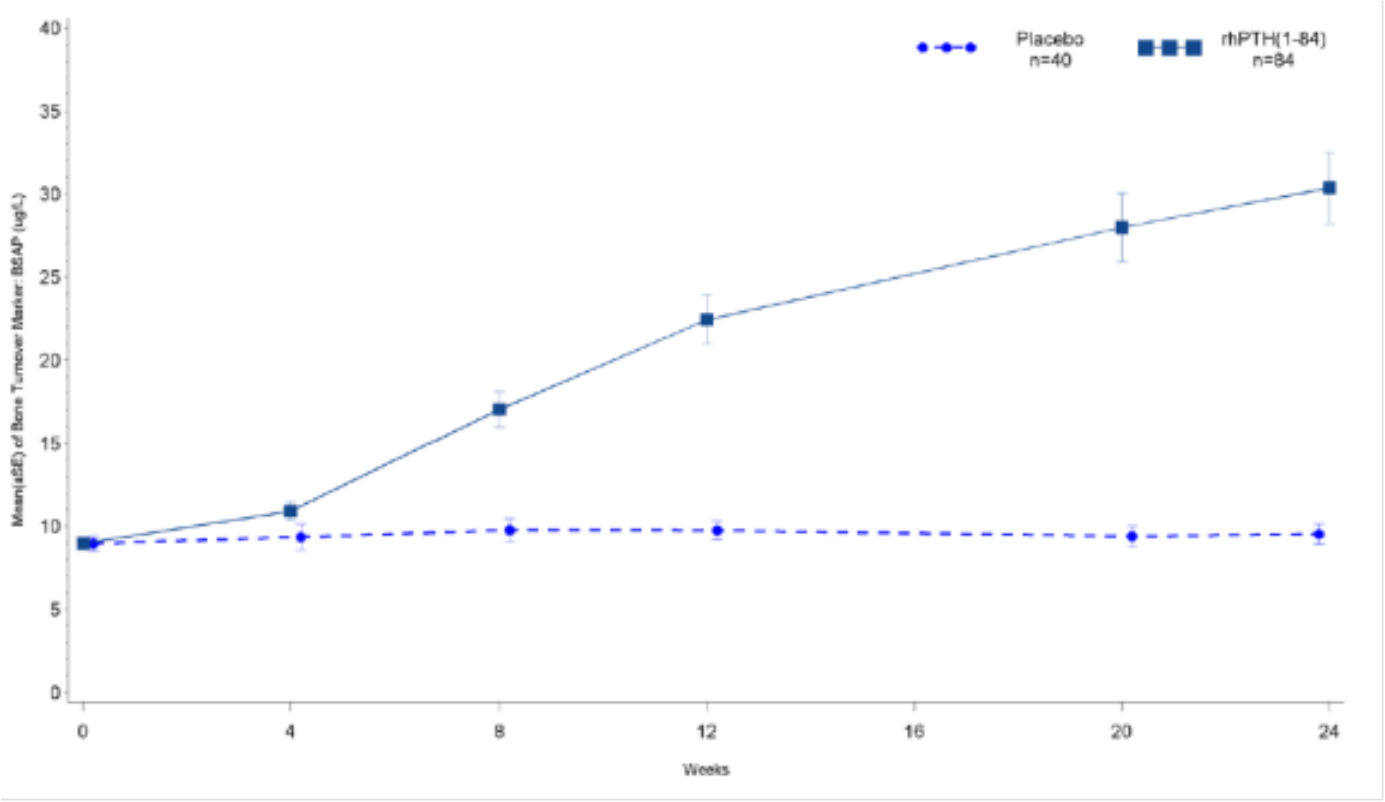
- In hypoparathyroid subjects, there is a low bone turnover state
  - Lower levels of bone markers
  - Associated with higher bone mineral density[1]

[1]Chan FK et al. Increased bone mineral density in patients with chronic hypoparathyroidism. New England Journal Of Medicine July 2003.

Bone Markers in the Pivotal Trial

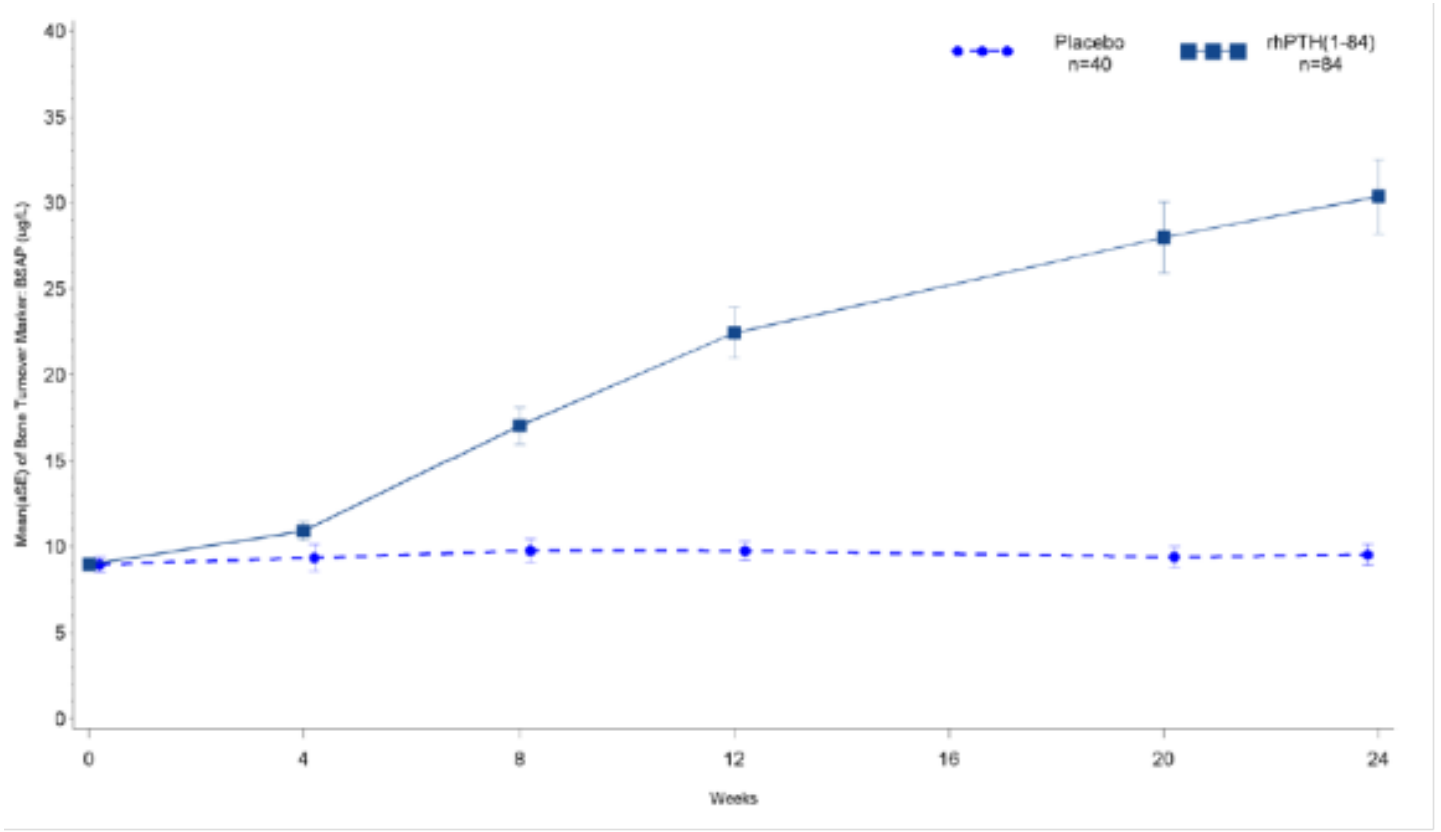
- Bone formation markers
  - Bone-specific alkaline phosphatase (BSAP)
  - Osteocalcin (OC)
  - N-terminal cross-linking propeptides of type I procollagen (P1NP)
- Bone resorption markers
  - C-terminal cross-linking telopeptides of type I collagen (CTx)

Mean (±SE) of Bone Specific Alkaline Phosphatase (ug/L) by Trial Week—ITT Population



From Applicant's Submission dated June 2, 2014, Figure 1b

Mean (±SE) of Serum Carboxy-Terminal Telopeptide-CTx (ng/L) by Trial Week—ITT Population



From Applicant's Submission dated June 2, 2014, Figure 2.1b

Bone Mineral Density

- BMD was measured by DXA at baseline and at Week 24
  - 24 weeks (12 weeks stable dose) insufficient duration to show clinically meaningful changes
- Seven DXA sites measured
- Exploratory endpoint
  - Not all subjects had DXA
  - Not all sites measured at each DXA visit
  - For hip-intertrochanter at Week 24, 18/40 subjects in placebo group and 43/84 subjects in the Natpara group had available measurements.

Bone Mineral Density: Z scores

- Z scores
  - Compares a patient's bone mineral density with mean value in a population of similar age, sex, and height
  - Score is in units of standard deviations
  - 0 is the norm, positive values indicate more dense bones, negative values indicate less dense bones

Bone Mineral Density: Results

- At baseline, mean Z scores were generally above 1, consistent with a higher rate of mineralization
  - Exception was distal one-third radius (mean Z score in both groups was approximately 0.3)
- Of the seven sites measured:
  - Total hip and Hip-trochanter had statistically significant changes compared to Placebo
  - Lumber spine, Hip-Intertrochanter, Hip-Ward's triangle, Hip-femoral neck, and distal one-third radius had changes which were not statistically significant compared to Placebo

Analysis of Z-scores

	Placebo		Natpara		P-value
	Mean Baseline Z-score	Change from Baseline at Week 24	Mean Baseline Z-score	Change from Baseline at Week 24	
Total hip	1.2	0.01	1.2	-0.16	<0.001
Hip-Trochanter	1.2	0.04	1.1	-0.20	<0.001
Lumbar Spine	1.6	0.05	1.7	-0.05	0.286
Hip-Intertrochanter	1.0	0.01	1.0	-0.10	0.033
Hip-Ward's triangle	1.3	0.04	1.6	-0.20	0.049
Hip-femoral neck	1.2	0.02	1.2	-0.20	0.001
Distal one-third radius	0.4	0.05	0.4	-0.01	0.395

Summary: Changes in Bone

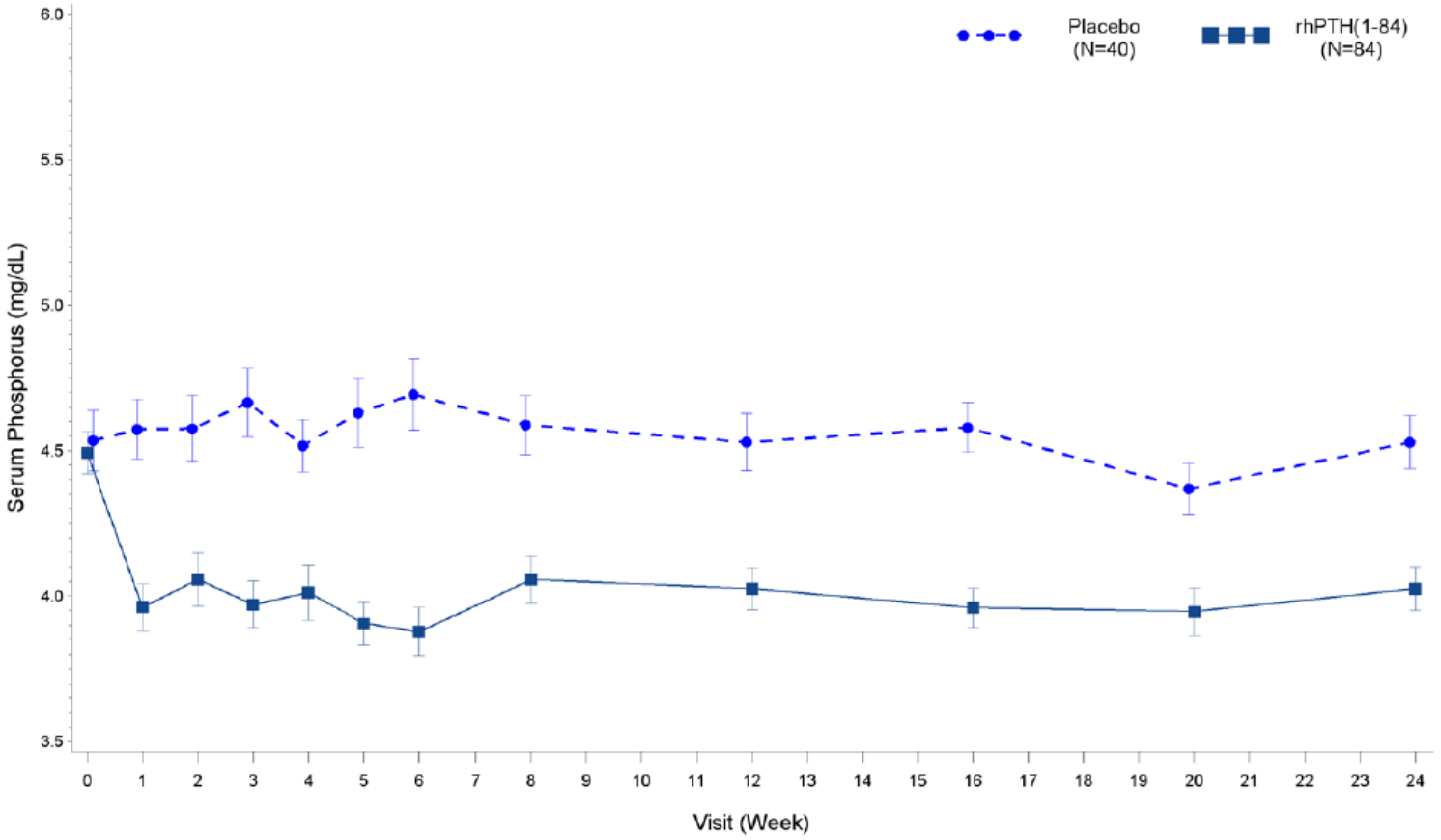
- Trend of increasing bone markers during Natpara treatment
  - Unclear if translates into meaningful clinical benefit
- DXA measurements reflect only 24 weeks of treatment
- Changes in DXA were statistically significant for 2 of 7 sites
- The changes observed have unclear clinical significance
  - Consideration of over-treatment with PTH

Subjects Who Had a calcium-phosphate Product Greater than 55 mg^2/dL^2 at Week 24

Observations Regarding Calcium-Phosphate Product in the Pivotal Trial

- At baseline, there was one subject in the Natpara group with an elevated product and no subjects in the placebo group with an elevated product.
- During the maintenance period (Week 12-24), there were no subjects in the Natpara group with an elevated product and one in the placebo group with an elevated product.

