

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125511Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 2, 2015
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review
BLA #	125511/000
Supplement#	
Applicant	NPS Pharmaceuticals Inc.
Date of Submission	October 24, 2013
PDUFA Goal Date	Initially October 24, 2014; changed to 01/25/2015 following issuance of a major amendment
Proprietary Name / Established (USAN) names	Natpara/ Recombinant Human Parathyroid Hormone (rDNA) or (rhPTH[1-84])
Dosage forms / Strength	Subcutaneous injection 25, 50, 75 or 100 mcg daily doses
Proposed Indication(s)	Replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism
Recommended:	Approval

1. Introduction

On October 24, 2013 NPS Pharmaceuticals submitted a Biologic License Application (BLA) for Natpara under section 351 of the Public Health Act. Natpara is a device-biologic combination. The active ingredient in Natpara is recombinant human parathyroid hormone or rhPTH[1-84], identical in sequence with the native PTH, and manufactured in E.coli. The proposed indication for this NDA is:

Natpara® (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism.

Recombinant human PTH 1-84 has never been approved for use in the US. It was the subject of an NDA application in 2005 for an osteoporosis indication in post-menopausal women at high risk of bone fractures, but received an “approvable letter” because of concerns of hypercalcemia at the proposed dose and device performance. The Applicant decided not to pursue the osteoporosis indication in the US and withdrew the NDA in 2011. RhPTH[1-84] received approval in the European Union in 2006 for the osteoporosis indication at a daily dose of 100 mcg under the trade name Preatact®. This year, NPS discontinued marketing Preatact® in the EU (May 16, 2014).

Natpara is an injectable product. It is to be self-administered once daily subcutaneously in the thigh at doses of 50 mcg, 75 mcg and 100 mcg following a rather complex titration regimen

beginning with the 50 mcg dose. The presentation is a dual-chamber cartridge (one chamber containing the drug product as a powder and one for the diluent) designed to be used first with a reusable mixing device (Natpara Mixing Device) for product reconstitution, and subsequently with a reusable pen (Natpara Q-Cliq) for the actual injection. The Natpara cartridge comes in multiple strengths including the already mentioned doses of 50 mcg, 75 mcg and 100 mcg, as well as a lower dose of 25 mcg in case down titration below the 50 mg starting dose is necessary in cases of poor tolerability.

Hypoparathyroidism is a rare disease, with a prevalence estimated between 65,000 and 100,000 in the US. The most common cause of hypothyroidism is post-surgical removal of the parathyroid tissue or damage to its blood supply during neck surgery, in particular following thyroidectomy. Less frequent causes include autoimmune destruction of parathyroid glands, genetic defects (calcium-sensor receptor mutations, chromosomal deletions such as Di George syndrome), or idiopathic.

Endogenous PTH secretion is the main physiologic response that counteracts the effects of hypocalcemia. PTH exerts its functions at three main sites: renal, bone and intestine. In the renal distal tubules it reabsorbs calcium and inhibits phosphate reabsorption. It stimulates osteoclastic bone resorption with subsequent releases of calcium and phosphate into circulation, and is responsible for bone remodeling. In the intestine it enhances absorption of calcium and phosphate, an effect that is mediated via active Vitamin D (PTH stimulates 1-alpha hydroxylation of 25-OH Vitamin D in the kidneys).

The clinical manifestations of hypoparathyroidism are those anticipated based on the physiologic functions of PTH, and consist in hypocalcemia-related symptoms: paresthesias, numbness, twitching, muscle cramps, seizures, tetany (including laryngeal spasm), increased bone density (due to decreased bone turnover), cardiac arrhythmias, and poor quality of life (many patients complain of decreased levels of activity, poor concentration ability, decline in cognitive functions all characterized by the term of “foggy brain”).

To date there is no hormone product approved for the treatment of hypoparathyroidism. There are two vitamin D products, ergocalciferol (Drisdol) and calcitriol (Rocaltrol) which have been approved decades ago (1941 for Drisdol and 1978 for Rocaltrol). The Drisdol indication is “use in the treatment of hypoparathyroidism, refractory rickets, also known as vitamin D resistant rickets, and familial hypophosphatemia.” The indication for Rocaltrol is “management of hypocalcemia and its clinical manifestations in patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism, and pseudo hypoparathyroidism.” None of these vitamin products is in PLR format.

The current standard of care in the treatment of hypoparathyroidism consists of oral supplementation with calcium given along with native vitamin D, active Vitamin D, or Vitamin D analogs. The goal of therapy is to normalize serum calcium and prevent the clinical manifestations and complications of hypocalcemia.

For many patients calcium and vitamin D supplementation is not a satisfactory treatment. For one, the doses of supplemental calcium, albeit variable, can be as high as 9 g/day in some

patients and the pill burden can significantly affect daily life. In addition, and most importantly, achieving a balance between calcium/Vitamin D supplements and serum calcium is not easy in all patients. Taking liberal doses of calcium may correct hypocalcemia but they are also associated with a rise in the amount of calcium excreted in the urine and subsequent complications (nephrolithiasis, renal function deterioration). To avoid such consequences, the current standard of care does not aim at achieving a serum calcium in the full normal range of (8.4 to 10.6 mg/dl (2.00-2.25 nmol/dl) but rather at maintaining serum calcium in slightly below normal to low-normal range, specifically 8-9 mg/dl. The goal of therapy is to reach a supplemental calcium and Vitamin D doses that prevent the clinical manifestations of hypocalcemia but low enough to reduce the risk of hypercalcemia/hypercalciuria. On such regimens some patients continue to have intermittent episodes of hypocalcemia that can significantly affect quality of life, family and social life, career choices.

Even if optimization of calcium/Vitamin D supplementation therapy is successful, this regimen has other limitations. For instance, it does not impact the hyperphosphatemia associated with the condition, increase calcium-phosphate product which may lead to soft tissue calcium precipitation. In addition, it does not address the bone disease associated with hypoparathyroidism (decreased bone turnover, increased bone density with abnormal bone architecture and decreased bone elasticity). Therefore, there are clear theoretical advantages to a rhPTH treatment over the existing standard of care.

While it is true that replacement therapy with PTH has the theoretical potential to be curative, in reality many hormone replacement therapies fall short of such a goal because they fail to reproduce the circadian secretory patterns of endogenous hormone secretion and the complex homeostatic adjustments. With this in mind, it should be emphasized from the very beginning that the scope of the Natpara program in hypoparathyroidism was relatively narrow. It was not designed to demonstrate a clinical benefit in reducing disease-specific complications, but rather to evaluate the potential benefit of a convenient once a day rhPTH injection on reducing the need for supplemental calcium and vitamin D, and investigation of potential benefit beyond dose reduction was mostly exploratory. Consequently, to what extent such a treatment regimen has relevance for the spectrum of clinical phenotypes of hypoparathyroidism is central to this application and will be the focus of this memorandum.

Finally and importantly, a related PTH product has been on the US market for more than a decade. Forteo® (teriparatide), a recombinant human parathyroid hormone analog manufactured by Eli Lilly and Company, was approved in 2002. Forteo® contains the first 34 amino acids of the PTH molecule (rhPTH[1-34]). The approved dose is 20 mcg subcutaneously once a day, and the approved indications are: 1) treatment of postmenopausal women with osteoporosis at high risk for fracture; 2) increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; and 3) treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture. The package insert for Forteo carries a boxed warning for the “potential risk of osteosarcoma,” states that, in rats, teriparatide caused an increase in the incidence of osteosarcoma, and indicates that treatment longer than 2 years has not been evaluated in osteoporosis patients. The relevance of the Forteo findings to Natpara will be further discussed in appropriate sections of this NDA.

2. Regulatory Background

The following are the major regulatory interactions that took place between DMEP and NPS Pharmaceuticals regarding the Natpara development program for the hypoparathyroidism indication:

- 1) FDA's Office of Orphan Products Development granted orphan drug designation to NPS's rhPTH on August 31, 2007 for the indication of "treatment of hypoparathyroidism."
- 2) Pre-IND meeting (December 17, 2007). Retrospectively, this meeting was very important because it set the overall direction and structure of the Natpara Phase 3 clinical program:
 - The Division objected to a proposal to conduct [REDACTED] (b) (4)
 - Instead, the Division advised NPS to conduct a placebo-controlled clinical trial in which Natpara was to be used as an add-on therapy to the current standard of care (i.e., oral calcium and oral Vitamin D).
 - The Division also indicated that a single Phase 3 clinical trial may be acceptable given the fact that hypoparathyroidism is a rare disease, but a final decision cannot be made without having a protocol to review. The sponsor was encouraged, however, to include additional clinical data from several investigator-sponsored INDs to which NPS had the right or reference.
 - The sponsor was encouraged to submit a 505(b)(1) application [REDACTED] (b) (4)
 - The Division accepted the proposed primary endpoint of achieving eucalcemia by week 12 and no later than Week 16 while targeting a clinically significant reduction in the requirement for supplemental calcium and Vitamin D. With minor modification (changing the time of assessment to Week 24), this remained the primary endpoint for the pivotal Phase 3 trial of this application.
- 3) IND 76514 was opened on September 19, 2008 with a protocol for a single Phase 3 clinical trial (the REPLACE trial). As advised, the sponsor proposed a placebo-controlled clinical trial in which Natpara was to be used as an add-on to calcium and Vitamin D (standard of care). The primary efficacy analysis was a drug-to-placebo comparison of the percentage of patients who demonstrated a 50% reduction from baseline in the amount of oral calcium and vitamin D supplements at week 24, while maintaining a stable serum calcium. DMEP had no objections regarding the proposed protocol and endpoints.

- 4) A type C meeting took place on July 6, 2010 to discuss the strategy needed to bridge the pen injector used in the pivotal Phase 3 clinical trial (the “Ypsomed pen injector”) to a new pen injector intended for commercialization (the “Haselmeier pen injector”). FDA representatives from CDRH and from the Office of Combination Products provided specific advice regarding how the new device should be evaluated prior to NDA submission, and specific requirements for a Usability Validation Study. The sponsor was told that a successful demonstration that two devices deliver the active ingredient in a highly similar manner is necessary and this should be demonstrated in an in vivo bioequivalence study comparing the Ypsomed and Haselmeier pen injectors.
- 5) A second Type C meeting took place on Sept 26, 2011. In this meeting the Division provided advice about the content and format of the future NDA/BLA. Issues discussed were the size of the efficacy and safety datasets, the contributory role of the data from the investigational trials and the previously submitted osteoporosis program.
- 6) The proprietary name, Natpara, was conditionally accepted on November 7, 2001.
- 7) In correspondence dated December 23, 2011, FDA confirmed that Natpara will be reviewed as a BLA and that the application will be a biologic-device combination.
- 8) Pre-BLA meeting (May 15, 2012). The meeting focused on BLA’s content and format, the completeness of the different BLA modules, QT assessment, format and content of individual studies, PREA-related questions. At the time of the meeting a usability study was still under review by DMEPA and CDRH. Subsequently, deficiencies in the proposed usability study were identified.
- 9) Type C meeting (February 5, 2013). The protocol for a new human factors study was discussed and generally agreed upon by DMEPA and CDRH .
- 10)  (b) (4)
- 11) BLA submission: October 24, 2013.
- 12) Major Amendment October 22, 2014, extending to PDUFA goal date to January 24, 2015.

