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APPLICATION NUMBER:

125511Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	January 23, 2015
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	125511
Applicant Name	NPS Pharmaceuticals
Proprietary / Established (USAN) Names	Natpara Recombinant Human Parathyroid Hormone (rhPTH[1-84])
Dosage Forms / Strength	Lyophilized for reconstitution for injection Starting dose 50 mcg once daily, up-titration to 75 or 100 mcg daily or down-titration to 25 mcg daily
Proposed Indication(s)	Replacement for endogenous parathyroid hormone (1-84) for long-term treatment of hypoparathyroidism
Action:	

1. Introduction and Discussion

This will be a brief summary of the basis for the regulatory action regarding Natpara and the reader should review the action package for more detail. Natpara is a recombinant parathyroid hormone (PTH)(1-84) manufactured in E. coli that is identical to the human 84-amino acid endogenous PTH. This application was submitted for use of Natpara as replacement for patients with endogenous PTH deficits. Natpara is combined with a mixing device for product reconstitution and a reusable pen injector. The recommended starting dose is 50 µg with adjustments between 25 µg to 100 µg based on calcemic response. Natpara was approved in the European Union for the treatment of osteoporosis, but was withdrawn from the market in 2014 for commercial reasons.

PTH is secreted by the chief cells of the parathyroid glands with effects of increasing the concentration of calcium, and decreasing the concentration of phosphate, in the blood. PTH controls calcium by increasing release from the bones, enhancing reabsorption from the distal tubules of the kidneys and enhancing absorption from the intestine by increasing the production of activated vitamin D (which occurs in the kidney). PTH decreases serum phosphate by reducing the reabsorption of phosphate from the proximal tubule of the kidney. Regulation of PTH secretion is controlled by serum calcium through negative feedback. Hypoparathyroidism has a prevalence between 65,000 and 100,000 and occurs most commonly as a consequence of thyroid surgery with collateral damage or removal of parathyroid glands. The consequence of hypoparathyroidism is decreased serum calcium with resultant paresthesia, tetany, increased bone density and cardiac arrhythmias.

There are not presently any approved hormone therapies for hypoparathyroidism. Two vitamin D products approved decades ago (ergocalciferol 1941, calcitriol 1978) carry indications for hypoparathyroidism. Teriparatide (Forteo), the N-terminal fragment of PTH

(1-34) has full biological activity but is currently only approved for the treatment of osteoporosis, and that therapy is recommended to not exceed 2 years during a patient's lifetime because the safety has not been evaluated beyond 2 years of treatment and there are concerns regarding possible osteosarcoma. For the majority of patients, long-term treatment is accomplished with use of oral vitamin D analogs and calcium supplementation (with some cases requiring large amounts). These therapies have drawbacks however as they are prone to hyper- and hypocalcemia. Also, without PTH control of renal calcium excretion, patients are at risk for renal stone formation, as well as calcification of the renal parenchyma with resultant renal impairment (this complication is minimized by targeting therapeutic serum calcium goal in the low-normal range). Further, non-hormone replacement therapy does not have the salutary bone effects of physiologic PTH and the number of pills necessary to replace calcium can be quite burdensome to some patients. Therefore, something that could replace the PTH deficit with the same physiologic effects would be an important milestone in treatment for this patient population.

The sponsor has demonstrated that Natpara has some PTH-like effects. This shouldn't be a surprise since it is identical to human PTH. However, as with all hormones (e.g. glucocorticoids, growth hormones, insulin) the further away from physiologic the dosing, the less the salutary effect with increases in adverse side effects. The same is true for Natpara as the dosing regimen that the sponsor has developed is far from physiologic and therefore does not have all the salutary effects that a clinician might wish for in a PTH replacement therapy. The sponsor has demonstrated that Natpara can decrease the amount of calcium and vitamin D supplements that are required, but they have not demonstrated decreases in urine calcium (below 300 mg in 24 hours). There are some indications in the data that Natpara is having an effect on bone, but it is unclear if these changes will be clinically relevant or whether the effect will be deleterious to bone because the dose is too high or dosing regimen not physiologic. As with teriparatide, there is also a concern regarding possible osteosarcoma. The benefits of PTH which were expected but were not demonstrated in the trial could have potentially been realized with greater dose range exploration (the sponsor did little), but without actual data it will always be theoretical whether more frequent dosing (of lower amounts) could improve benefits.