Mean (±SE) of Serum Phosphorus (mg/dL) –ITT Population



From Applicant's Submission, August 11, 2014

Mean Phosphorus (mg/dL) Levels—ITT Population

Time Point	Placebo N=40	Natpara N=84
Baseline	4.5 (0.7)	4.5 (0.7)
Week 4	4.5 (0.6)	4.0 (0.8)
Week 8	4.6 (0.6)	4.1 (0.7)
Week 16	4.6 (0.5)	4.0 (0.6)
Week 24	4.5 (0.5)	4.0 (0.7)

Upper Limit of Normal=4.8, Lower Limit of Normal=2.4

Percentage of Subjects with Elevated Phosphorus (>4.8 mg/dL)

	Placebo N=40		**Natpara N=84**	
	m	n (%)	M	n (%)
Baseline	40	6 (15)	82	15 (18)
Week 3	38	8 (21)	78	7 (9)
Week 6	36	5 (14)	73	2 (3)
Week 8	37	3 (8)	81	7 (9)
Week 12	31	4 (13)	80	4 (5)
Week 16	33	6 (18)	74	2 (3)
Week 24	33	3 (9)	78	2 (3)

Efficacy Conclusions for the Pivotal Trial

Primary Endpoint

- Compared to the standard of care, Natpara was successful in maintaining calcium in the reference range while decreasing the amount of calcium supplements and Vitamin D metabolites/analogues by at least 50%.
  - The largest difference between Natpara and placebo in the individual components was in the reduction of oral calcium supplements by ≥50%

Efficacy Conclusions, continued

- Using a more stringent definition for normalized calcium (8.4-10.6 mg/dL), the primary endpoint was still met.
  - Treatment difference was 29.5%.

Efficacy Conclusions, continued

Secondary Endpoints

- Oral calcium supplementation was reduced by 51.8% in the Natpara group, compared to an increase of 2.4% in the placebo group
  - In Natpara-treated subjects, oral calcium supplementation was reduced from a median of 2000 mg daily to 750 mg daily.
- At the primary efficacy time point, 43% of Natpara-treated subjects and 5.4% in the placebo arm achieved independence from Vitamin D metabolites/analogues while reducing the supplemental calcium to no more than 500 mg daily.

Efficacy Conclusions, continued

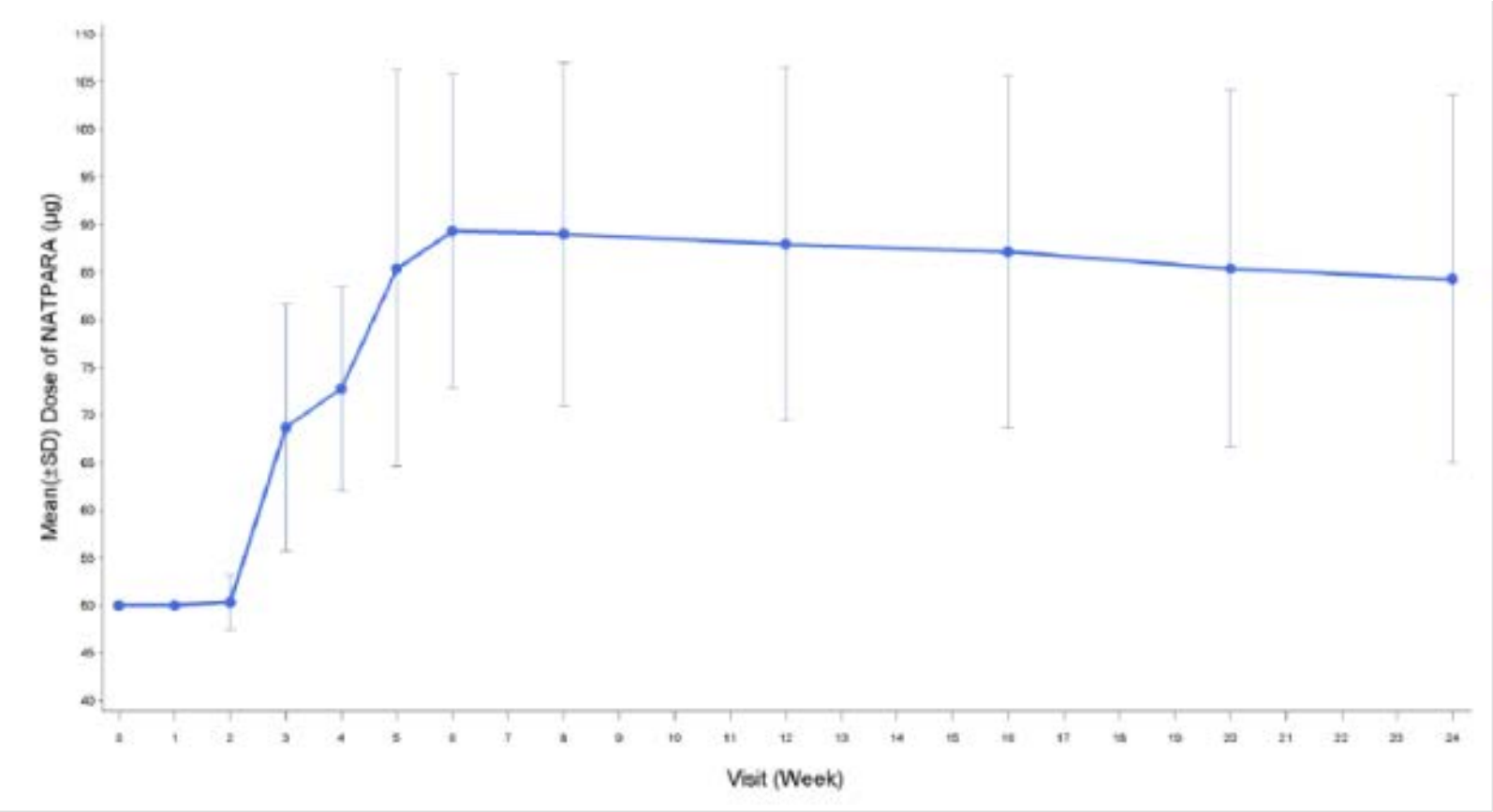
Exploratory Endpoints

- There were decreases in mean urinary calcium in placebo and Natpara groups.
  - After 24 weeks of treatment, hypercalciuria remained an issue in both groups.
- While there were increases in the levels of bone markers, the clinical importance of these changes is unclear.
- Statistically significant changes in DXA were observed in 2 of 7 sites.
  - Clinical significance unclear
- There were no Natpara-treated subjects with an elevated calcium-phosphate product after the titration period.

Summary of Final Doses in Pivotal Trial

- Natpara: General Aspects
- Currently Available Treatment for Hypoparathyroidism
- Products Related to Osteosarcoma and Natpara
- Natpara Clinical Development Program
- Pivotal Trial (040)
- Efficacy
  - Primary Efficacy and Related Analyses
  - Secondary Efficacy and Related Analyses
  - Exploratory Efficacy and Related Analyses
  - Efficacy Conclusions
- **Summary of Final Doses in Pivotal Trial**
- Safety
  - General
  - Analyses of Hypocalcemia and Hypercalcemia
  - Safety Conclusions
- Trial 008

Mean (±SD) Daily Dose of Natpara by Visit—ITT Population



Summary of Final NPSP558 Dose—ITT Population

Final NPSP558 Dose	NPSP558 N=84 n (%)
50 µg	15 (18)
75 µg	22 (26)
100 µg	47 (56)

Safety in Pivotal Trial

- Natpara: General Aspects
- Currently Available Treatment for Hypoparathyroidism
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- Summary of Final Doses in Pivotal Trial
- **Safety**
  - General
  - Analyses of Hypocalcemia and Hypercalcemia
  - Safety Conclusions
- Trial 008

Safety Analyses of Natpara

- Because of mechanism of action of PTH, overlap of efficacy and safety
- Focus on analyses of hypocalcemia and hypercalcemia

Analyses of Hypocalcemia and Hypercalcemia: Pivotal Trial

- Reported Adverse Events
  - Investigator-reported
  - Reflect events that occurred in-between mandated visits
  - Reflect clinical symptoms related to hypo- and hypercalcemia
  - Reflect abnormal laboratory results
  - Limitation: Abnormal laboratory parameters may have not been reported as an adverse event
- Objective Laboratory Measurements
  - Protocol-mandated

General

- Mean exposure to Natpara was 168 days.
- There were no deaths in the pivotal trial.
- Most subjects in both groups experienced at least one Adverse Event during the treatment period:
  - 95% of Placebo group
  - 91% of Natpara group
- Serious Adverse Events during the treatment period:
  - 5% of Placebo group
  - 6% of Natpara group

Adverse Events ≥10% in the Natpara Group During the Treatment Period*

Preferred Term	Placebo N=40 n (%)	Natpara N=84 n (%)
Paresthesia	10 (25)	26 (31)
Muscle Spasms	12 (30)	21 (25)
Headache	9 (23)	21 (25)
Hypocalcemia	8 (20)	21 (25)
Nausea	7 (18)	15 (18)
Hypercalcemia	1 (3)	14 (17)
Hypoesthesia	4 (10)	12 (14)
Diarrhea	1 (3)	10 (12)
Vomiting	0	10 (12)
Arthralgia	4 (10)	9 (11)

*Treatment Period defined as from the day of the first dose to the day of the last dose

Incidence of Hypocalcemia-related AEs during Treatment Period

	Placebo N=40 n (%)	Natpara N=84 n (%)
Paresthesia	10 (25)	26 (31)
Muscle spasms	12 (30)	21 (25)
Hypocalcemia	8 (20)	21 (25)
Hypoesthesia	4 (10)	12 (14)
Tetany	4 (10)	8 (10)
Oral paresthesia	3 (8)	6 (7)
Facial hypoesthesia	2 (5)	5 (6)
Muscle twitching	4 (10)	4 (5)
Anxiety	0	4 (5)
Tremor	1 (3)	3 (4)
Blood calcium decreased	1 (3)	2 (2)