3. CMC/Device

The CMC review recommends approval pending a recommendation from the Office of Compliance, Biotech Manufacturing Branch and a recommendation from microbiology team regarding sterility assurance of the drug substance (DARRTS 6/27/14).

Drug substance

The drug substance, recombinant human parathyroid hormone 1-84 (rhPTH (1-84)) is confirmed to be identical in primary sequence to native human PTH.  (b) (4)



RhPTH is manufactured in a modified strain of E. coli (b) (4)

The CMC reviewer finds the proposed release specifications for the drug substance to be acceptable¹. They are based on the experience accumulated with the manufacturing of 18 commercial scale batches at the proposed commercial site. Release specifications include testing for product related substances and impurities (e.g. (b) (4) are such specific product-related impurities that are measured as part of drug substance release testing (b) (4). Process related impurities (endotoxin, bioburden, (b) (4) are also measured using acceptable assays. Biological activity of rhPTH is measured with a bioassay that measures changes in (b) (4). The PTH biological activity of rhPTH(1-84) is expressed as relative potency against the rhPTH(1-84) Reference Standard.

Based on long-term, real-time stability studies from primary stability batches at production scale, the CMC reviewer recommends a shelf-life of (b) (4) months for the drug substance when stored at (b) (4) °C.

Drug product

The Natpara drug product contains rhPTH(1-84) and several compendial excipients supplied in a disposable multiple-dose, dual-chamber glass cartridge. The excipients include sodium chloride (b) (4), mannitol (b) (4), citric acid monohydrate (b) (4), (b) (4) m-cresol (b) (4).

The review indicates that:

- “all methods for release testing of the drug product have been adequately described and are validated”
- “the selected parameters tested on drug product have been adequately justified and are considered acceptable”
- “sufficient batch analysis results confirm the consistency of the drug product”
- “no new impurities [were] formed during the manufacture of the drug product and the purity profile of the drug product is comparable to that of the drug substance”
- “the proposed limits are considered acceptable”

¹ The proposed release specifications include appearance, identification (peptide mapping and HPLC), assay/peptide content (HPLC), bioactivity (cell-based assay), individual peptide related impurities (RP HPLC, cation exchange (CEX) and size exclusion chromatography (SEC), (b) (4), (b) (4) bioburden, and bacterial endotoxin.

Using the commercial process, 65 batches were produced at commercial scale at the commercial site, and they met the specifications proposed.

The CMC reviewer is granting a shelf-life of 24 months prior to reconstitution when stored at refrigerated conditions, and 14 days post-reconstitution when used according to the labeled instructions.

He concludes that “from [a] CMC perspective, [this] BLA is recommended for approval. All chemistry related issues are satisfactorily resolved at this stage.”

The manufacturing site was inspected by CDER in November 2013 and classified NAI. A similar memo recommended a waiver of the pre-approval inspection for the site that manufactures the Natpara multi-dose dual chamber syringe (Vetter Pharma-Fertigung GmbH & Co. KG, Schützenstrasse, Ravensburg, Germany).

[REDACTED] (b) (4)

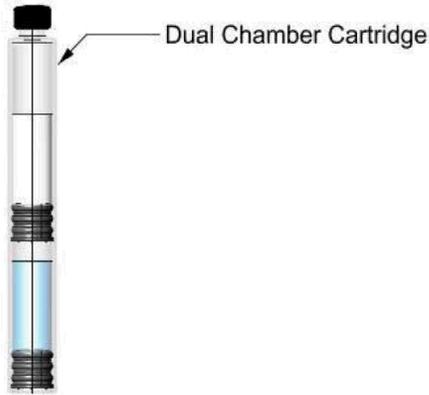
Office of Compliance recommendations

CDER Office Compliance (OMPQ) and CDRH Office of Compliance (Division of Manufacturing Quality) have issued acceptable recommendation for facilities associated with the drug substance, drug product and device (DARRTS 9/29/14).

Drug presentation and reconstitution

Natpara is supplied as a disposable glass cartridge that is designed for use with a reusable Natpara Mixing Device for product reconstitution and a reusable Natpara Q-Cliq™ pen injector for subcutaneous administration. These three items (cartridge and cartridge holder, mixing device, pen injector) are packaged separately.

The Natpara cartridge has two chambers. One chamber contains rhPTH as a sterile lyophilized powder, and the other contains the sterile diluent for reconstitution. The two chambers are separated by a rubber septum (see figure below). The cartridge is intended for multiple-dose use and is disposable. The dual-chamber cartridges are available in 4 dosage strengths: 25, 50, 75, and 100 µg/dose, each differs only by the amount of drug substance in their respective formulations.



Before use, the cartridge is placed in a cartridge holder which in turn is attached to the Natpara® Mixing Device (both displayed below). There are 4 different cartridge holders, one for each of the 4 Natpara doses: 25 mcg, 50 mcg, 75 mcg, and 100 mcg, and they are distinguished from each other by color and the labeled dosage strengths. The Mixing Device is used to reconstitute the drug product by manually turning a “reconstitution wheel” which in turn allows the diluent to mix with the lyophilized drug product.

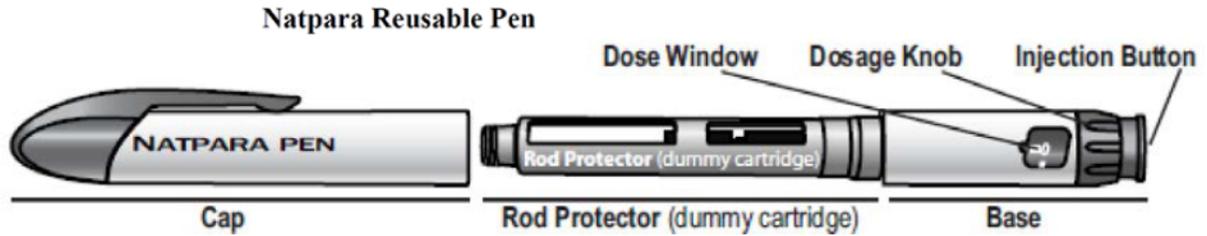
Cartridge Holder (available in four dosage strengths/colors)



Natpara Mixing Device



After reconstitution, the cartridge holder is unscrewed from the Mixing Device and screwed onto the reusable pen injector (Natpara Q-Cliq), shown below, and is ready for use. Using the Natpara Q-Cliq, each medication cartridge delivers 14 doses (71.4 μL); each dose contains 25, 50, 75, or 100 mcg of rhPTH(1-84) depending on the dosage strength of the specific cartridge.



The dual-chamber medication cartridge, as well as the reconstituted cartridge, is stored refrigerated (2 to 8°C).

There are three CDRH consults in DARRTS:

- 1) An Office of Compliance review recommends approval following an inspection of NPS pharmaceuticals which was classified as VAI (DARRTS 9/8/2014)
- 2) A human factor study review (DARRTS 9/9/2014). It identifies several errors in using the device, which may result in underdosing or missed doses. Following internal communications and clarifications/discussions with the applicant, the reviewer “accepted” the human factors study results with the knowledge that the applicant had submitted a Risk Mitigation Strategy. The consult recommended that the applicant “emphasize the requirement on training in the product IFU and communication to prescribing physicians”. It should be emphasized that in the clinical trial there were no adverse events of underdosing, and hypocalcemia (a potential consequence of missed doses or underdosing) occurred with similar frequency with Natpara and control and there were no SAEs of hypocalcemia. Therefore, I believe that the concern raised by the CDRH review can be addressed via adequate labeling, rather than a REMS.
- 3) A device consult that summarizes multiple communications and information requests sent to the applicant during this review cycle. The consult concludes that after review of the data there are no remaining issues regarding the device from an engineering perspective.

4. Nonclinical Pharmacology/Toxicology

Both the primary nonclinical pharmacology/toxicology review (DARRTS 7/31/14) and the supervisory memorandum (DARRTS 7/31/14) recommend approval without additional studies.

The toxicology profile observed with Natpara in rat and monkey studies is consistent with that of an exaggerated pharmacodynamic response. Tissue mineralization secondary to hypercalcemia was the main toxicological finding, and it was manifest across multiple organ systems including the cardiovascular system. Particularly affected was the renal system wherein hypercalcemia resulted in the formation of renal calculi, mineralization and

subsequent damage to the renal tubules and occasionally injury to the renal parenchyma. Calcification of the major vessels, heart and/or stomach was also observed.

Another consistent toxicological finding with Natpara was a dose-dependent reduction in the level of all types of blood cells. This was a consequence of an exaggerated anabolic effect in bone, which lead to osteosclerosis and occlusion of the bone marrow space, causing a reduction in blood cell precursors.

Of particular importance but unclear significance, was the observation made in rat carcinogenicity studies of a dose-dependent increase in incidence of bone neoplasms, particularly osteosarcoma. This effect is similar to that seen with Forteo (teriparatide) also in rats. This finding should not be surprising, though, given that the main activity of human PTH has been located to the 1/3 N-terminal region of the molecule, and Forteo contains the first 34 amino acids of the 84 amino acid PTH molecule.

Three rhPTH doses were investigated in the rat carcinogenicity study. Osteosarcomas were observed at moderate and high doses but not at the low dose which helped to define a NOEL. The exposure margin between the NOAEL defined in this study and the human exposure associated with the maximum daily dose of 100 mcg was calculated to be approximately 4-fold. These data have been presented to the Executive Carcinogenicity Assessment Committee which agreed with the view of the nonclinical toxicology team that the 4-fold safety margin is not reassuring, and a risk for development of bone tumors in humans cannot be ruled out.

Similar observations made more than a decade ago in the Forteo program had resulted in a boxed warning for Forteo describing the potential risk of osteosarcoma; a REMS which consists of a medication guide and a communication plan; and two post-marketing studies: a 15-year osteosarcoma surveillance study and a Forteo User Registry Study. Both postmarketing studies are ongoing, with final reports expected in 2019 and 2022, respectively. Interim data describing the first 7 years of experience for the surveillance study have been published and do not describe any cases of osteosarcoma in patients who had been previously treated with Forteo.