Incidence of Hypercalcemia-related AEs during Treatment Period

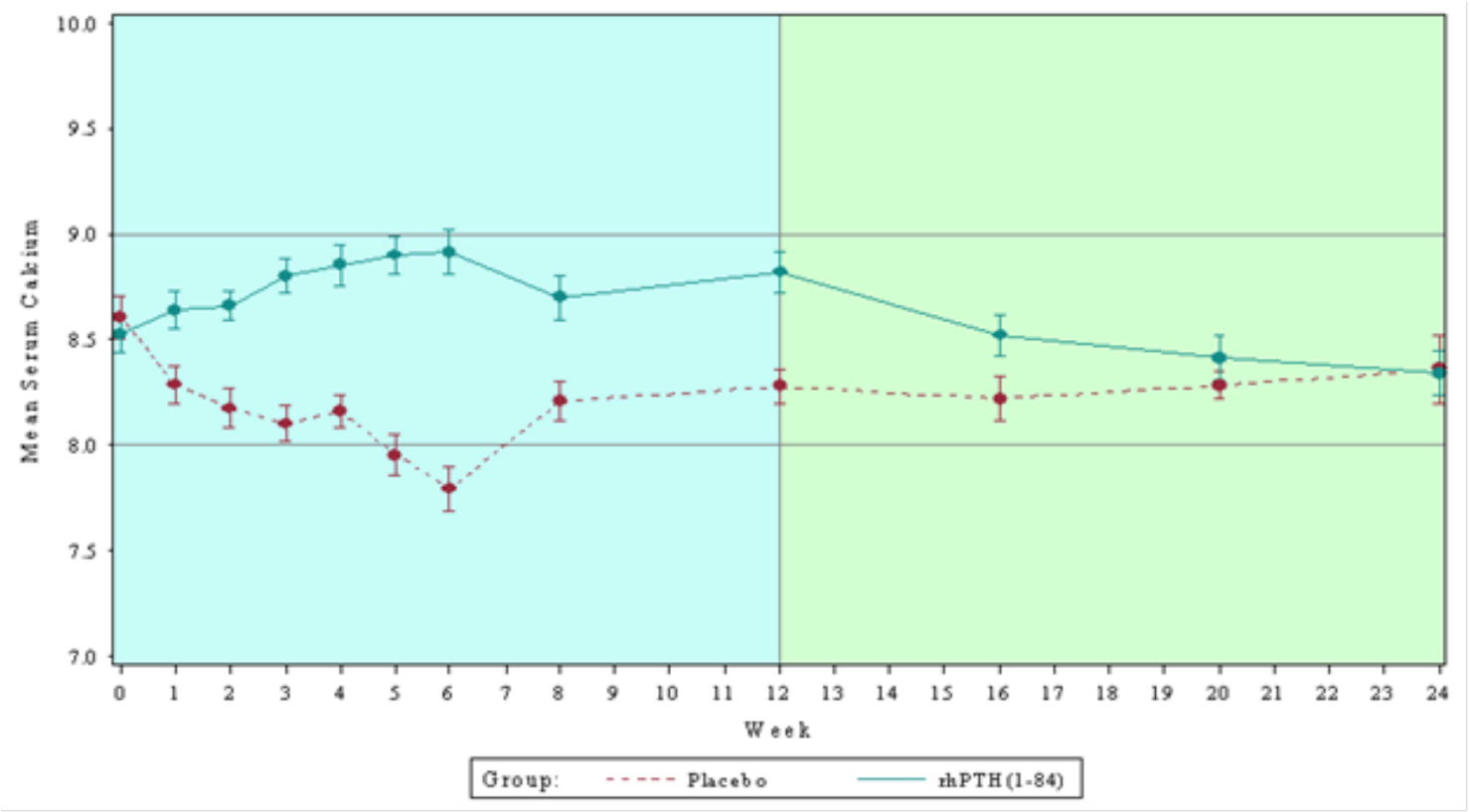
	Placebo N=40 n (%)	Natpara N=84 n (%)
Nausea	7 (18)	15 (18)
Hypercalcemia	1 (3)	14 (17)
Fatigue	8 (20)	8 (10)
Hypercalciuria	1 (2.5)	6 (7.1)
Myalgia	3 (8)	6 (6)
Thirst	0	4 (4.8)
Somnolence	0	3 (4)
Blood Calcium Increased	0	2 (2.4)
Constipation	1 (3)	1 (2)
Dry Mouth	0	1 (1)
Depression	0	1 (1)

Calcium-related Serious Adverse Events during the Treatment Period

	Placebo		NPSP558	
Preferred Term	**N=40 n (%)**	**Events**	**N=84 n (%)**	**Events**
Hypocalcemia	0	0	0	0
Hypercalcemia	0	0	1 (1)	1

Serious Adverse Event defined as an AE resulting in any of the following: death, life-threatening, significant incapacity, hospitalization, congenital anomaly,/birth defect

Mean (±SE) of Albumin-corrected Total Serum Calcium –ITT Population

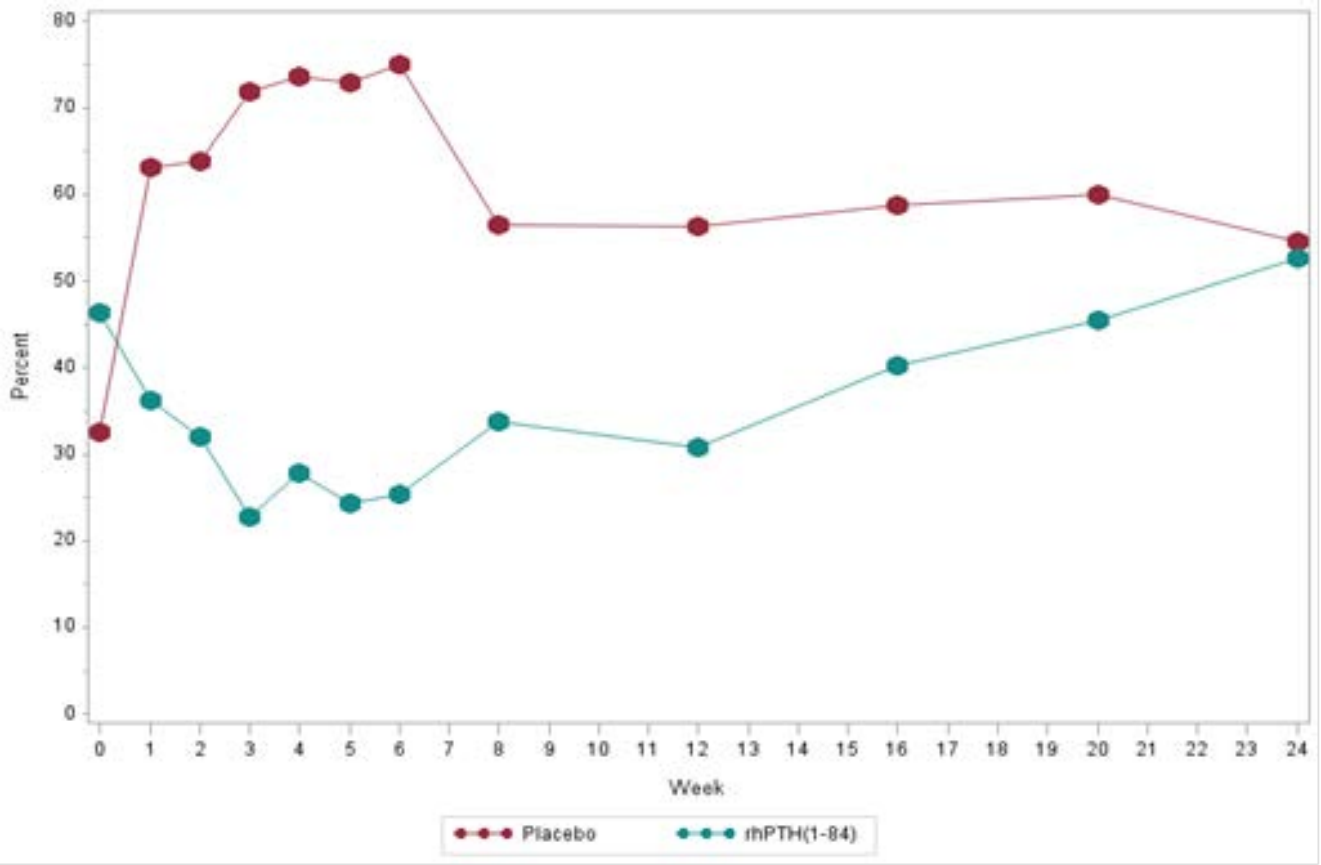


ULN=10.6 mg/dL and lower limit of normal=8.4 mg/dL

Percentage of Subjects with Serum Calcium Below 8.4 mg/dL

Time Point	Placebo n (%)	Natpara n (%)
Baseline	13 (33)	39 (46)
Week 6	27 (75)	19 (25)
Week 12	18 (56)	25 (31)
Week 16	20 (59)	31 (40)
Week 20	18 (60)	35 (46)
Week 24	18 (55)	41 (53)

Percentage of Subjects with Low Serum Calcium (below 8.4 mg/dL) Over Time



Percentage of Subjects with Serum Calcium ≥10.6 mg/dL

Time Point	Placebo n (%)	Natpara n (%)
Baseline	0	2 (2)
Week 6	0	2 (3)
Week 12	0	1 (1)
Week 16	0	1 (1)
Week 20	0	2 (3)
Week 24	1 (3)	2 (3)

Safety Conclusions

- There were no deaths in the pivotal trial.
- There was one SAE related to hypercalcemia in the Natpara group.
- In analyses of terms related to hypocalcemia and hypercalcemia
  - there was little difference between the 2 groups in hypocalcemia
  - more subjects in the Natpara group were reported to have hypercalcemia-related symptoms

Safety Conclusions, continued

- Mean values of serum calcium were maintained from baseline to Week 24
- The percentage of subjects with hypocalcemia (below 8.4 mg/dL) worsened in both groups during the trial
  - Similar in both groups by Week 24
- The percentage of subjects with hypercalcemia did not change in either group.

Trial 008

- Natpara: General Aspects
- Currently Available Treatment for Hypoparathyroidism
- Products Related to Osteosarcoma and Natpara
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- Pivotal Trial (040)
- Efficacy
  - Primary Efficacy and Related Analyses
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  - Safety Conclusions
- **Trial 008**

Trial 008

- Ongoing, long-term, open-label trial in adults with hypoparathyroidism
- To assess safety and tolerability of varying doses of NPSP558 during long-term treatment
- Goal to reduce requirements for supplemental calcitriol and oral calcium supplementation to as low as safely possible while maintaining total serum calcium levels and controlling hypercalciuria.
- No control group
- Eligible for enrollment if completed Trial 040 or Trial 007
- Starting doses of 25 or 50 µg, depending on an algorithm

Trial 008: Observations

- Data suggest that one can sustain the reduction in supplements along with maintaining a normal calcium beyond the 24 weeks seen in the pivotal trial.
- There were no additional decreases in 24-hour urinary calcium during 52 weeks of treatment .
- No new safety issues were identified.

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Endocrinologic and Metabolic Drugs
Advisory Committee Meeting
College Park, MD
12 September 2014

FDA Review of the Nonclinical Carcinogenicity Assessment

BLA 125-511

PTH 1-84, Natpara®

Ronald Wange, Ph.D.
Supervisory Pharmacologist
Division of Metabolism and Endocrinology Products

Outline

- Results of FDA's analysis of the rat carcinogenicity study conducted with Natpara® (PTH 1-84)
- Perceived clinical relevance of identified PTH 1-84-related tumors
- Agency determination that there are no clinically meaningful differences in the rodent carcinogenic potency of PTH 1-84 and PTH 1-34

Carcinogenicity Study

- Rat (F344)
  - 104 Week study*
  - 60/sex/group
  - 0, 0, 10, 50, 150 µg/kg/day by SC injection

*HD males:

Dosing terminated in Week 94

Sacrificed Week 101

Agency Determination

- Study was positive for bone neoplasms (osteosarcoma, osteoblastoma and osteoma) in both sexes at the MD & HD of Natpara®
- No significant increase in bone neoplasms at the LD (NOAEL)
- ECAC concluded that this did not exclude human risk because of the narrow safety margin at the NOAEL (*explained in next slide*)

Osteosarcomas in F344 Rats Treated with PTH 1-84 (Natpara®)

Percent of Rats With Osteosarcoma (Male & Female Combined)

	Natpara® (PTH1-84)			
Dose Group	**C**	**LD**	**MD**	**HD**
Dose (µg/kg/day)	**0**	**10**	**50**	**150**
Mean Exposure Ratio (AUC_{rat}/AUC_{human}*)	**-**	**4**	**22**	**63**
Osteosarcoma (%)	**0.8**	**0.8**	**15.0**	**33.3**

*Mean AUC_{human} for Natpara® at 100 µg/day = 0.92 ng•h/ml (Clinical study C09-002)

Osteosarcomas in F344 Rats Treated with PTH 1-84 vs. PTH 1-34

Percent of Rats With Osteosarcoma (Male & Female Combined)

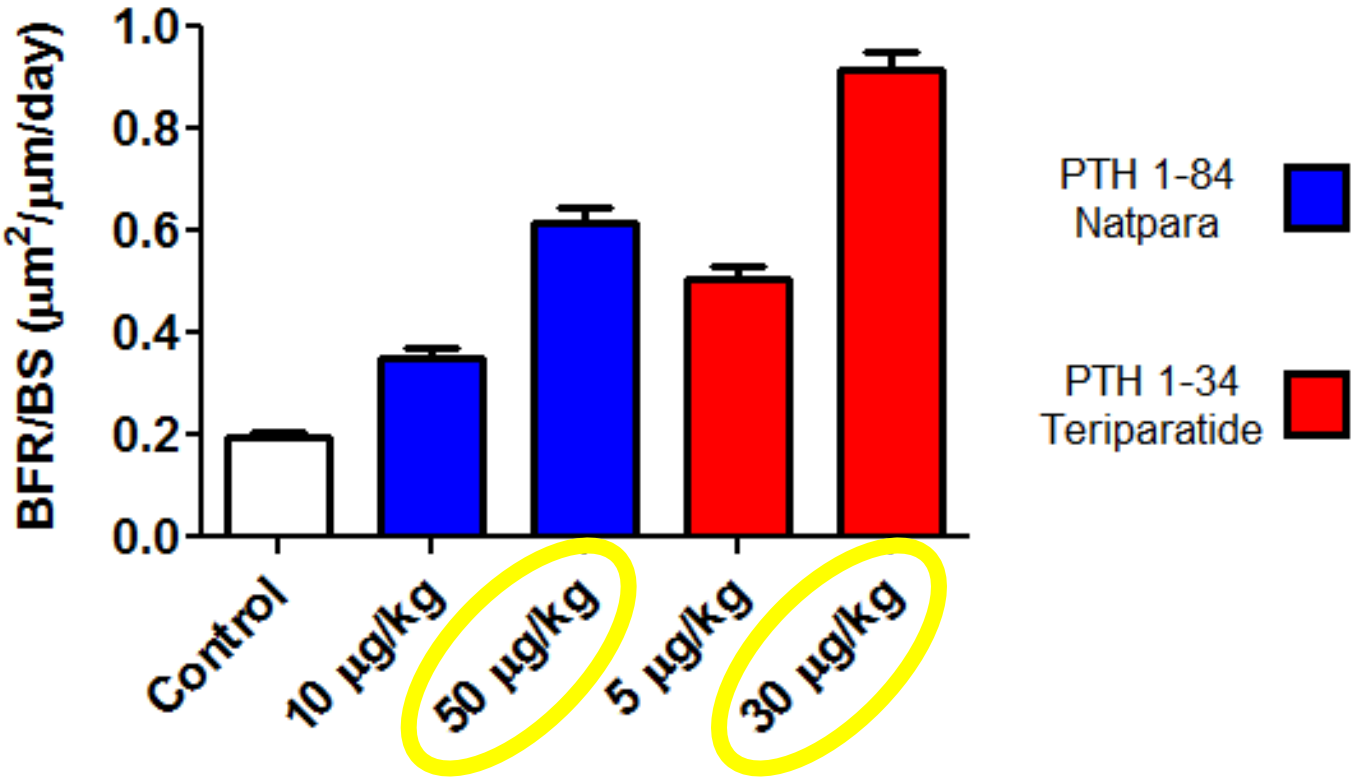
	Natpara® (PTH 1-84)				Forteo® (PTH 1-34)			
Dose Group	**C**	**LD**	**MD**	**HD**	**C**	**LD**	**MD**	**HD**
Dose (µg/kg/day)	**0**	**10**	**50**	**150**	**0**	**5**	**30**	**75**
Exposure Ratio (AUC_{rat}/AUC_{human*})	**-**	**4**	**22**	**63**	**-**	**3**	**21**	**58**
Osteosarcoma (%)	**0.8**	**0.8**	**15.0**	**33.3**	**0**	**5.8**	**27.5**	**45.0**

***Mean AUC_{human} for Natpara® at 100 µg/day = 0.92 ng•h/ml (Clinical study C09-002)**

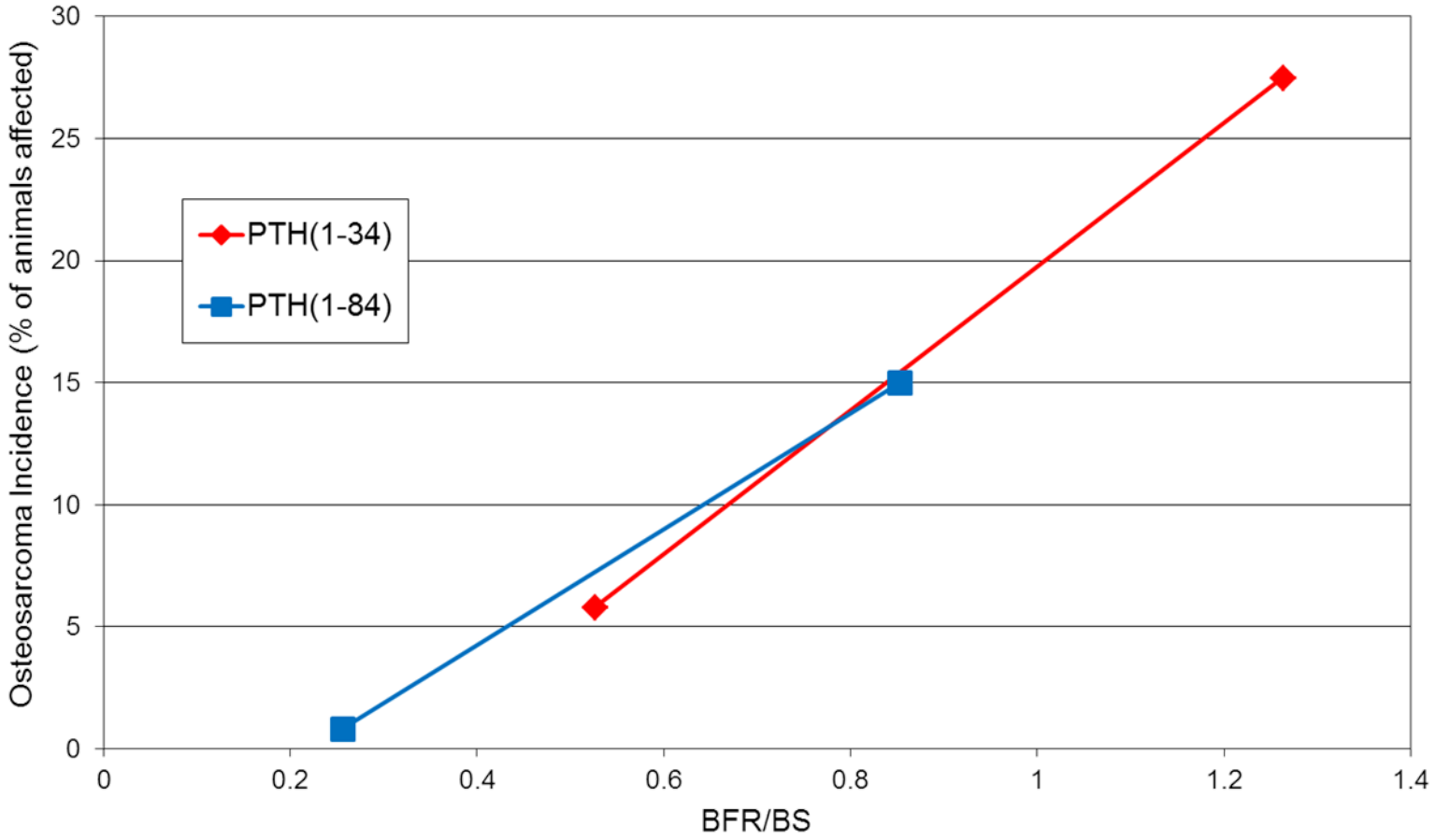
Challenges to Interpretation of the Data

- Carcinogenicity studies were not conducted in a head-to-head comparison
  - Potential for uncontrolled variables
- Comparison based on mass of drug administered (or exposure reported in terms of drug mass) does not take into account differences in the specific activity of PTH(1-34) and PTH(1-84)
- Availability of head-to-head data on PTH bone anabolic activity allows for normalization of tumor data to a measure of pharmacodynamic activity

Bone Formation Rate
PTH(1-84) vs. PTH(1-34)
F344 Rats (PH04-025)



Normalization to Bone Formation Rate (BFR/BS) Gives Comparable Osteosarcoma Rates for PTH(1-34) and PTH(1-84)



BRF/BS data are from study PH-04-025, conducted by NPS. Tumor incidence data are from each of the respective 2-year F344 rat carcinogenesis studies.

Conclusion

- Natpara® causes osteosarcomas in rats
- The clinical safety margin to the NOAEL in rats is low, and does not permit a conclusion of negligible clinical risk
- When normalized to a measure of pharmacodynamic activity, there is no discernable difference between the carcinogenic activity of PTH(1-34) and PTH(1-84) in rats

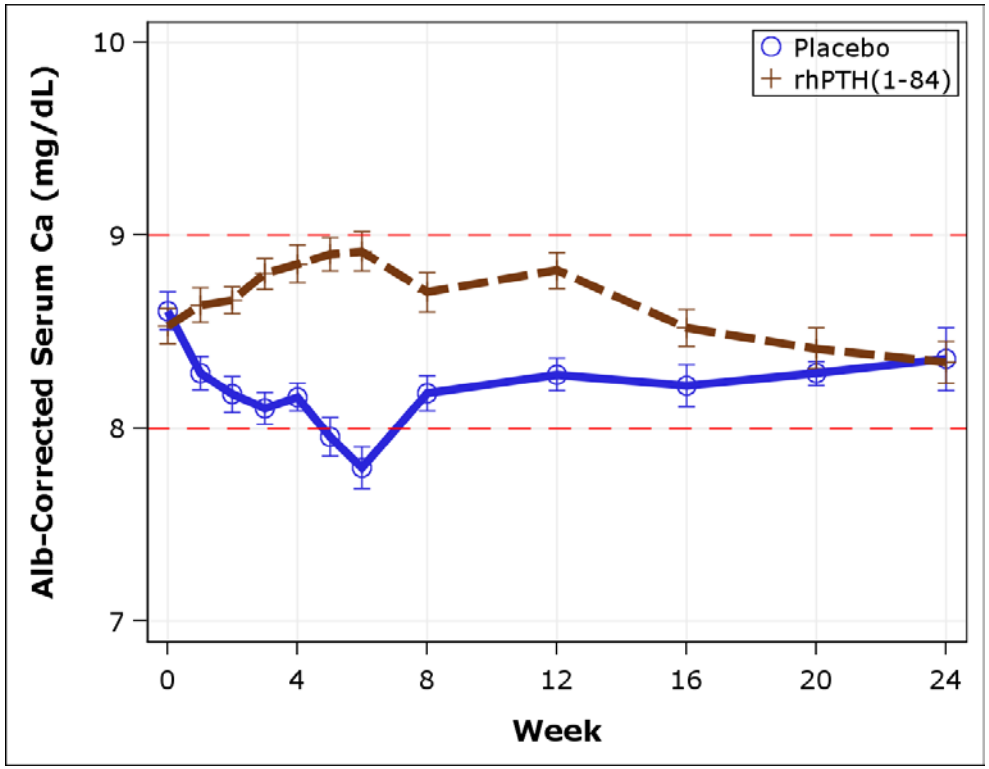
Clinical Pharmacology Review of Natpara® (BLA 125511)

Endocrinologic and Metabolic Drugs Advisory Committee
Advisory Committee Meeting, September 12, 2014

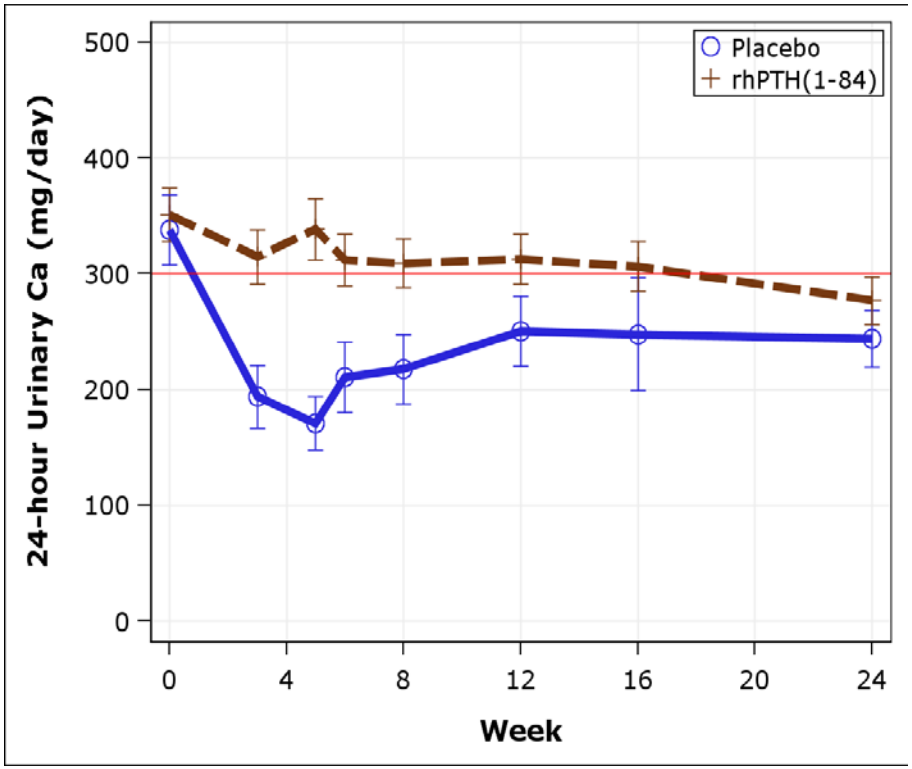
Manoj Khurana, PhD
Immo Zadezensky, PhD
Nitin Mehrotra, PhD
Office of Clinical Pharmacology