The toxicology review provides a comparison of incidence of bone tumors across the Natpara and Forteo programs. The following table, reproduced from the supervisory memo, presents the dose specific incidence of bone tumors while describing, for context, the rat-to-human exposure ratio, based on AUC values. It indicates that for similar exposure ratios Natpara and Forteo are associated with a dose-dependent increase in incidence of osteosarcoma. Although the incidence rates of osteosarcoma appear to be smaller with Natpara for similar exposure ratios, when data are normalized to activity rather than expressed as mass, the small between-group differences disappear. This suggests that the carcinogenicity effects in rats are similar for both Forteo and Natpara.

Table 3 -- Incidence (Animals Affected) of Bone Neoplasms in F344 Rats: Comparison of ALX1-11 to Teriparatide (male & female combined)									
	ALX1-11					Teriparatide			
Number examined	120	120	120	120	120	120	120	120	120
Dose Group	C1	C2	LD	MD	HD1*	C	LD	MD	HD
Dose ($\mu\text{g}/\text{kg}/\text{day}$)	0	0	10	50	150	0	5	30	75
Exposure Ratio ($\text{AUC}_{\text{rat}}/\text{AUC}_{\text{human}}^{**}$)	-	-	4	23	63	-	3	21	58
Osteoma (n)	0	0	0	2	3	0	0	2	2
(%)	0	0	0	1.67	2.50	0	0	1.67	1.67
Osteoblastoma (n)	0	0	0	5	13	0	1	3	10
(%)	0	0	0	4.17	10.83	0	0.83	2.50	8.33
Osteosarcoma (n)	2	0	1	18	40	0	7	33	54
(%)	1.67	0	0.83	15.00	33.33	0	5.83	27.50	45.00
All Bone Neoplasms (n)	3	0	2	28	48	0	8	37	61
(%)	2.50	0	1.67	23.33	40.00	0	6.67	30.83	50.83

*Male HD1 only dosed for 94 weeks and necropsied after 101 weeks.

** $\text{AUC}_{\text{human}}$ at 100 $\mu\text{g}/\text{day}$ = 0.924 ng h/ml (Clinical study C09-002)

As acknowledged by the nonclinical toxicology team, there are limitations to this comparison since it is made across programs and not side-by-side in the same study. With this caveat, it points out that we do not have currently strong evidence to deem the two products different from an animal carcinogenicity perspective. Implications of these observations for labeling and for postmarketing will be discussed in other sections of this memorandum.

In the end, I am in agreement with the recommendation proposed by the pharmacology/toxicology team that the results of rat toxicology data, specifically the dose-dependent increased incidence in osteosarcoma associated with rhPTH (1-84) should be included in a Natpara label as a Boxed Warning, as already done for Forteo. The language proposed is reproduced below:

In male and female rats, Natpara 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 Natpara ranging from 3 to 71 times the exposure in humans given a 100 μg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, Natpara should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. Natpara 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, open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) (see WARNINGS and PRECAUTIONS, Carcinogenesis).

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review (DARRTS 9/9/2014) recommends approval. The review also recommends that the indication be restricted to "reduction in the oral calcium and

vitamin-D supplement dose in management of patients with hypoparathyroidism”, and that the labeling should reflect lack of benefit in controlling hypercalciuria. In addition, the following recommendation is made for a post-marketing requirement:

Conduct a clinical trial to compare an alternative dosing regimen or dosing regimen with a slow release profile to the proposed once daily dosing regimen of Natpara, with an aim to control hypercalciuria while maintaining normocalcemia.

Clinical trial simulations (incorporating variability and various titration strategies) should be conducted to substantiate the choice of dose and/or regimen. The details of the trial design including endpoints and dosing regimen should be discussed with the agency.

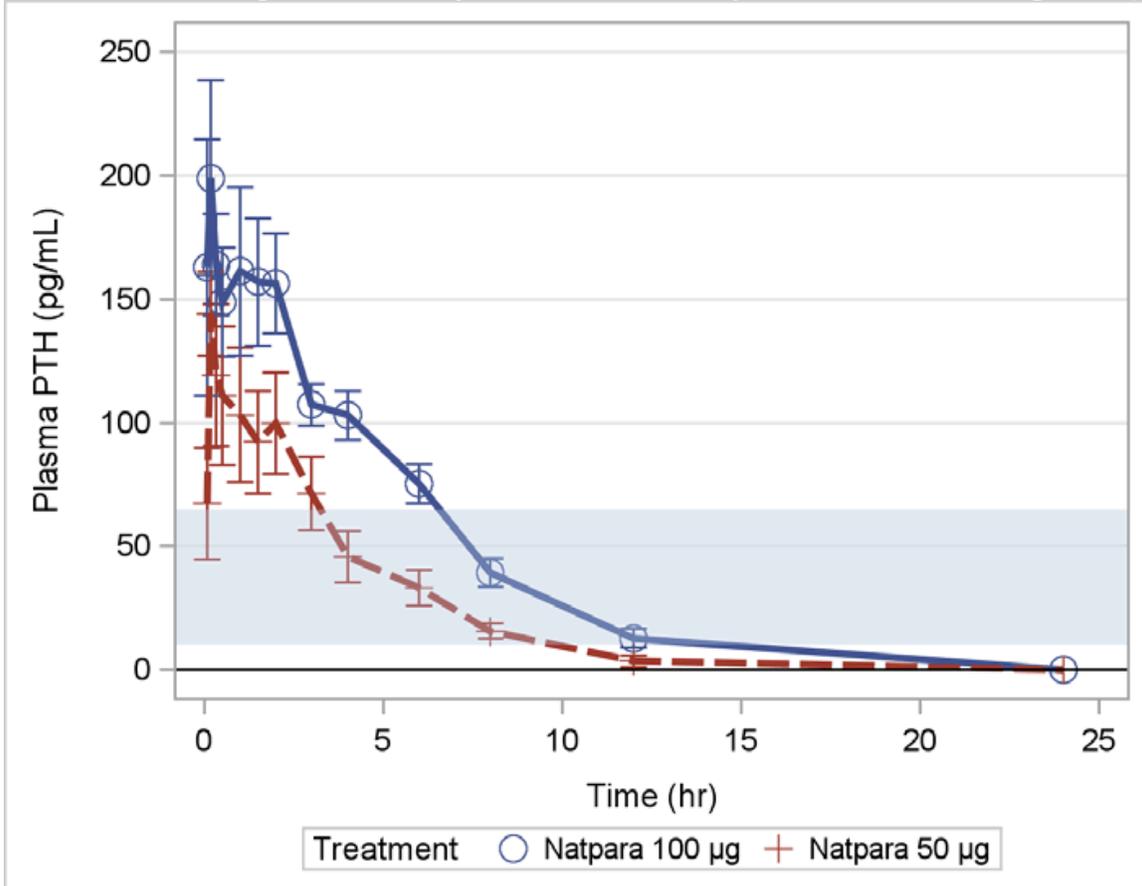
Pharmacokinetics and pharmacodynamics

PTH (1-84), like other native hormones has a very short T_{1/2} of only 2 – 5 minutes when administered intravenously. It is metabolized primarily in the liver in Kupffer cells wherein it is cleaved into N- and C-terminal fragments. The N- terminal fragments are further degraded intracellularly by peptidases, while the C-terminal fragments are released back into circulation and hydrolyzed to amino acids in the kidneys.

The PK of the subcutaneously administered doses of Natpara (50 and 100 mcg, respectively) in patients with hypoparathyroidism is presented below (Figure 7 of the clinical pharmacology review). It includes data from Study CL09-002 which measured the short-term effects of subcutaneous Natpara administration on the PD markers of interest in patients with hypoparathyroidism.

Plasma rhPTH[1-84] levels increased rapidly following injection. The baseline adjusted C_{max} of 174 and 233 pg/mL for the 50 and 100 mcg dose exceeded the upper limit of normal for serum PTH (normal range: 10-65 pg/mL). Plasma rhPTH[1-84] levels returned to pre-dose levels by 12 hours post-dose. The T_{1/2} was approximately 3 hours with both doses. As illustrated, Natpara systemic exposures initially exceed the normal physiological range, more so with the 100 mcg dose. Both the 50 and 100 mcg doses are clinically relevant because close to 80% of patients used these two doses at the end of the pivotal trial (to be further discussed in the Efficacy section).

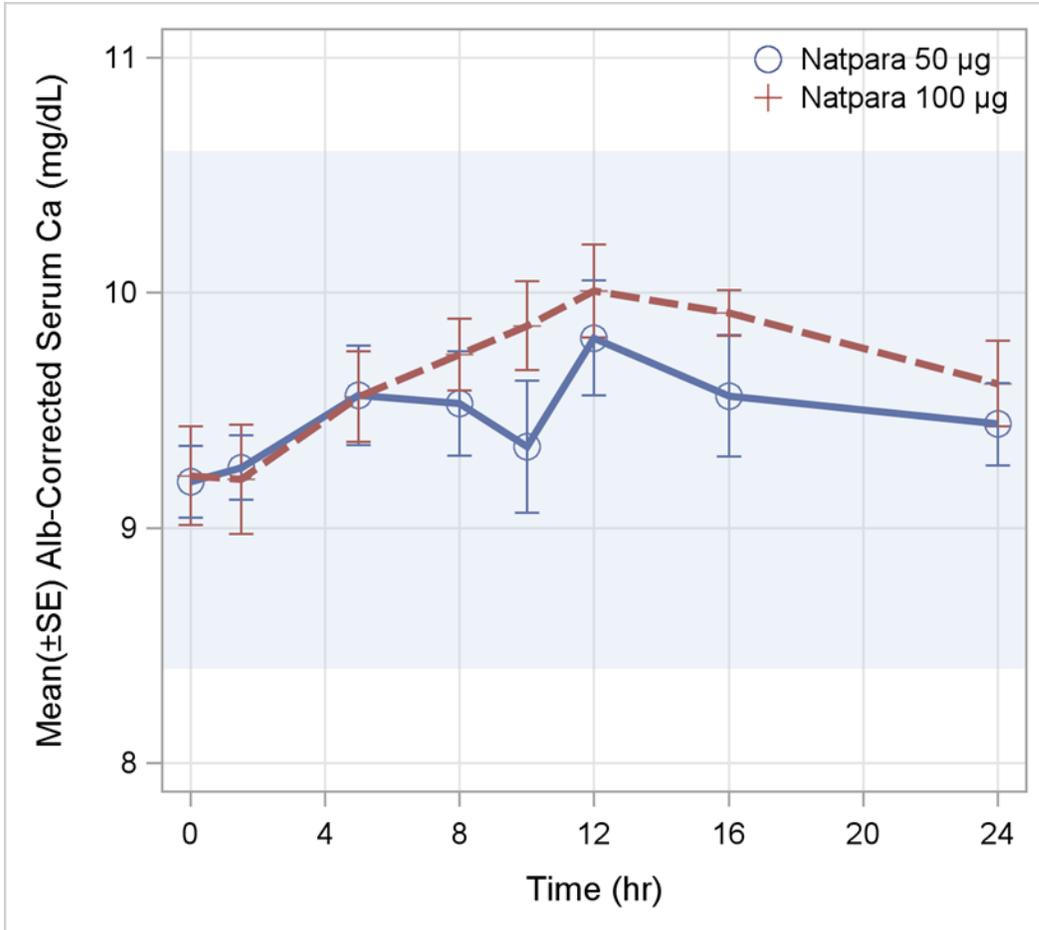
Figure 7 Mean plasma concentration versus time profile of Natpara (single 50 and 100 µg SC doses in the thigh of same subjects, minimum 7 days washout between 2 periods).