Control on 24-hour Urinary Calcium was Not Apparent with Natpara in the Registration Trial (CL1-11-040)

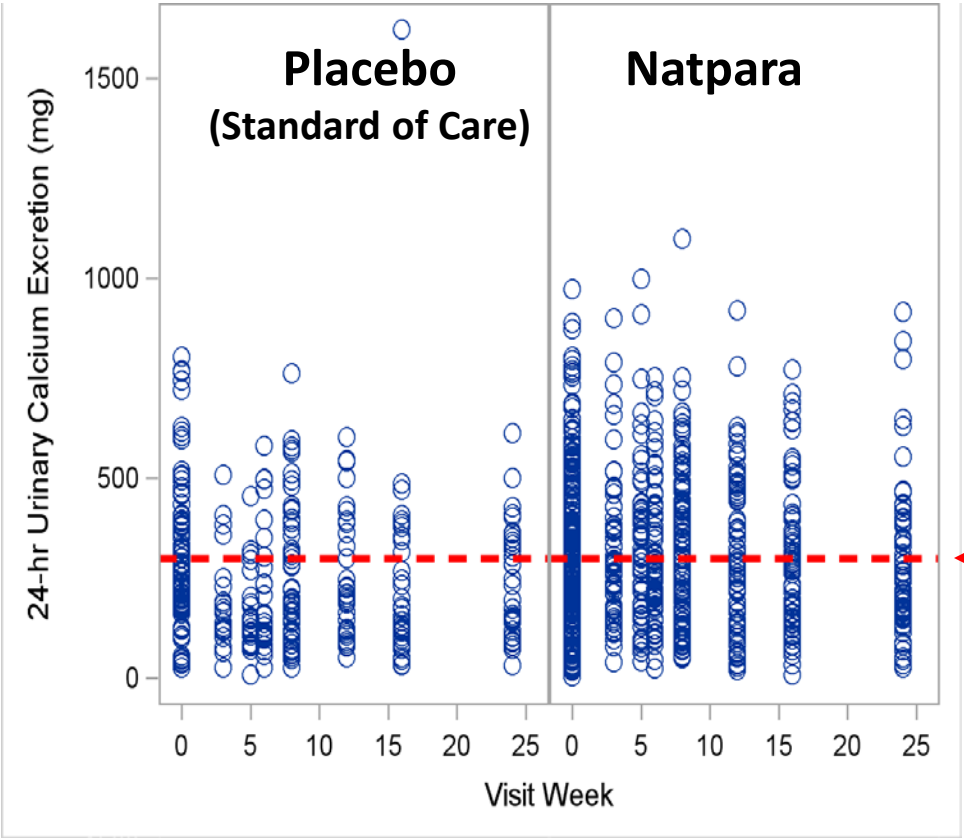
Mean (±SE) Serum Calcium



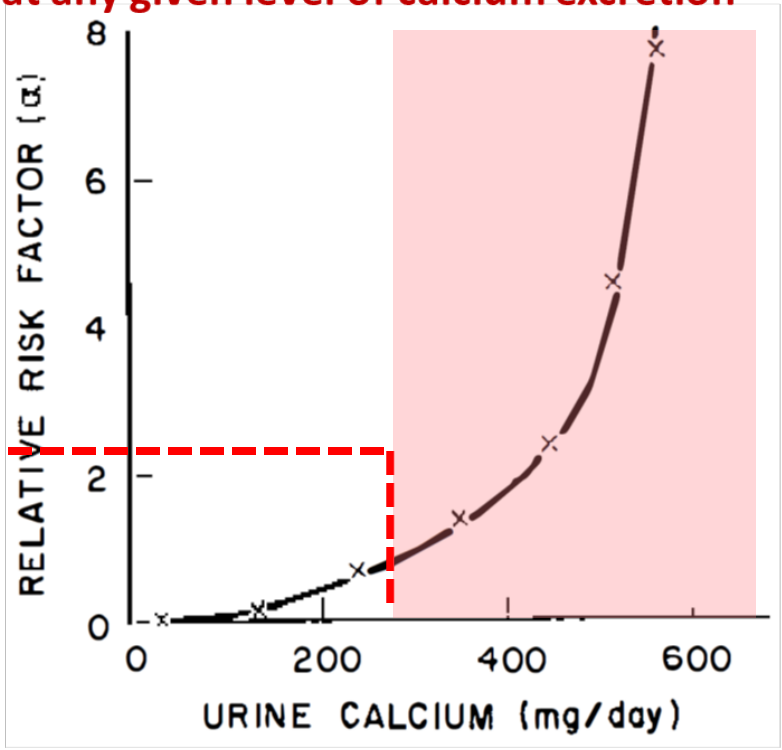
Mean (±SE) 24-hr Urinary Calcium



Control on 24-hour Urinary Calcium was Not Apparent with Natpara – Long-term Risk?



Relative risk of calcium stone formation at any given level of calcium excretion*

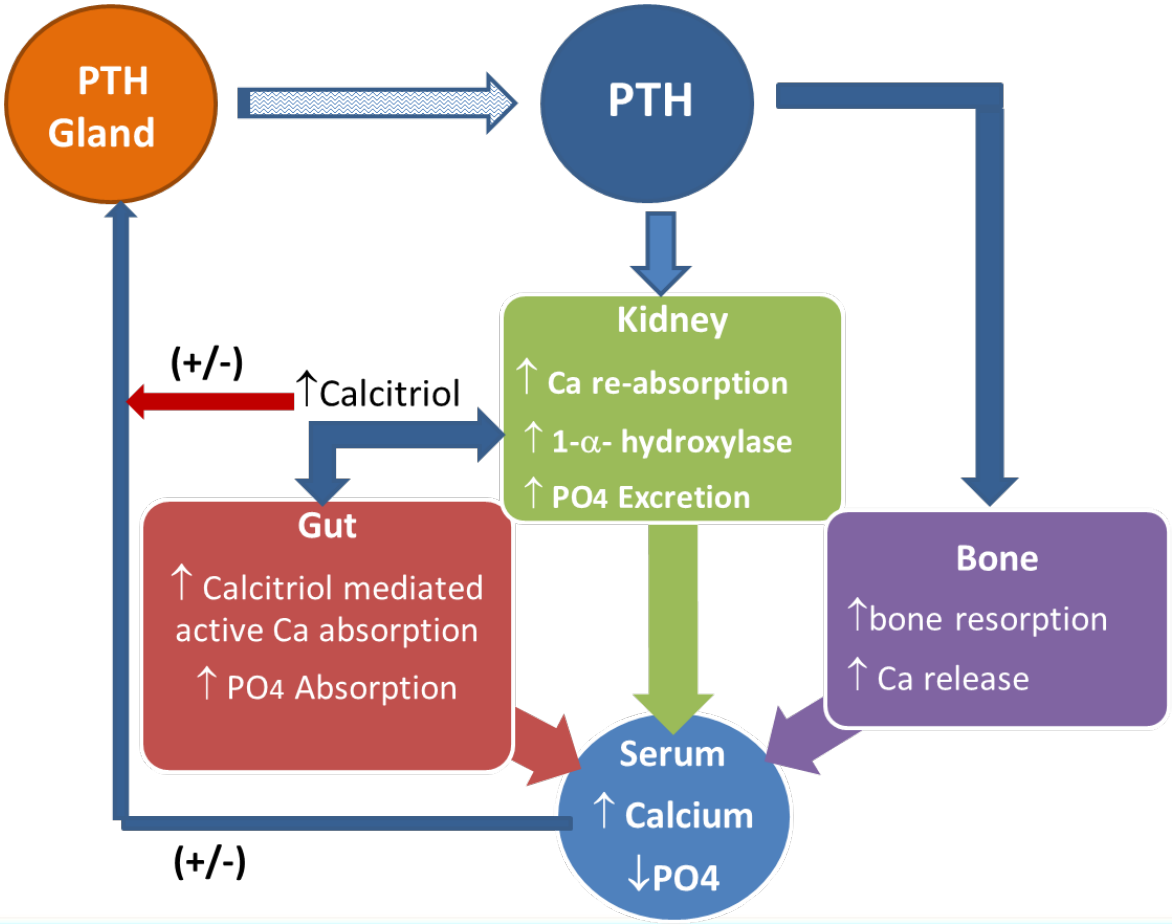


*Andrew F. Stewart and Arthur E. Broadus. Ann Rev Med. 32: 457-73 (1981).

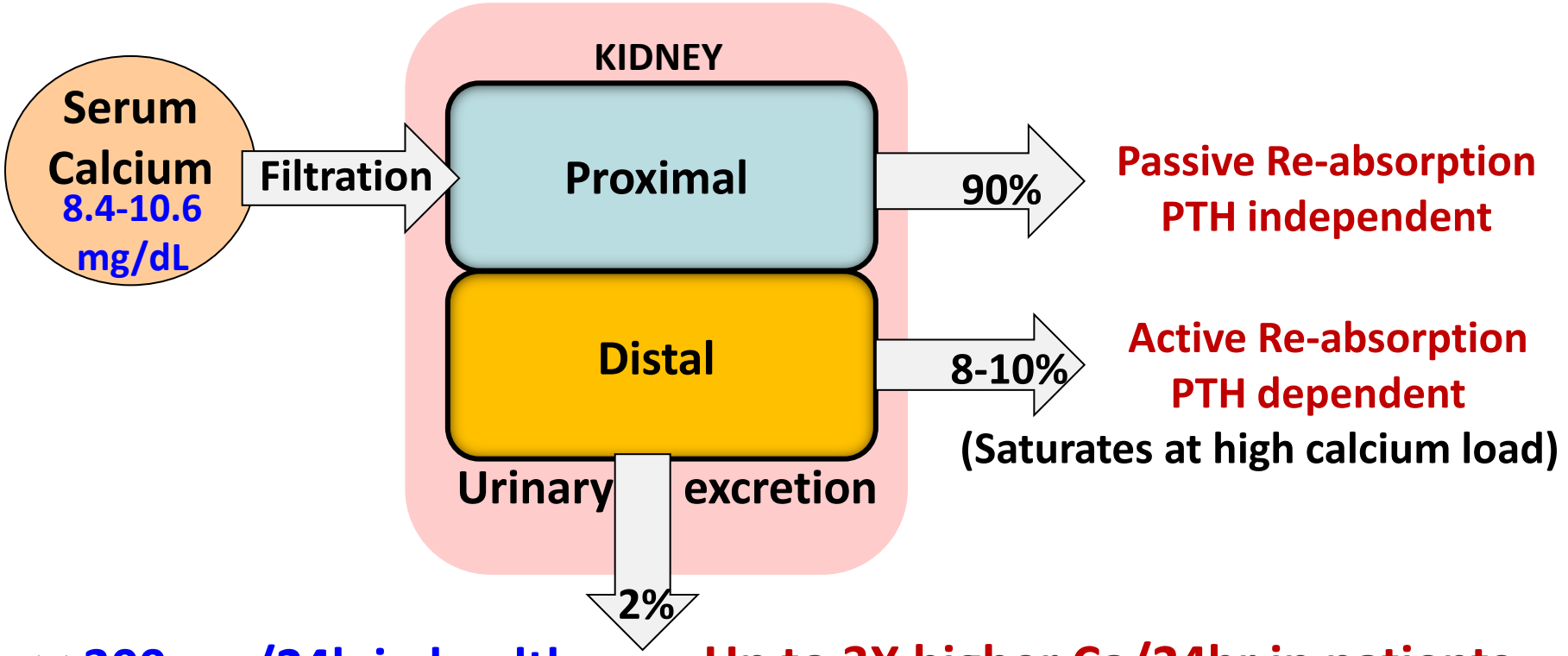
Outline

- Highlight important mechanistic aspects of PTH
- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of Natpara in patients with hypoparathyroidism
  - Relevance of PD effects on urinary calcium excretion to clinical data
- Can we obtain better control on hypercalciuria?
  - Is different dosing regimen a solution?
- Summary