[Shaded area represents the normal physiological range of endogenous PTH]

Following rhPTH[1-84] injection, there was a dose-related increase in serum total calcium levels, indicating a pharmacodynamic effect on serum calcium lasting for up to 24-hours . The maximum changes, which also occurred at 12 hours, were approximately 0.6 mg/dL and 0.8 mg/dL, with the 50 µg and 100 µg doses, respectively.

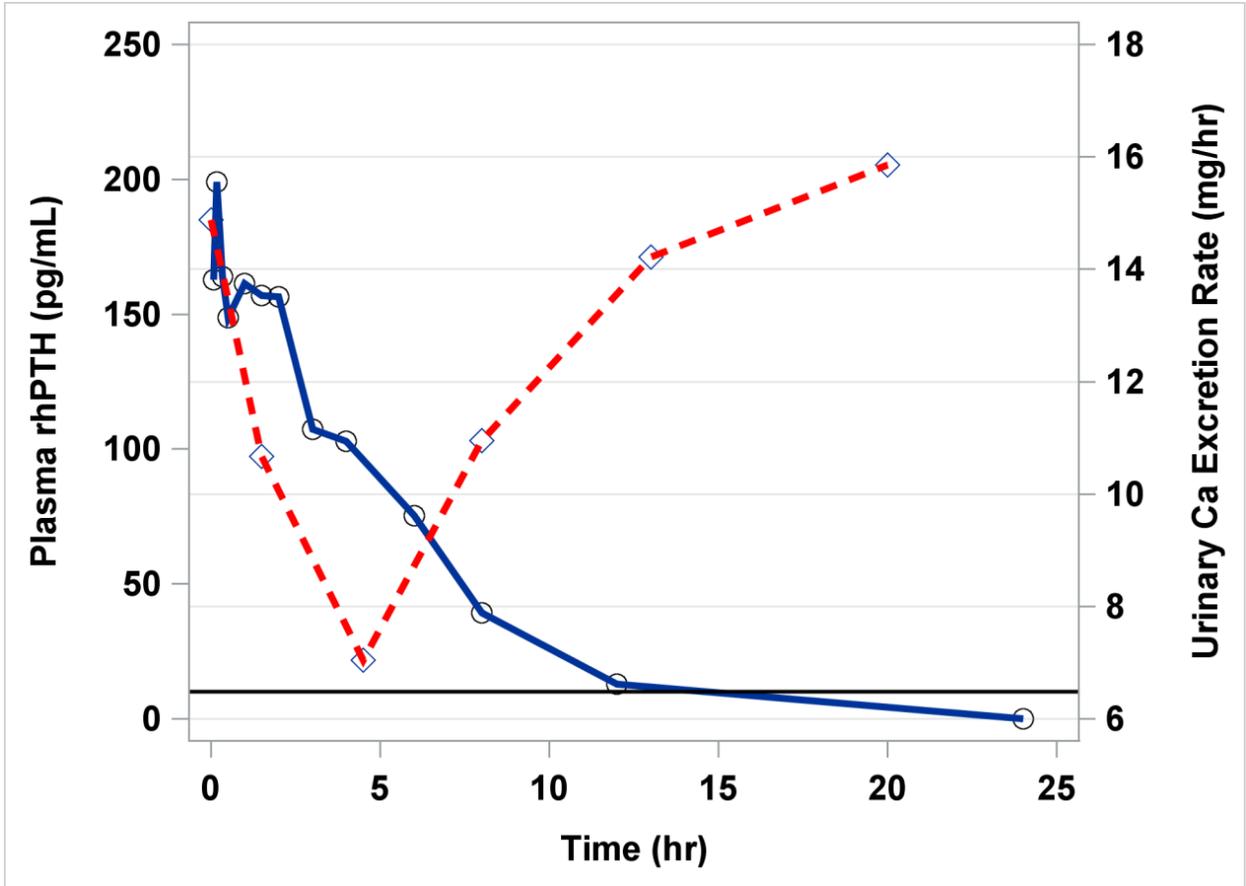
Dose-Related Increase in Serum Calcium with Natpara



Source: The Clinical Pharmacology presentation to the EMDAC on September 12, 2014

Although the increase in serum calcium lasted for almost up to 24 hours, the changes in urine calcium were of shorter duration. The following figure was part of the FDA presentation at the November 12, 2014 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting. It overlays the timecourse for the Natpara PK and for the urinary calcium PD measured by urinary calcium excretion rate. The illustration indicates that as the rhPTH levels increase, there is a decrease in urinary calcium excretion. Once the rhPTH returns to baseline by approximately 12 hours of treatment, the urinary calcium excretion rate returns to baseline at the same time. Thus, although dose-related reduction effects on urinary calcium were observed with Natpara (13% for the 50 mcg dose and 23% for the 100 mcg dose) such reductions are short lived (10-12 hours) following a single daily injection of Natpara at proposed doses.

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



Source: The Clinical Pharmacology presentation to the EMDAC on September 12, 2014

The clinical pharmacology reviewer developed an elegant mathematical based pharmacology model of calcium homeostasis in an attempt to better understand the relationship between dose, dose frequency and urinary calcium responses. For details, refer to the Clinical Pharmacology description of the model, its validation and its applicability to the Natpara program. Although beyond the immediate scope of this NDA review, which is expected to assess the merits of the Natpara dose regimen as it has been evaluated in the current clinical program, it provides evidence that a Natpara regimen that is administered more frequently than once a day or a slow release formulation will likely provide a better pharmacodynamic effect for urine calcium which may result in better control of hypercalciuria. Such observations can constitute a starting point for future Natpara drug regimens.

6. Clinical Microbiology

The microbiology review for the drug substance (DARRTS 8/22/2014) recommends approval with three postmarketing commitments that have been agreed by the applicant already:

1. Establish a bioburden limit for the (b) (4) after the bioburden monitoring results for 10 more batches are available.
2. Provide bioburden method qualification data from two additional lots of the (b) (4), and the drug substance. In addition, provide method qualification data from three lots of the (b) (4).
3. Provide LAL kinetic chromogenic method qualification data from two additional lots of drug substance. Provide LAL gel clot method qualification data from two additional lots of the (b) (4)

The microbiology review for the drug product (DARRTS 7/25/2014) does not identify any deficiencies and recommends approval without any additional Phase 4 studies.

7. Clinical/Statistical- Efficacy

The Natpara clinical program for hypoparathyroidism included 5 clinical safety and efficacy trials. This memorandum will focus on the results of trial CL1-11-040 or the “REPLACE” trial because it is the largest and the only placebo-controlled Phase 3 trial, and because it includes the most diverse range of efficacy assessments in the clinical program. All other trials will be referenced as needed. For general reference, Table 1 from Dr. Lowy’s Clinical Review (DARRTS 7/13/14) is reproduced below.

Table 1 Efficacy and Safety Studies in Hypoparathyroidism

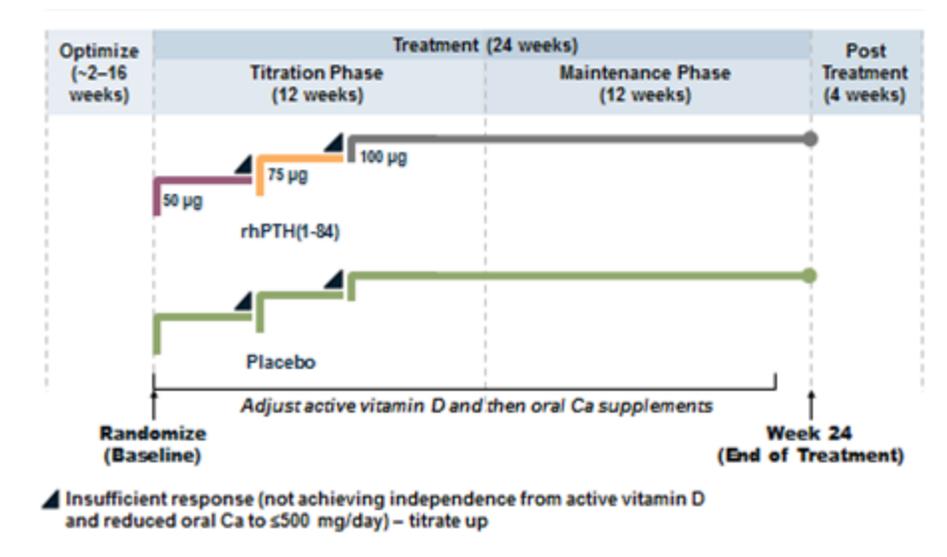
Study	Objectives	Design/Control	Dose ^a	# Subjects	Duration
NPS-Sponsored Efficacy and Safety Studies in Hypoparathyroidism					
CL1-11-040 (REPLACE)	Efficacy and safety	Randomized, double-blind, placebo-controlled	50, 75, and 100 µg (flexible doses) or placebo	rhPTH(1-84), 90; placebo, 44	24 weeks
PAR-C10-007 (RELAY)	Efficacy and tolerability	Randomized, dose-blinded	25 or 50 µg (fixed doses)	25 µg, 23; 50 µg, 24	8 weeks
PAR-C10-008 (RACE)	Safety and tolerability	Open-label	25, 50, 75, and 100 µg (flexible doses)	53	52 weeks + extension ONGOING
PAR-C10-009 (REPEAT)	Safety and tolerability	Open-label	50, 75, and 100 µg (flexible doses)	24	24 weeks
Investigator-initiated Trial (IIT) in Hypoparathyroidism					
Bilezikian IIT	Safety and efficacy	Open-label study, prospective	25, 50, 75, and 100 µg (flexible doses)	79	6 month pilot, 2-year study with multiple 1-year extensions

^a All doses of rhPTH(1-84) in the NPS-sponsored trials were daily SC injections in the thighs. Dosing in the Bilezikian IIT was either daily or less than daily.

Clinical Trial CL1-11-040 (REPLACE)

REPLACE was a randomized, double-blind, placebo-controlled, international (33 sites in 8 countries; 20 sites in the US), 6-month, Phase 3 clinical trial that investigated the use of Natpara for the treatment of adults with hypoparathyroidism. Following Division’s recommendations made at the December 17, 2007, pre-IND meeting, NPS evaluated Natpara as an add-on therapy to the standard of care (oral calcium and Vitamin D supplements). In essence, REPLACE was a placebo-controlled, dose-sparing trial. It lasted 6 months and was designed to assess a Natpara titration regimen that included sequential daily doses of 50µg, 75µg and 100µg.

Because of the complexity of the titration regimen in REPLACE, this memorandum will describe this trial’s design in some detail. The schematic of the trial is displayed below. REPLACE included three major periods: optimization (at the end of which randomization took place), titration and maintenance, and a 4-week follow-up (a period wherein patients were returned to the pre-Natpara treatment regimens).



Optimization Period (“screening and stabilization period”)

The goal of the optimization phase was to ensure a homogenous calcium and active Vitamin D/Vitamin D analog supplementation for all subjects prior to randomization. During this period subjects underwent adjustments of pre-enrollment calcium and active Vitamin D/analog regimens, received dietary instructions, and were given additional native Vitamin D to normalize their Vitamin D status, if needed. Please note that in this memorandum I will use the term active Vitamin D/analog to encompass calcitriol (an active form of Vitamin D) and alfacalcidol (a metabolically active Vitamin D analog), while the term native Vitamin D will refer to the non-activated form of Vitamin D (e.g. cholecalciferol and ergocalciferol).

Diet changes were implemented to ensure a stable daily dietary calcium intake during the trial (1000-1200 mg; U.S. Dietary Reference Intake) and to avoid excessive intake of phosphate-rich foods. Serum levels of 25-OH Vitamin D (considered the best measure of Vitamin D sufficiency) were normalized in all patients and a standard daily dose of 400 IU/day of Vitamin D3 was subsequently given.

Most importantly, modifications were made to the calcium and active vitamin D/ analog regimens. Because subjects enrolled in the study were on a variety of calcium and active vitamin D/analog, all subjects were switched to a single brand of calcium (calcium citrate) and one brand of active Vitamin D (calcitriol in North America) or Vitamin D analog (alfacalcidol in Europe). Following this switch, all patients had their calcium and active Vitamin D/analog supplements titrated with the goal of achieving and maintaining a target serum calcium in the low or around the low normal range of 8.0 to 9.0 mg/dL (minimum of 7.5 mg/dL). This choice reflects the current standard of care in hypoparathyroidism which attempts to treat hypocalcemia while reducing the risk of hypercalciuria and tissue calcifications. Please note that in this review, unless otherwise specified, serum calcium means albumin-corrected total serum calcium.

At the end of the Optimization Period subjects were randomized 2:1 to either once daily Natpara or placebo if they achieved a stable calcium level and stable supplementation with calcium and active Vitamin D/analog.²

Titration and Maintenance Periods

The titration period (12 weeks) and the maintenance period (12 additional weeks) represent the double-blinded period of the trial during which the two treatment regimens were compared. All comparative data, be it efficacy or safety, were based on this 24-week period.

Natpara titration was done gradually from a starting daily dose of 50 mg to a maximum dose of 100 mcg via an intermediate 75 mcg dose. The goal of the study was to reduce the need for calcium and active vitamin D/analog supplements while maintaining a stable serum calcium in a desired range (8-9 mg/dl).

Initiation of Natpara (or placebo) daily treatment was coupled with a 50% reduction in active Vitamin D/analog. The initial reduction of active Vitamin D/analog was aimed at preventing hypercalcemia since both active Vitamin D/analog and PTH increase serum calcium. Subsequent Natpara dose escalation was followed by reductions in supplemental calcium and active vitamin D/analog as long as the serum calcium was maintained in the desired range of 8-9 mg/dl. Reductions of supplemental calcium and active Vitamin D/analog were to continue until all supplements, except for 500 mg/day of oral calcium, were discontinued. The choice to retain this small supplemental calcium dose may have to do with the concern of hypocalcemia. Close to half of the patients in the Natpara arm were titrated to a dose of 100 mcg, the rest reached the desired effect with either 50 mcg or 75 mcg daily.

At subsequent measurements, deviations of serum calcium from the goal of 8-9 mg/dl triggered a complex set of interventions described in more detail in Dr. Lowy's review. Although the titration scheme was flexible and ultimately left at the discretion of the investigator, it had detailed step-by-step instructions.³ Retrospectively, the trial could have

² Not all subjects who entered the optimization period were randomized. In fact, of the 196 patients screened only 134 were randomized and entered the placebo-controlled phase. In order to be randomized, subjects had to meet several additional criteria: 1) the required supplemental calcium, calcitriol and alpha calcidol had to be at or above specific thresholds: 1000 mg for calcium, 0.25 mcg for calcitriol, and 0.50 mg for alphacalcidol (of note, the relative potency of calcitriol is twice that of alfacalcidol); 2) they maintained a serum calcium > 7.5 mg/dl and below the upper limit of normal and the serum calcium did not decline from the prior 2 week measurement; 3) the calcium and active Vitamin D /Vitamin D analog were stable (i.e. dose adjustments were not \geq 25% within last 2 weeks).

³ Serum calcium elevations above prespecified thresholds (indicative of overtreatment) triggered, sequentially, vitamin analog/metabolite reductions, followed by calcium supplement reductions, all to various degree depending on the degree of serum calcium change and the specific time point in the trial. If the increase was substantial (above upper limit of normal), temporary discontinuation of Natpara was instituted. The results of all such changes were verified with repeat serum calcium measurements, and in turn new adjustments were initiated until the target serum calcium of 8-9 mg/dl was achieved.

Serum calcium reductions below 8 mg/dl (indicative of undertreatment) resulted in an opposite sequence of interventions: calcium supplements were increased, and were followed, if necessary, by elevation of the vitamin D metabolite/analog dose.

benefited from a simpler decision algorithm. Effective conversion of the algorithm used in the trial in labeling instructions for the DOSAGE AND ADMINISTRATION Section of the proposed label is likely to be very challenging.

During the maintenance phase, serum calcium was kept on the dose established at the end of titration, and adjustments in supplemental calcium and active Vitamin D/analog were made as necessary to maintain calcium in the desired 8-9 mg/dl range. At the end of the trial (week 24) 56% of patients were titrated to a daily dose of 100mcg, 26% used 75 mcg and 18% ended with a 50 mcg dose.

The trial enrolled adult patients with hypoparathyroidism of greater than 18 months duration (hypoparathyroidism was diagnosed initially on the basis of evidence of hypocalcemia and two serum intact PTH concentrations below the lower limit of normal measured at least 21 days apart within 12 months prior to randomization). The etiologies of hypoparathyroidism were diverse. For most patients they were secondary to neck surgery (thyroidectomy most frequently), but they also included autoimmune, genetic, and idiopathic causes. Of note, the trial excluded patients with hypoparathyroidism due to calcium sensor receptor gene activating mutations or impaired responsiveness to PTH (pseudohypoparathyroidism) – it is important that such exclusions be identified in the label.

Efficacy results

The study randomized a total of 134 patients, 90 to Natpara and 44 to placebo (2:1 randomization drug-to-placebo). However, due to multiple Good Clinical Practice violations found at one site during a routine OSI inspection, it was agreed internally that data contributed from this site (1002) cannot be relied upon and should be excluded from the analyses. Therefore, all efficacy and safety analyses included in this memorandum, in Dr. Lowy's Clinical Review and in the EMDAC Briefing Document include 84 Natpara-treated patients and 40 placebo patients (10 patients from the original dataset were excluded, 4 placebo- and 6 Natpara-treated).

The two randomized groups were relatively well balanced at baseline with respect to main demographic characteristics, and daily active Vitamin D/analog and calcium doses. The mean dose of supplemental calcium was around 2000 mg with a few patients taking as much as

Patients who have not achieved independence from active vitamin D metabolite/analog and who did not succeed in reducing oral calcium supplementation to 500 mg/day on the initial dose of Natpara, were escalated sequentially from 50 µg dose to 75 mcg and to a maximum 100 µg dose. Most patients were titrated to a 100 mcg dose (52.2%), about ¼ to a dose of 75 mcg (26.7%), and 1/5 to 50 mcg (21.1%). The mean Natpara dose in the trial is displayed below (0008 2/19/2014 submission). Move to dose?

Patients who achieved the stated goal of maintaining serum calcium between 8-9 mg/dl, eliminated vitamin D metabolite/analog supplement and reduced supplemental calcium to 500 mg daily at a particular dose, could have their Natpara dose further escalated if the urine calcium was above normal (>300 mg/day) and if the calcium phosphate product was elevated (> 55).

12,000 mg, the equivalent of 24 tablets containing 500 mg of calcium each. The mean dose of active Vitamin D /analog was 0.9 mcg (calcitriol doses in clinical practice are between 0.25 and 2 mcg/day). Completion rates were high (94% for Natpara and 82.5% for placebo), as was compliance (median compliance, assessed from subjects’ diaries, was 99% in each treatment group).

The clinical trial achieved its proposed objective in that the Natpara treatment was able to maintain serum calcium in the desired low-normal range (8-9 mg/dl) while at the same time reducing the calcium and active Vitamin D/analog doses. The prespecified primary efficacy analysis compared the proportions of responders at Week 24 between the Natpara and placebo arms. A responder was defined as a subject who had at least a 50% reduction from baseline in oral calcium and active Vitamin D/analog supplementation and maintained serum calcium between 7.5mg/dl (slightly below the LLN of 8.4 mg/dl) and 10.6 mg/dl (ULN). The results of the primary efficacy analysis are reproduced below from the statistical review: 55% of patients in the Natpara group and 3% in the placebo group were responders and the difference was statistically significant (p<0.0001). There are no major differences between the applicant’s and FDA’s primary efficacy analysis.

Table 1: Primary Endpoint Results

	Placebo (N=40)	Natpara (N=84)	P
	n (%)	n (%)	
Non-Responder	39 (97%)	38 (45%)	<.0001
Responder	▶ 1 (3%)	▶ 46 (55%)	

The statistical review (DARTTS,6/26/14) re-did the primary efficacy analysis under different scenarios and imputations including a worst case scenario analysis wherein all subjects with missing assessments in the Natpara arm were imputed as non-responders while those in the placebo arm were imputed as responders. The difference between treatments arms remained statistically significant. Similarly, using a much more restrictive definition of responder in which the serum calcium values for the responder were restricted to 8-9 mg/dl (rather than 7.5 to 10.6), the difference was still statistically significant. This latter sensitivity analysis was done because the definition of responder, somewhat ambiguously worded in the original protocol, was redefined in a subsequent amendment (Amendment 7; this issue is discussed in detail in Dr. Lowy’s review).⁴

⁴ The initial description in the protocol referred to “a serum calcium level that is clinically stable in the opinion of the Investigator and just below or within the lower half of the normal range.” With the Amendment 7 it changed to “serum calcium concentration that is normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the upper limit of the laboratory normal range.” Using a pre-Amendment 7 definition the

Sequential testing of secondary endpoints was allowed because the primary efficacy analysis was statistically significant. Under such a statistical plan, the reduction from baseline in supplemental calcium dose for the Natpara group (51.8%) was statistically different when compared with placebo (6.56%; $p < 0.001$). Similarly, an analysis that compared the percentage of subjects who achieved independence from supplemental active vitamin D/analog and who reduced their calcium supplementation to ≤ 500 mg daily was statistically significant (41.67% Natpara vs. 2.5% placebo; $p < 0.001$).