Parathyroid Hormone Affects Multiple Systems to Maintain Calcium Homeostasis



PTH Regulated Renal Calcium Re-absorption is a Key Step in Calcium Homeostasis

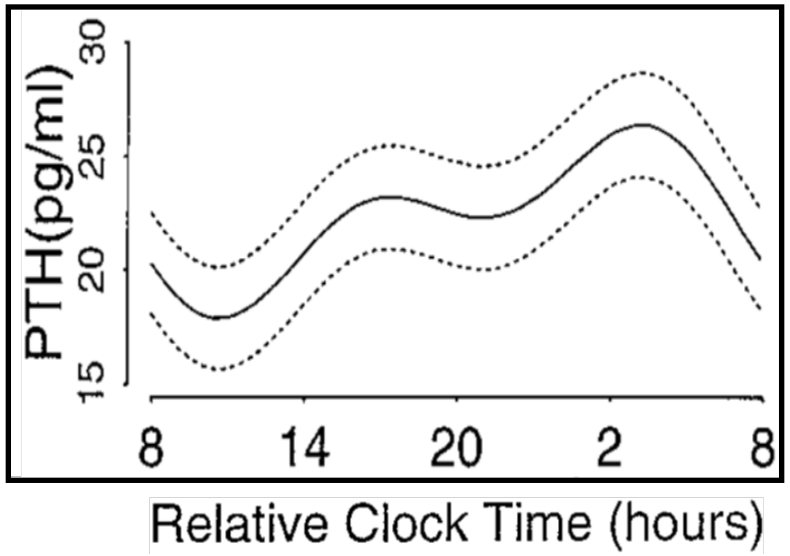


<< 300 mg/24h in healthy vs. Up to 3X higher Ca/24hr in patients

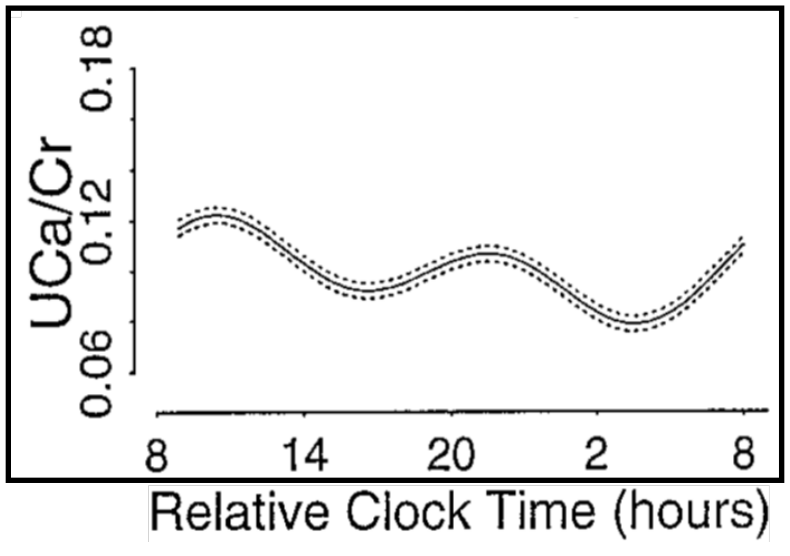
Adapted from: 1. G A Clines and T A Guise. Endocrine-Related Cancer. 12: 549–583 (2005).
2. R J M Bindels. J. exp. Biol. 184: 89–104 (1993).

Sustained Levels of PTH Over 24 hour Keep Urinary Excretion of Calcium Under a Tight Control

PTH versus Clock Time



UCa/Cr Ratio versus Clock Time



Figures based on Mean (±2SD) in 11 healthy men*

*G el-Hajj Fuleihan et al. J Clin Endocrinol Metab. Jan; 82(1):281-286 (1997).

PK/PD Characteristics of Natpara

- Highlight important mechanistic aspects of PTH
- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of Natpara in patients with hypoparathyroidism
  - Relevance of PD effects on urinary calcium excretion to clinical data
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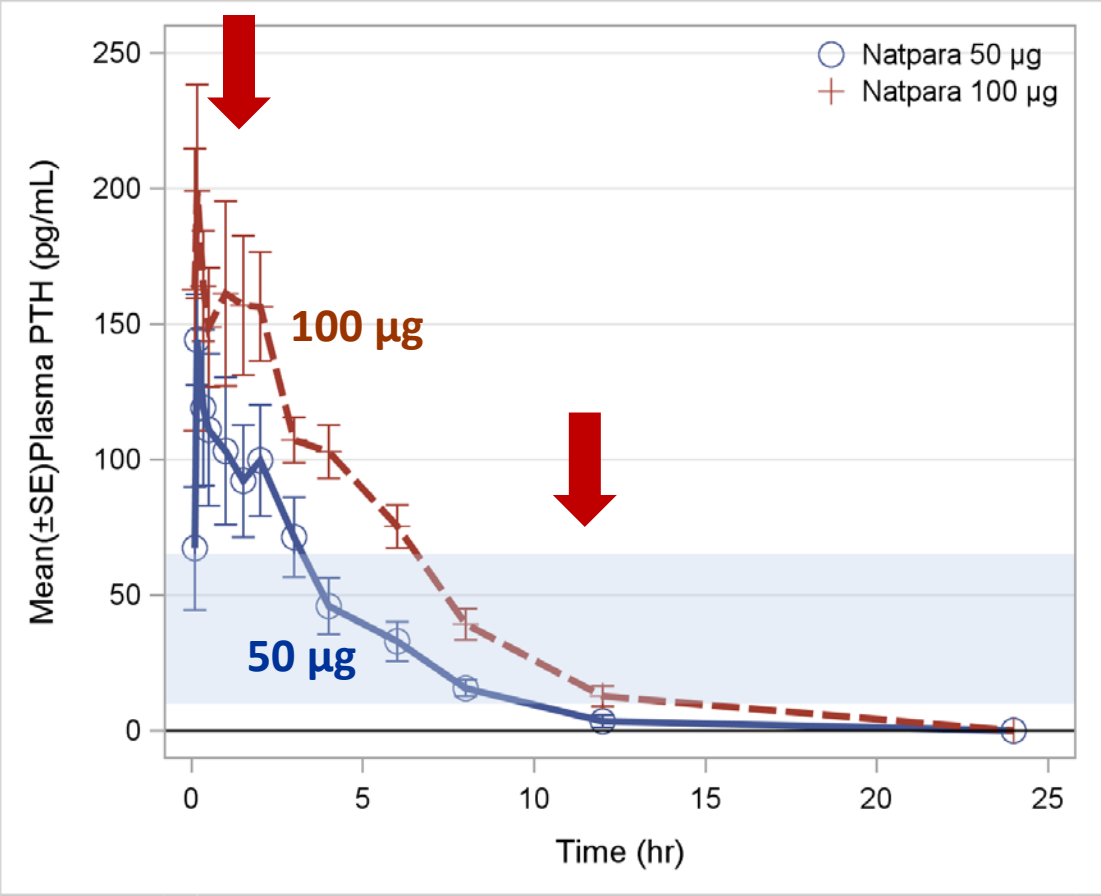
Key PK/PD Study Design Features

- **C09-002**
  - Single-dose study in 7 patients with hypoparathyroidism
  - 50 µg (Period 1) and 100 µg (Period 2) dose
  - PKPD
    - Serial PK
    - Serial serum calcium
    - Timed urine collection over 24-hr

PTH Levels Initially Exceed the Normal Range and Return to Baseline by 12 hour with Natpara

C09-002 Study – Natpara Pharmacokinetics

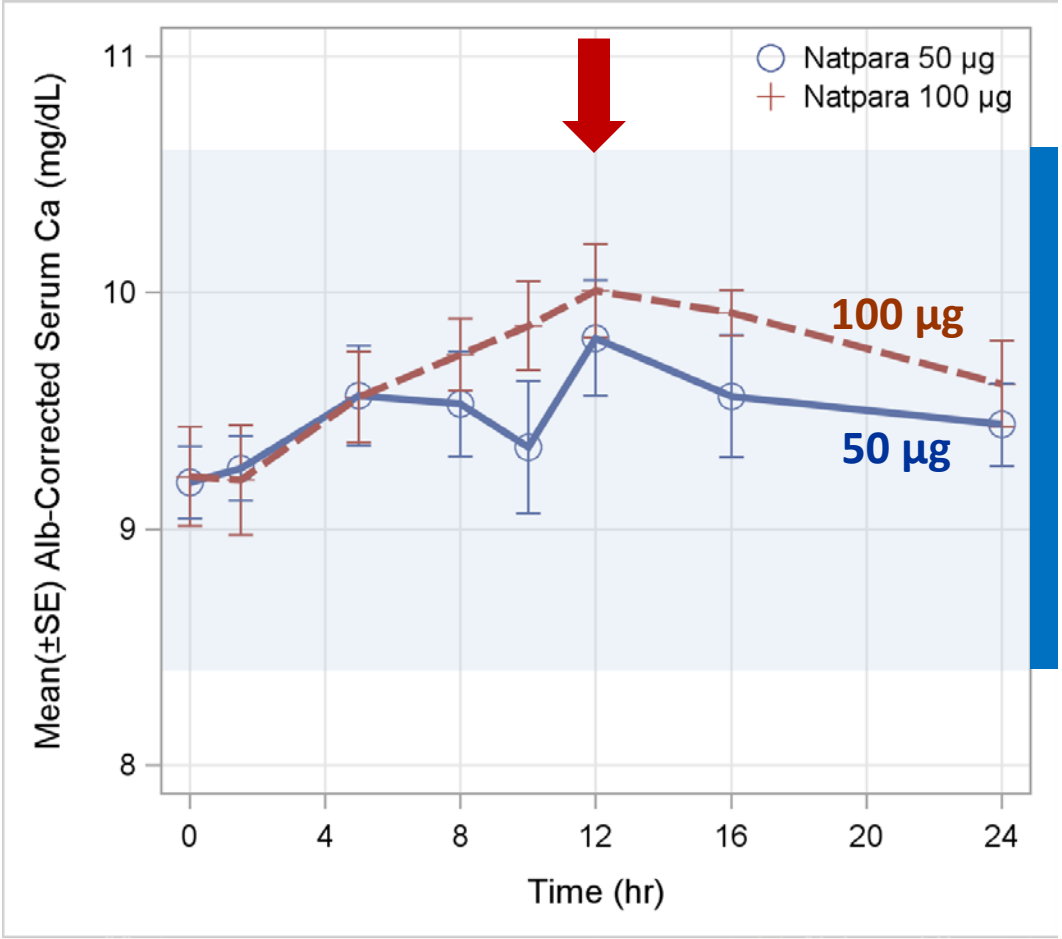


Normal Physiological range (10 – 65 pg/mL)*

*Karen K. Winer et al. J Clin Endocrinol Metab. 83: 3480–3486 (1998).

Dose-Related Increase in Serum Calcium with Natpara

C09-002 Study – Natpara Pharmacodynamics: Serum Calcium



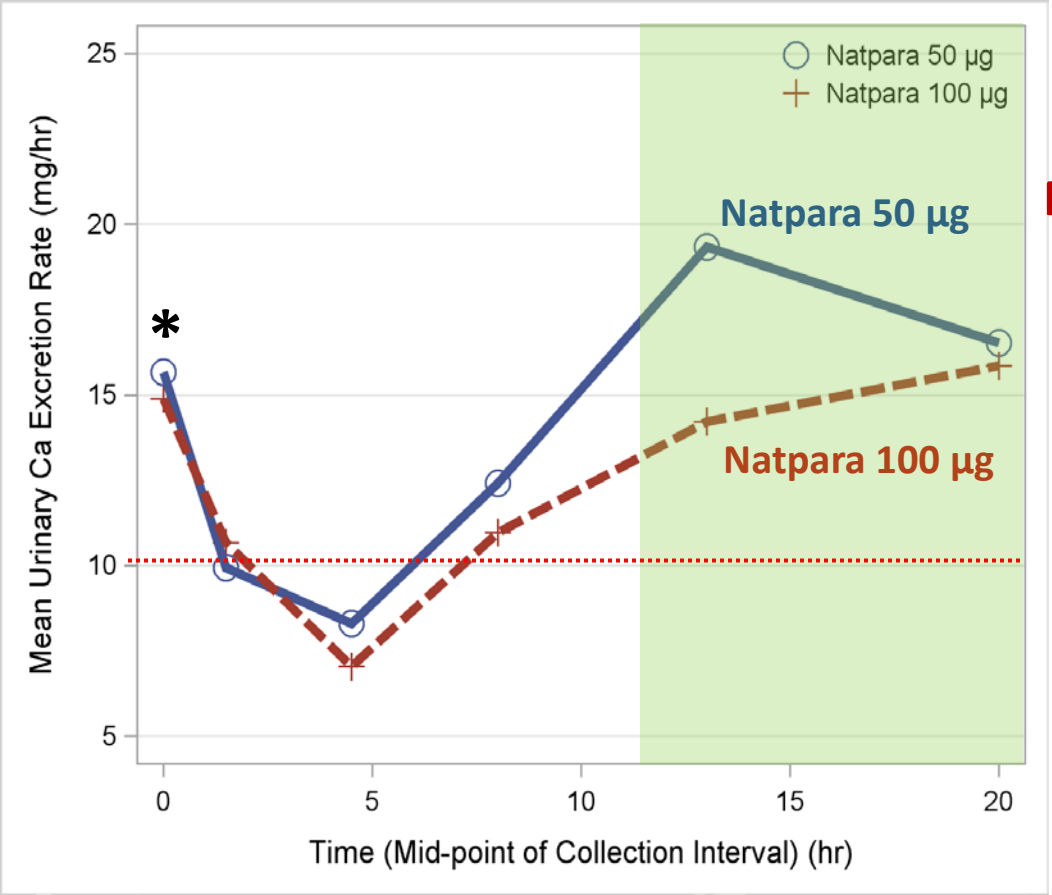
ULN – 10.6 mg/dL

Normal range

LLN – 8.4 mg/dL

Reduction in Urinary Calcium Excretion is Short-lived

C09-002 Study – Natpara Pharmacodynamics: Urinary Calcium



Modest ↓24-h Ca excretion:

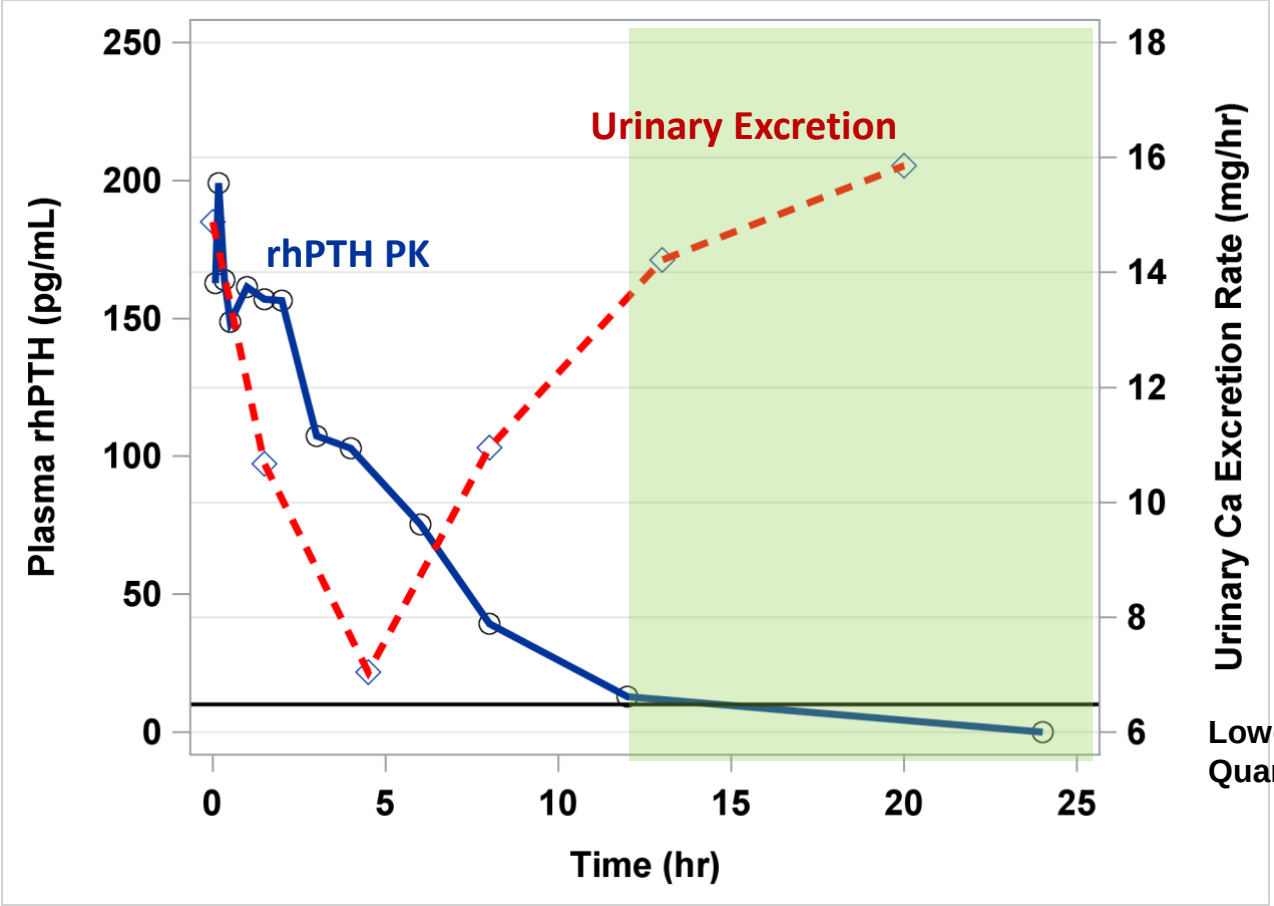
50 µg – 13%

100 µg – 23%

*** Day -1, 16-24h data**

Short-lived Renal Effect is a Reflection of PK Profile

C09-002 Study – Natpara PKPD (Urinary Calcium Excretion)



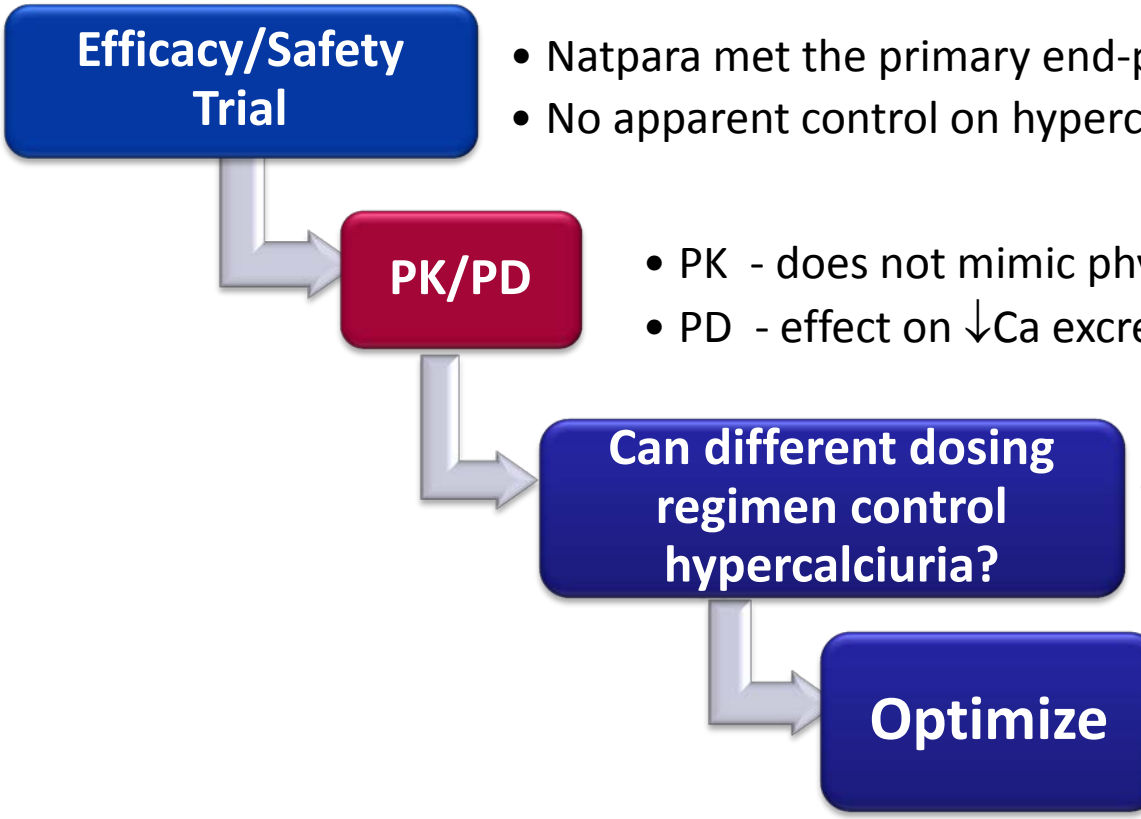
Conclusions from PKPD

- PTH levels initially exceed the normal physiological range, followed by return to baseline by 12 hours
- Dose related effect on serum and urinary calcium excretion
- Reduction in urinary calcium excretion is short-lived (10-12 hours)
- PKPD characteristics from multiple QD administration (Mosekilde-IIT) did not differ from the single dose (C09-002)

Optimizing Natpara Dosage Regimen Based on PKPD

- Highlight important mechanistic aspects of PTH
- Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of Natpara in patients with hypoparathyroidism
  - Relevance of PD effects on urinary calcium excretion to clinical data
- Can we obtain better control on hypercalciuria?
  - Is different dosing regimen a solution?
- Summary

Overall Concept and Strategy



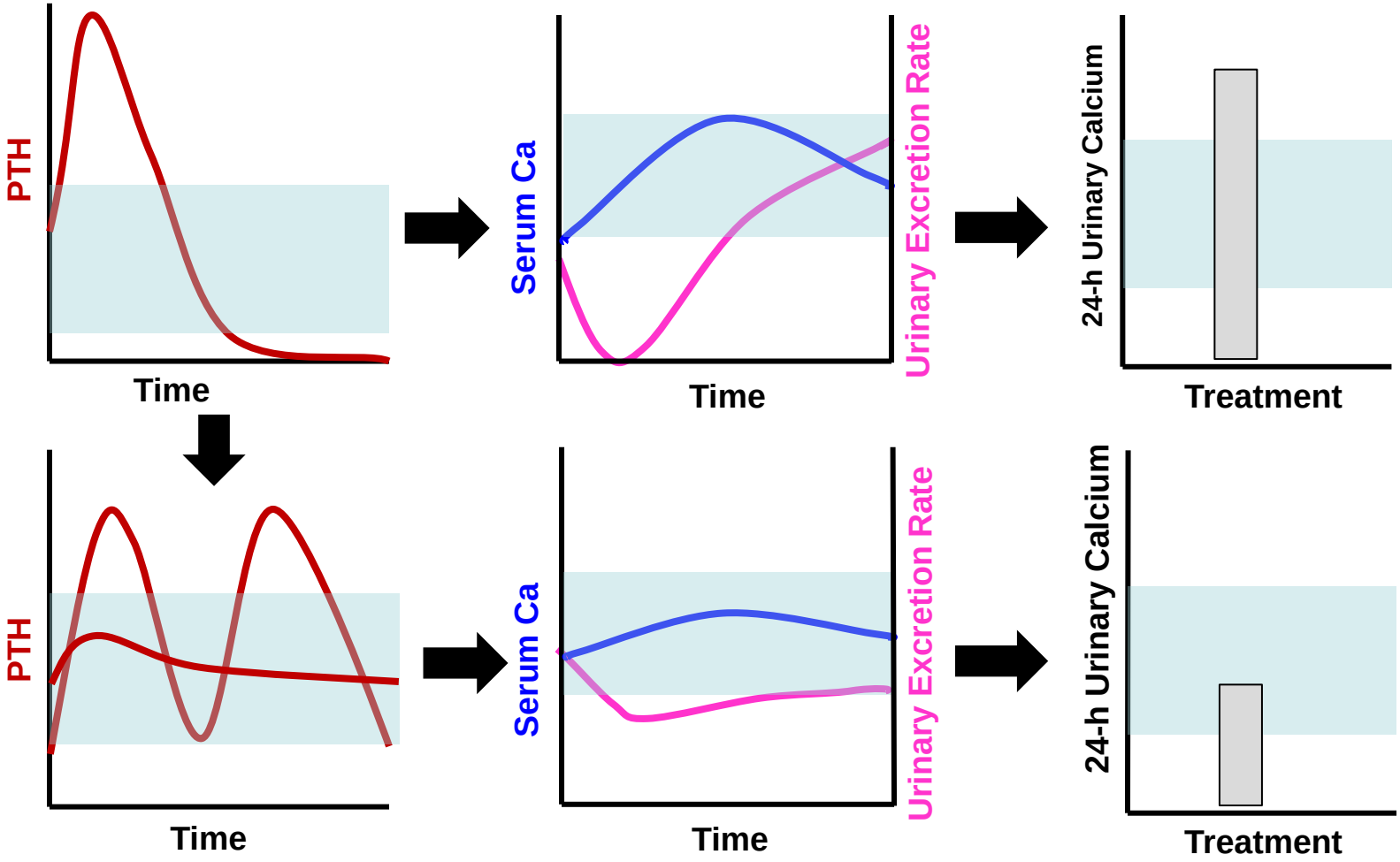
- Natpara met the primary end-point
- No apparent control on hypercalciuria

- PK - does not mimic physiological PTH profile
- PD - effect on ↓Ca excretion is short-lived

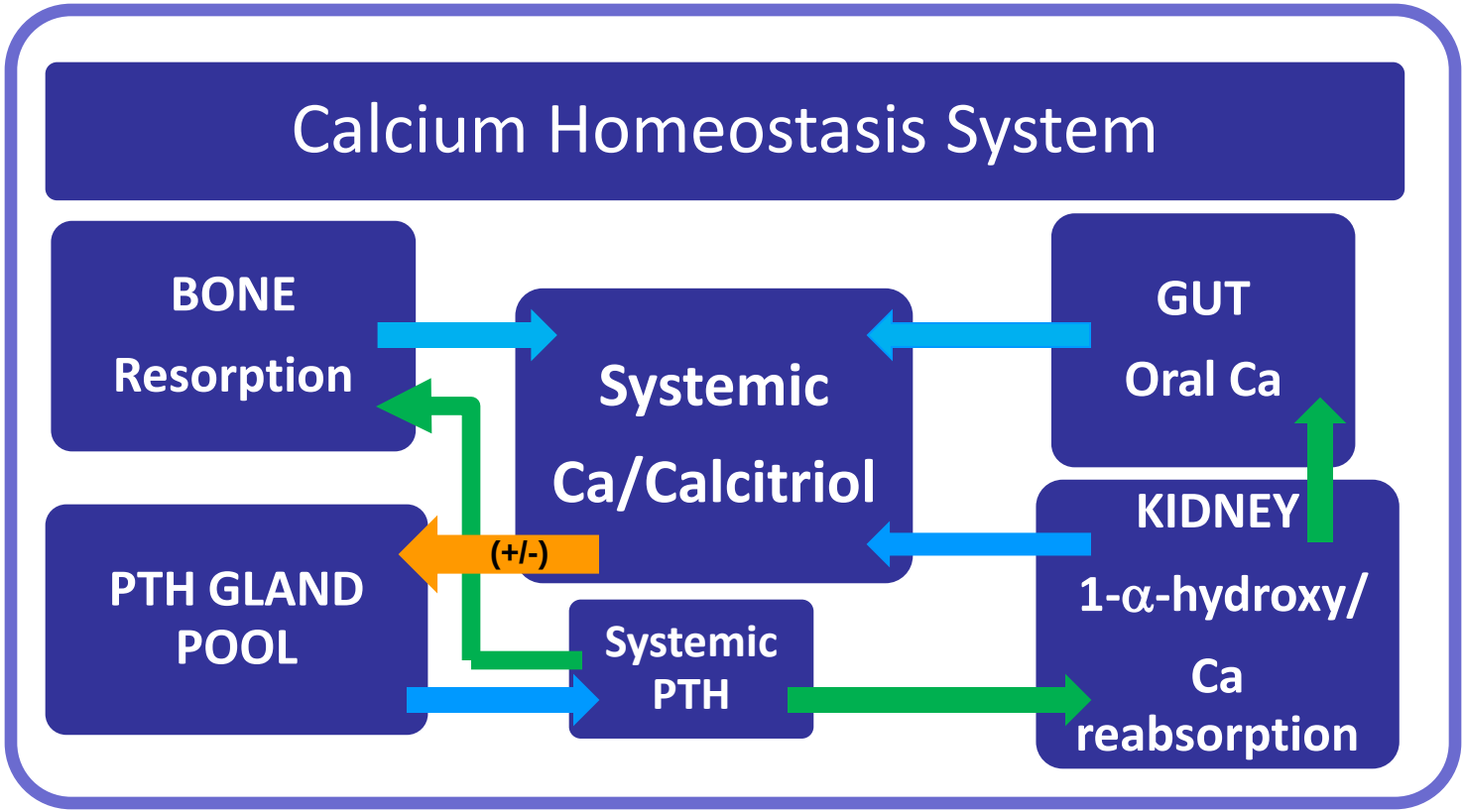
- No dose finding study

- Projection of PKPD using calcium homeostasis system

Optimizing the PKPD – Conceptual Framework



Calcium Homeostasis System Has Almost All Components That We Sought



Model adapted from:
A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Mark C. Peterson and Matthew M. Riggs. Bone 46:49–63 (2010).

Effect of Altered Regimen or Release Profile on Serum Calcium and Hypercalciuria

Setting

- Patient with 99% reduction in PTH pool

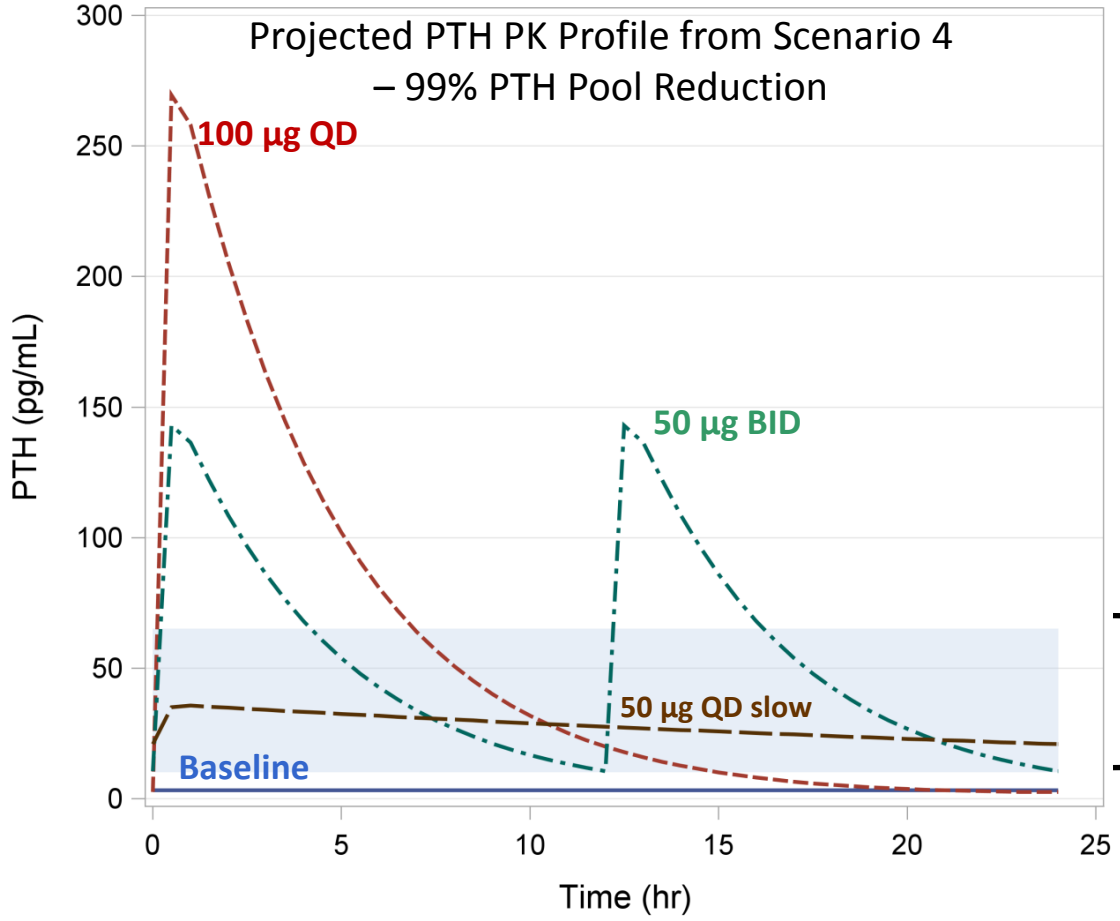
Background Therapy

- 1000 mg Oral Calcium, QD
- 0.5 µg Oral Calcitriol, QD

PKPD Profile

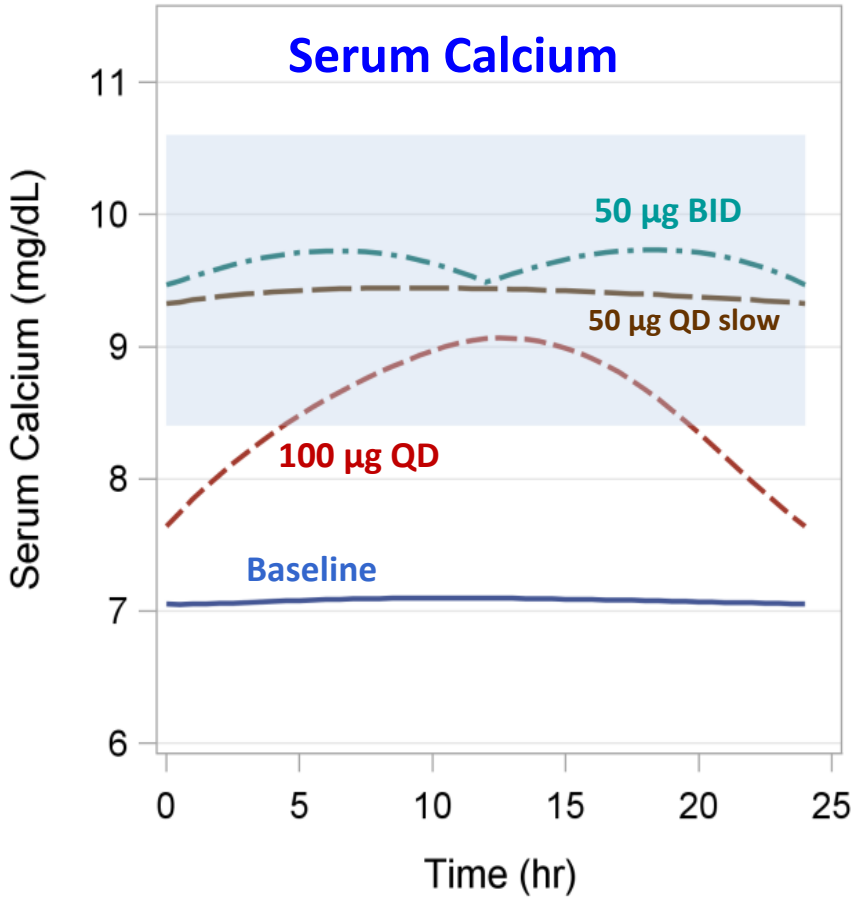
- Baseline (No PTH)
- 100 µg QD
- 50 µg BID
- 50 µg QD (slow release)

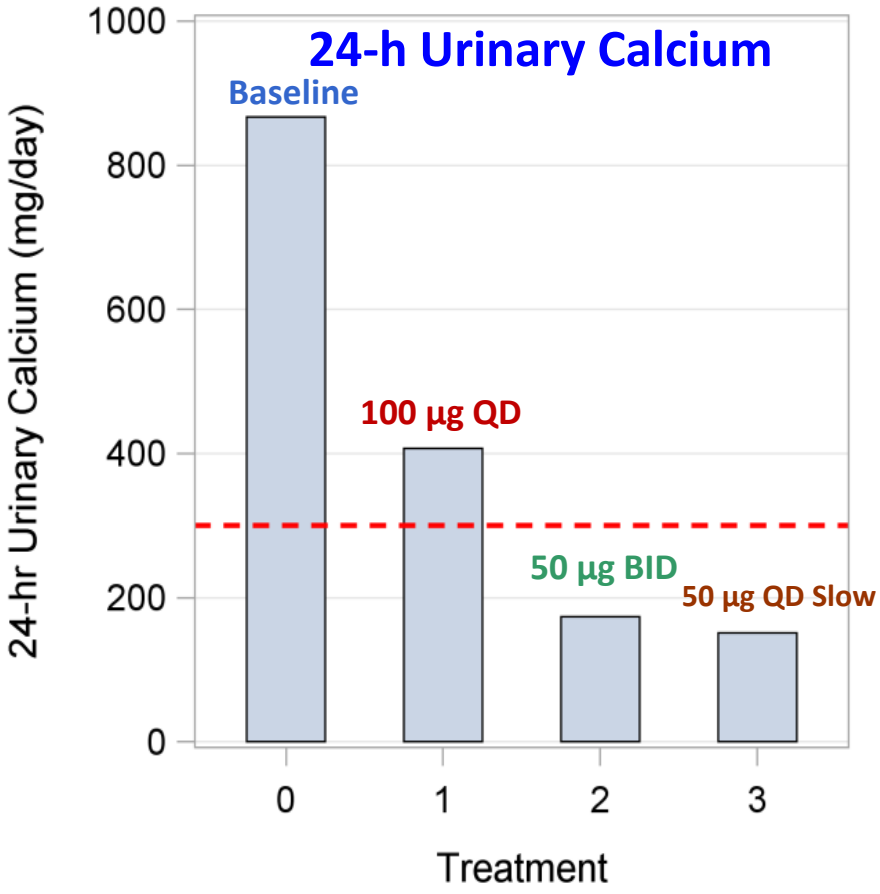
Altering Regimen (QD to BID) or Release Profile Bring PTH Levels Close to the Physiological Levels



Normal Physiological range (10 -65 pg/mL)*

Altering Regimen (QD to BID) or Release Profile Controls Hypercalciuria While Maintaining Normocalcemia





Summary

- Proposed QD regimen was able to control serum calcium, reduce oral calcium and vitamin D requirement
- Proposed QD regimen was not optimal in control on hypercalciuria
- Natpara QD administration does not produce PTH levels to cover the entire 24 hours
- The effect on urinary calcium excretion is short-lived
- Using systems pharmacology model we showed that control on hypercalciuria is feasible with more frequent regimen or a slow release PTH profile at lower systemic exposure than 100 μg QD
- For hormone replacement therapy, applying PKPD data for optimization of dosing regimen is important

Acknowledgements

- Liang Li
- Jeffry Florian
- Naomi Lowy
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Thank you for your attention