In their totality, the efficacy analyses conducted in the REPLACE trial demonstrate that rhPTH can maintain serum calcium in the desired range (low normal) while reducing the need for calcium supplements and active Vitamin D/analog. This conclusion, supported by the above described statistical analyses, is captured visually by the following three figures that describe, in order, the time-course of dose adjustments for Natpara, calcium supplementation and active Vitamin D/analog supplementation.

Figure 1: Mean (\pm SD) Daily Dose of Natpara by Visit-ITT Population

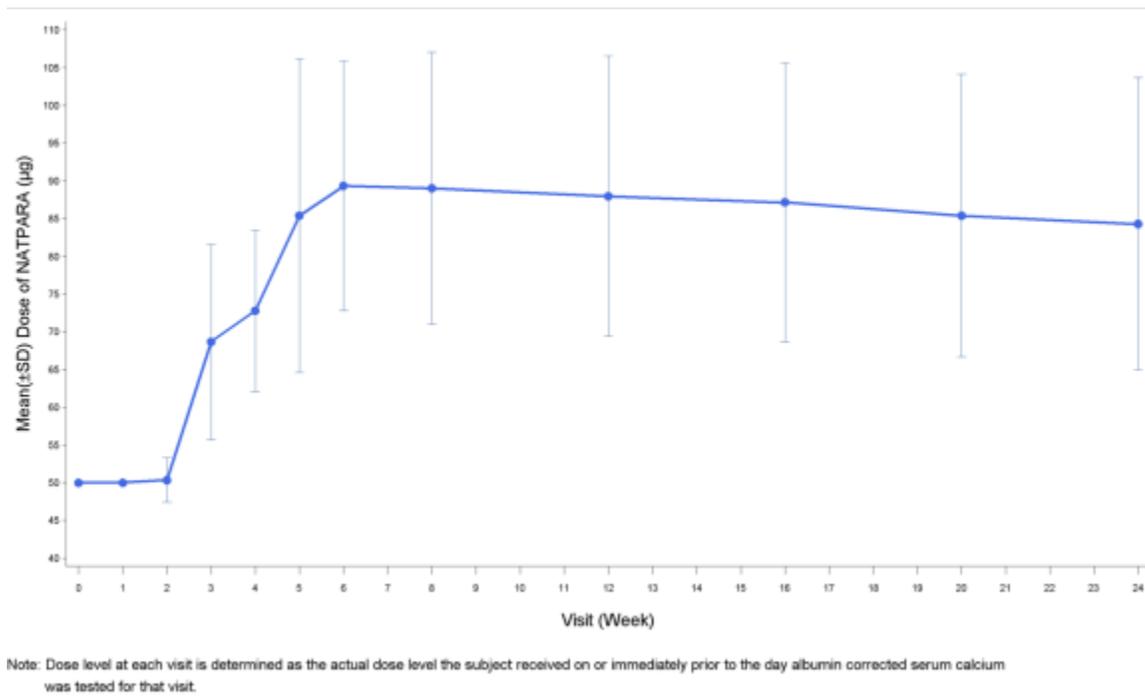
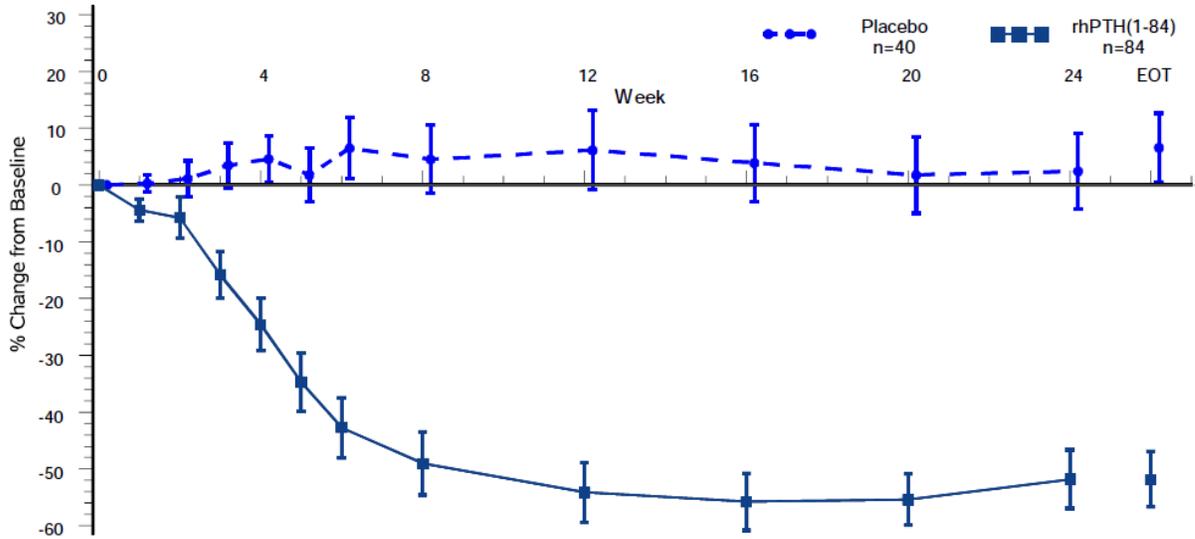
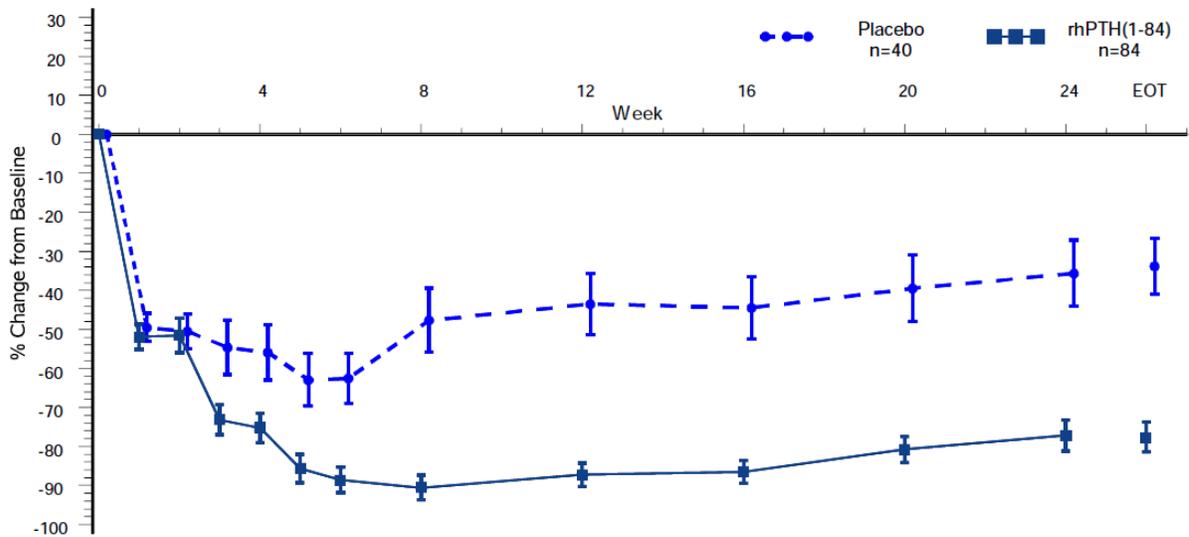


Figure 4: Mean (\pm SE).Percent Change from Baseline in Calcium Supplementation ITT Population

number of responders decreased from 46 (55%) to 27 (32%) in the Natpara group, but remained the same in the placebo arm [1(2.5%)], and the difference was still statistically significant (< 0.0001).



Mean (\pm SE) of Percent Change from Baseline in Active Vitamin D/Vitamin D Analog Dose -ITT Population⁵



While successful in demonstrating that the specific rhPTH dose regimen evaluated in this trial can be used as an alternative to the current standard of care, the REPLACE trial has also provided evidence of the limitations of such a regimen. With the recognition that the applicant was not asked to conduct a clinical trial that would evaluate benefit beyond biochemical control of serum calcium, REPLACE provided also information on the limitations of this rPTH regimen. REPLACE included several exploratory endpoints that measured the drug regimen’s effect on urine calcium, calcium-phosphate product, bone turnover markers, and bone mineral density.

⁵ The decline in Vitamin D in the placebo group relative to baseline suggests that subjects in the placebo-group could maintain similar serumcalcium levels with a less aggressive Vitamin D regimen than that used prior to enrollment.

To this end, the Clinical Review analyzed changes from baseline in mean urine calcium, compared the percentage of patients with evidence of hypercalciuria (defined as urine calcium > 300 mg/dl), and presented scatterplots of individual urine calcium measurements for different phases of the trial. None of these analyses supports an argument of clinical benefit for Natpara relative to standard of care beyond biochemical control of serum calcium. Acknowledging that the clinical trial was not powered to determine such changes, descriptive analyses of mean changes from baseline in urine calcium show minor and inconsistent between-group differences at the end of the trial, dosing (Table 19, page 65 of the clinical review). Meaningful comparisons of the percentage of subjects with normalized urine calcium excretion during or at the end of the maintenance phase cannot be made because only two timepoints are included (weeks 16 and 24) and the data are not consistent for these two timepoints (Table 20, page 67 of the Clinical Review). Visual comparison of scatterplots indicate multiple values in the abnormal range in both treatment groups (Figures 18 and 19, pages 66 and 67 of the clinical review).

Greater reductions in mean calcium - phosphate product, a measure of the risk of tissue calcifications, were observed with the Natpara arm, but baseline mean levels were below the level at which increased risk of calcium-phosphate crystal deposition could occur, and all but one subject had normal levels at baseline (Figure 24, page 73 of the Clinical Review). Therefore the significance of the between-treatment difference favoring Natpara is unclear. The reduction in mean calcium - phosphate product is likely secondary to the phosphate reduction seen with Natpara (an expected pharmacological effect) since serum calcium levels were relatively stable.

Similar observations are made with respect to changes in bone biomarkers and bone mineral density. Although a favorable trend was observed for bone formation and bone resorption biomarkers with Natpara relative to the placebo (standard of care) arm, it is unclear if the magnitude of such changes (largely manifestations of the physiologic effect of PTH) is associated with a clinical benefit. The changes in bone mineral density measured with DXA scans were statistically significant at only 2 out of the 7 different anatomical sites evaluated, and the changes from baseline were very small. This should not be surprising given the short duration of the trial which, excluding the titration period, lasted only 12 weeks, a time insufficient to see meaningful effects on bone mineral density.

During an open-label single-arm extension trial, PAR-C10-008 (RACE), the treatment effect observed with Natpara in REPLACE persisted to up to 52 weeks. Although data from RACE provide evidence of persistence of effect for up to 2 years, the quantitative efficacy data obtained from such an open-label, uncontrolled trial should not be used for labeling because, by the very nature of its design, the trial selected a patient population likely to have benefited from the drug, and a control group is lacking.

In conclusion the efficacy results indicate that a regimen of daily subcutaneous Natpara injections in the range of 50-100 mcg, can maintain a serum calcium in the low normocalcemic range and slightly below the lower limit of normal consistently, while significantly reducing the need for oral calcium and active Vitamin D/analogues. In doing this, it is clear that Natpara

can be used as alternative treatment to the current standard of care, particularly in a subgroup of patients who require large daily doses of calcium and active Vitamin D/analogs. The evidence of benefit beyond the dose-sparing effect was limited to favorable changes in several bone biomarkers, but the clinical importance of these changes is unclear, as they were not accompanied by meaningful changes in bone mineral density. There was no evidence of clinical benefit with Natpara over placebo (standard of care) regarding reduction in urinary calcium for the duration of the study. Based on the data available for review, it is not clear if the lack of benefit beyond dose-sparing is a consequence of the dose and/or dose regimen selection (pharmacodynamic data indicates that the urine calcium lowering effect is limited to only 12 hours) or the short duration of the trial (only 12 weeks of maintenance therapy). This conclusion is also in agreement with the statistical review which concludes that:

From a statistical perspective, the information supplied in this package supports the efficacy claim of using Natpara to treat patients with hypoparathyroidism to reduce oral calcium, vitamin D, and maintaining serum calcium levels.

8. Safety

As with efficacy, safety analyses from the REPLACE trial must be considered the most informative and relevant, given the design of this study which included a placebo (i.e. standard of care) control arm. When comparing the two regimens side-by-side, there were no imbalances in serious adverse events, no deaths, approximately equal rates of treatment – emergent adverse events (95% placebo, 91% Natpara), and too few discontinuations due to adverse events to suggest a specific pattern. The safety observations made in the uncontrolled studies were consistent with those seen in the Natpara arm during the REPLACE trial. This was the case for both short trials and for the extension trial RACE (in this trial data were analyzed for up to 52 weeks).

Due the fact that initiation of Natpara treatment involves changes to an established regimen of calcium and active Vitamin D/analog, there is a theoretical risk of hyper- or hypocalcemia until a new balance is reached among these three treatments. Therefore, the Clinical Review paid special attention to the occurrence of out-of-range calcium values and related adverse events, and conducted several analyses in order to characterize the frequency and severity of such findings.

Beginning with serum calcium evaluations, the general pattern that emerged is that hypocalcemia was noted more frequently and with greater severity in the placebo arm during the titration phase of the trial. This is not unexpected because the study protocol mandated a decrease of active Vitamin D/analog dose, and the expected effect of such a reduction was a decline in intestinal calcium absorption. Between-group differences attenuated, however, during the maintenance phase when the treatment regimens reached a new equilibrium, but hypocalcemia was still observed. This may have to do with the fact that the goal of treatment was to maintain serum calcium in the low normal and slightly below normal range. It is reassuring though that there were no SAEs of hypocalcemia during the treatment phase in

either group. In addition the incidence rates of TEAEs of hypocalcemia were comparable for the duration of treatment (20% placebo vs. 25% Natpara).

In contrast, hypercalcemia was seen almost exclusively with the Natpara regimen particularly during the titration phase. It decreased in frequency and severity during the maintenance period. These observations suggest that Natpara titration may need to be pursued less aggressively, and the label should include language to this effect in order to reduce the risk of hypercalcemia. Although more treatment-emergent adverse events of hypercalcemia occurred with Natpara (16.7% vs. 2.5% with placebo), the frequency of severe adverse events of hypercalcemia during Natpara treatment was low (only one SAE).

During the post-treatment period several events of hypocalcemia were observed after the reintroduction of standard calcium and Vitamin D supplementation. This may be relevant in clinical practice for non-compliant patients or for patients who may discontinue Natpara and decide to return to calcium and Vitamin D only treatment. Although not a complication of Natpara treatment *per se*, it is of clinical importance and should be labeled as a potential risk.

Two different pens were used during the Natpara clinical program. The to-be-marketed pen (Haselmeier) was introduced half-way into the RACE trial. A comparison of injection pen complaints between the Haselmeier pen and the pen used in the pivotal trial (Ypsomed) did not indicate any glaring differences. The number of injection pen complaints was low and generally comparable between the two products.

Immunogenicity evaluation in the clinical program was complicated by the fact that the applicant used two different antibody detection assays: a radioimmunoassay (RIA) from (b)(4) for which validation could not be confirmed, and a validated assay (MSD-ECL from (b)(4)⁶). In REPLACE, RIA assessment indicated that no patients had anti-drug antibodies (ADA) at baseline and end of treatment, and only one patient in each group developed antibodies at week 28 (i.e. 4 weeks after treatment discontinuation). Unfortunately only about 1/3 of samples could be re-tested with the MSD-ECL assay, and only for the end-of treatment timepoint (none of the baseline samples were available). According to this sensitive and validated assay approximately 10% of patients in the placebo arm and 25% in the Natpara arm were found to be antibody-positive on initial screening and only up to 6% in either arm during the next confirmatory testing step (see applicant's Tables 2-1 and 2-2 reproduced on page 10 of the Office of Biotechnology Products (OBP) memorandum in DARRTS, 9/12/2014).

The immunogenicity data using the MSD-ECL method is summarized in Table 2-9 on page 6 of the OBP review. Leaving aside the data generated in the REPLACE trial and discussed above, any attempt to interpret the information contributed by the other clinical trials in the Natpara program is hindered by the fact that patients from REPLACE were re-enrolled in these trials, as was the case with both RELAY (trial "007") and RACE (trial "008"). As such, any comparison of ADA status at end of trial to baseline does not necessarily assess immunogenicity in treatment-naïve patients. This lack of clarity as to which patients were truly naïve to treatment at baseline, combined with the relatively small number of enrollees that are

⁶ MCD-ECL = Meso-Scale Discovery.

reported as ADA positive in these trials hinders any efforts to draw specific quantitative conclusions. One can however point out that the occurrence of specific ADA antibodies was not frequent. Additional analyses conducted by the immunogenicity reviewer indicate that in general antibody titers were low and they did not appear to impact rhPTH kinetics. Neutralizing antibodies were noted in only one patient who also had negative titers.

Immunogenicity status and clinical data for all patients who developed ADA are summarized in Table 1 (page 14) of the OBP review. There were no clinically relevant findings such as severe TEAEs, or out of proportion lack of absence of efficacy associated with the presence of antibodies. Although the percentage of patients with hypoparathyroidism who developed ADA (16%) was higher than that observed in the osteoporosis program (3-5%), no conclusions should be drawn regarding this comparison because the two clinical programs used different assays.

The OBP reviewer concludes that, within the limitations imposed by the change of the immunogenicity assay during the clinical program, the immunogenicity testing is “acceptable” and recommends approval.

In conclusion, there were no unexpected adverse event occurrences identified during the Natpara clinical program in patients with hypoparathyroidism. Most adverse events were anticipated on the basis on the known pharmacology of PTH and the natural history of hypoparathyroidism. Hypercalcemia and hypocalcemia fall under this category, and, generally, they were not particularly severe. Another concern, albeit not identified in the clinical program, is that patients with PTH gene deletion may develop neutralizing antibodies following repeated exposure to exogenous PTH. Such genetic causes of hypoparathyroidism, however, tend to be very rare and represent only a minority among patients with hypoparathyroidism. Finally, observations made in the non-clinical program raise the same concern of a potential risk of osteosarcoma that had been previously identified in the Forteo clinical program. This issue will be further discussed in the risk benefit section of this memorandum.

9. Advisory Committee Meeting

This BLA was discussed at an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting held on September 12, 2014. Members of the committee voted 8 in favor and 5 against approval of Natpara for the proposed indication. The voting question asked if the efficacy and safety findings observed at the proposed dose regimen support approval of Natpara for the long-term treatment of hypoparathyroidism.

In addition to the voting question, the committee was asked to discuss 1) the efficacy data in the REPLACE trial and opine if these data represent substantial evidence of clinically meaningful benefit to patients with hypoparathyroidism; 2) the risk of hypercalcemia and hypocalcemia associated with the use of Natpara and possible ways to mitigate it; 3) the risk of osteosarcoma associated with long-term use of Natpara in patients with hypoparathyroidism;

4) any additional concerns the committee may have related to risks or benefit not raised in the previous questions.

There was general agreement that the REPLACE trial has met its primary efficacy objective and reached statistical significance for two additional efficacy endpoints, and that this demonstration of efficacy matched the requirements set forth by DMEP at the beginning of the Natpara development program for the hypoparathyroidism indication. On the other hand, many Advisory Committee members voiced disappointment that efficacy analyses that evaluated clinical benefit beyond dose reduction of supplemental calcium/Vitamin D were not robust and, in fact, many of them failed to demonstrate a clear benefit. Recognizing that REPLACE was not powered to demonstrate a benefit for a hypercalciuria reduction, most committee members did not see an advantage of Natpara over standard of care treatment for this exploratory endpoint. This observation is significant because, once serum calcium is normalized, the goal of treatment in hypoparathyroidism is to prevent complications, including those associated with hypercalciuria (kidney stones, loss of renal function). The pharmacological effect on bone turnover biomarkers was acknowledged, but it was also pointed out that bone disease in hyperthyroidism is not severe enough in the majority of patients, and the benefit of the observed changes is not clear.

The committee discussed extensively the choice of administering Natpara as a once a day regimen, and there was general consensus based on the pharmacokinetic and pharmacodynamic data presented that once daily regimen is likely to have a limited response on calciuria, and that a twice a day regimen should be evaluated. That being said, the same committee members who made this recommendation also indicated that they do not recommend that drug approval should be halted until a twice daily regimen is formally tested in another clinical trial.

Hypercalcemia and hypocalcemia risk were discussed in some detail. There was general agreement that the risk of hypercalcemia was neither unexpected (especially during the initial titration phase), nor particularly significant. Hypocalcemia, on the other hand, raised multiple comments, partly because it remains one of the most distressing events in the daily life of patients with hypoparathyroidism (“hypocalcemic crashes”) and is also a continuous concern for physicians who manage such patients. It was noted that Natpara treatment does not reduce the incidence of hypocalcemia relative to the standard of care, but at the same time most hypocalcemic events were not severe in nature, and physicians caring for patients with hypoparathyroidism have a lot of expertise in managing this complication.

The issue of the osteosarcoma risk received a lot of attention and raised multiple comments. There was general agreement that the risk of osteosarcoma, although based entirely on animal data, has biological plausibility in humans, and is concerning, especially in the light of the fact that treatment for hypoparathyroidism is life-long, osteosarcoma is a devastating disease, and there are not enough or adequate data from the postmarketing experience accumulated with Forteo to provide reassurance. The oncologist on the panel pointed out that there are also major limitations to extrapolating data from osteoporosis to hypoparathyroidism; among them, differences in pathogenesis of these two conditions, dissimilar bone findings (increased mineral density in hypoparathyroidism and opposite changes in osteoporosis), and in

hypoparathyroidism osteoblasts are more susceptible to PTH stimulation . Some patient subgroups such as children with open epiphyses, patients with concomitant conditions that increase susceptibility to cancers (Paget disease, Li-Fraumeni syndrome, Rothmund-Thompson syndrome, etc.) may be particularly at risk for osteosarcoma. As such, several committee members recommended some form of postmarketing risk management and surveillance program. The need for a registry or a similar tracking system was endorsed by most committee members. The risk management discussion was a little more confusing, partly because of the lack of familiarity of the panel to the options that risk evaluation and mitigation strategy (REMS) can offer. Although several panel members recommended a REMS, when clarifications were provided by FDA about what the regulatory requirements are for issuing a REMS, most indicated that they desire a post marketing risk management, but leave it up to the FDA to choose the appropriate modality of accomplishing such task.

Finally, most committee members who voted for or against approval indicated that their decision was not an easy one. Members who voted against approval stated that they had done it because the evidence of clinical benefit beyond supplemental calcium/Vitamin D reduction was not strong, and in the face of potential risks (hyper- and hypocalcemia, osteosarcoma), the evidence of benefit should be higher. Panel members who voted for approval acknowledged the statistical “win” of Natpara in REPLACE, the trend of clinical benefit observed in some of the exploratory endpoints, the lack of good options for patients - in particular for those with a high pill burden (and subsequent poor compliance with existing regimen) - and, very importantly, the unmet medical need in hypoparathyroidism.

10. Pediatrics

Natpara received Orphan Designation on August 31, 2007 (designation request 07-2467) for the indication of “treatment of hypoparathyroidism.” Therefore this application is exempted from PREA requirements.

11. Other Relevant Regulatory Issues

An Office of Scientific Investigation consult (DARRTS 8/24/2014) identified multiple Good Clinical Practice violations at one site (site 1002), deemed the data generated at this site to be “unreliable”, and issued a classification is Official Action Indicated (OAI) for this site. This information was discussed with the review teams at several internal meetings and was the basis for asking the applicant to remove all data from this site in their presentations made at the EMDAC meeting. Similarly all analyses conducted by the FDA disciplines were conducted on datasets from which results this site were removed. OSI inspected several other sites. One of them received a No Action Indicated (NAI) classification; a third site, the applicant, and the CRO received Voluntary Action Indicated classifications, but OSI does not believe that the violations noted would impact the primary efficacy and safety analyses.

A QT Interdisciplinary Review Team consult (DARRTS 6/9/2014) concluded that Natpara had a benign cardiovascular safety profile. It states that data from REPLACE “sufficed to rule out clinically relevant effects on vital signs, and PR and QRS intervals”. Although the QTc declined by about 10 ms, largely paralleling the rise in serum calcium, this change was not deemed clinically relevant. The consult commented that there were no differences between Natpara and placebo with respect to conduction abnormalities, and the data observed in RELAY and RACE, complemented and confirmed the observations made in REPLACE.

The proprietary name Natpara was deemed acceptable from a safety and promotional perspective by the Division of Medication Error Prevention and Risk Management (DARRTS 1/10/24) and was communicated to the applicant. DMEPA has also reviewed the container label, carton labeling, and Instructions for Use and found them to be acceptable (DARRTS 10/7/14).

A risk management plan was submitted that includes in addition to the physician insert a Medication Guide, a Q-Cliq and Mixing Device Training Guide, and initiation of a hypoparathyroidism registry (“PARADIGHM”). The proposed risk management plan did not include a REMS initially. However, will be discussed in Section 13, at the request of the agency, the applicant is developing a REMS with ETASU.

Three CDRH consults were issued and they have been referred to or summarized at the end of the CMC section.

12. Labeling

Labeling negotiations are in progress. The following should be added or emphasized in the label:

- A boxed warning similar to that issued for Forteo should be added to the Natpara label; it should emphasize the results of the animal carcinogenicity study, identify patient subgroups at risk (children with open epiphyses, patients with conditions that predispose to developing malignancies).
- The indication should be restricted to control of serum calcium and no claims should be made about additional clinical benefit since substantial evidence of benefit beyond the dose sparing effect has not been provided in this application.
- The DOSAGE AND ADMINISTRATION section should describe with clarity the principles of titration, indicate that aggressive titration may lead to hypercalcemia, and should include advice about sequence of interventions that must be followed should hyper- or hypocalcemia occur. This section of the label will pose challenges because the titration regimen in the REPLACE trial had a complex algorithm that needs to be considerably simplified in the label.
- Hypercalcemia and hypocalcemia should be included in the WARNINGS AND PRECAUTIONS section with recommendations for mitigation of these adverse

- reactions. The risk of hypocalcemia following Natpara discontinuation should be described as well.
- The risk of osteosarcoma should be added to the WARNINGS AND PRECAUTIONS section.
 - The CLINICAL TRIALS section should emphasize the results of the primary and secondary endpoints that reached statistical significance, and should provide a graphic description of Vitamin D and calcium dose reduction. Only data from the REPLACE trial, the only placebo controlled trial, should be included in this section.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval.

- Risk Benefit Assessment

The benefit that the Natpara program has demonstrated to date is that the once daily rhPTH[1-84] regimen of 50-100 mcg can maintain a serum calcium in the low normocalcemic range or slightly below the lower limit of normal consistently, while significantly reducing the need for oral calcium and active Vitamin D/analogues. As such, Natpara can be used as an alternative treatment to the current standard of care. Although reductions in supplemental Vitamin D and calcium will not be a necessary goal for all patients with hypoparathyroidism given the variability in the clinical presentation of this condition, they are likely to be important for some patients. Specifically, patients with large calcium requirements (some require up to 9 grams of calcium a day, which is equivalent to 18 tablets of 500 mg each), and patients who are not easy to manage on current regimens will likely benefit from having an additional therapeutic choice.

Evidence of clinical benefit beyond reductions in supplemental calcium and Vitamin D has been weak and insufficient in the REPLACE trial. Although the trial has not been powered to demonstrate prevention of hypoparathyroidism-related complications, and it is conceivable that a larger or longer trial would be able to detect changes in health-related quality of life questionnaires or hypercalciuria, such benefits have not been demonstrated in the Natpara program to date and considerations of potential rather than measured benefit have not influenced my recommendation.

On the other hand, one should also acknowledge that maintaining stable serum calcium concentrations – which Natpara has demonstrated in REPLACE and several other trials - is necessary for preventing the acute life-threatening complications of hypocalcemia, including seizures, laryngospasm, and cardiac arrhythmias. A controlled clinical trial aiming at proving

that Natpara can reduce the rate of these life-threatening events is not ethical because one would have to withdraw standard of care treatment in the comparator arm, exposing patients to serious medical risks. Although not stated explicitly in the pre-IND meeting minutes, this argument may have been behind the recommendation given by DMEP to the applicant with respect to trial design and endpoint selection for the current Phase III program.

The safety of the proposed once daily Natpara regimen is acceptable and, in combination with the above described demonstration of benefit, supports a favorable benefit-to-risk profile. Neither the hypocalcemic nor the hypercalcemic events seen with the once daily regimens studied in REPLACE were severe or frequent enough to cancel out the benefit provided by Natpara treatment. The risk of osteosarcoma remains theoretical at this stage, as it still is for another rhPTH product, Forteo, 12 years after having been approved and marketed. That being said, I am not recommending that this potential risk be ignored. On the contrary, I recommend that events of osteosarcoma should be surveyed postmarketing, and a risk management plan should be implemented for proper patient population selection in order to minimize any risk of osteosarcoma (see below).

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Following a full review of the Natpara clinical program submitted in this BLA, osteosarcoma remains the only major uncertainty from a safety perspective. The potential risk of osteosarcoma has received considerable attention at the November 12, 2014 EMDAC meeting. Although it is unclear if the observations made in the rat carcinogenicity study are relevant to humans, and, if so, to what extent, one also has to recognize that there is biological plausibility for such a risk. I concur with many of the concerns raised by the EMDAC members who recommended a cautious approach to the marketing of Natpara, including postmarketing surveillance, avoidance of treating patients with genetic predispositions to bone malignancies, and cautious and selective use in children because active bone formation puts them at greater risk. A REMS with ETASU is currently under discussion, and I am in agreement with such a consideration.

- Recommendation for other Postmarketing Requirements and Commitments

I am in agreement with the recommendation made by the clinical pharmacology reviewer that a postmarketing clinical study that uses a more frequent Natpara dosing frequency (e.g. twice daily) is needed in order to assess whether such a regimen is able to reduce or maybe even control hypercalciuria. Although an exploratory measure of efficacy in REPLACE, hypercalciuria is equally a safety concern because it is mechanistically associated with clinically important complications such as nephrocalcinosis and subsequent reductions in renal function. Such a study, may also address some of the questions raised by several EMDAC panel members regarding whether twice daily Natpara regimens are more effective than once daily administration.

I am also recommending an enhanced pharmacovigilance program for reports of osteosarcoma in patients with hypoparathyroidism treated with Natpara. The program should include assessment and analysis of spontaneous reports of osteosarcoma and follow-up to collect additional information on these cases.

Finally, the following postmarketing commitments have been agreed by the Applicant in response to microbiology requests:

1. Establish a bioburden limit for the (b) (4) after the bioburden monitoring results for 10 more batches are available.
2. Provide bioburden method qualification data from two additional lots of the (b) (4), and the drug substance. In addition, provide method qualification data from three lots of the (b) (4).
3. Provide LAL kinetic chromogenic method qualification data from two additional lots of drug substance. Provide LAL gel clot method qualification data from two additional lots of the (b) (4).

- Recommended Comments to Applicant

Pending, because the final configuration of the REMS and PMRs are still under discussion.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DRAGOS G ROMAN
01/02/2015

JEAN-MARC P GUETTIER
01/06/2015