Natpara clearly has an effect on calcium homeostasis, but the question becomes whether the effect at the currently proposed dose provides the appropriate risk to benefit or whether alternative dosing regimens could improve the benefits above what was observed in the pivotal trial and along the line of what is expected based on the known physiologic role of the hormone. This leads to the question of whether further dosing regimen exploration is required, should this exploration be performed before approval, or can we find a mechanism to assure that it would be performed after approval, such that patients in need now would not be denied therapy while optimization of the dosing regimen is being studied. It is always difficult to know if the 'sweet spot' has been found regarding dosing, particularly if there hasn't been adequate dose exploration. To require further dose regimen exploration would delay this therapy for several years for patients (if it were developed at all as the sponsor may just stop development) and in the end it may not be possible to exactly mimic physiology using pharmacologic means (e.g., insulin therapy for diabetes works but achievement of normal glucose control is difficult). So the question to grapple with is if the risk to benefit

considerations of this drug contained within this application such that the drug can be approved. I believe it should be approved, but I also believe we have a mechanism to require the sponsor to perform further dose exploration.

Efficacy

Plasma Natpara levels increased rapidly following injection. The baseline adjusted Cmax 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) returning to pre-dose levels by 12 hours. The $T_{1/2}$ is approximately 3 hours.

There were 4 efficacy and safety supportive studies and one (CL1-11-040-REPLACE) primary registration study listed in the table below (Dr. Lowy's review, page 21).

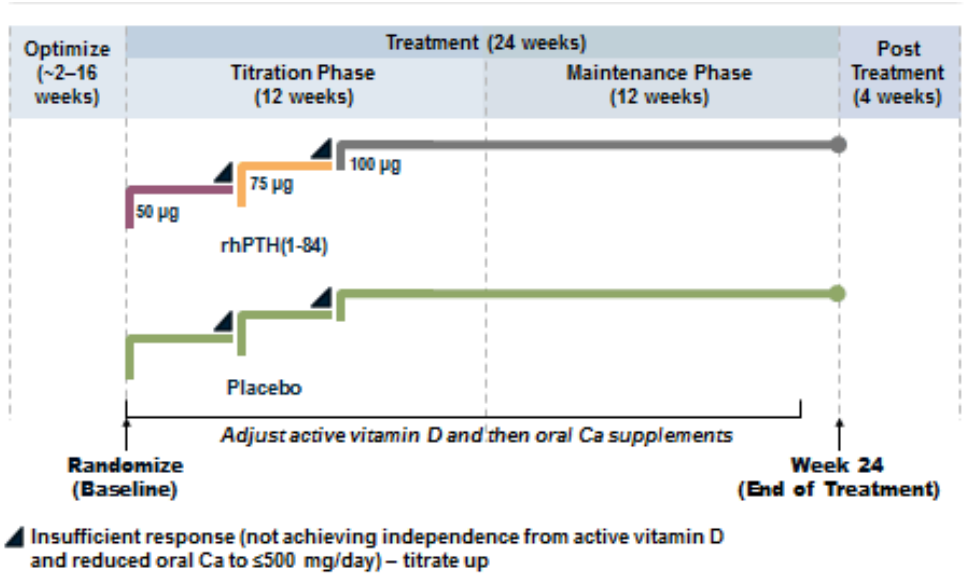
Table 1 Efficacy and Safety Studies in Hypoparathyroidism

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.

Trial 040 was a randomized, double-blind, placebo controlled study which used a 2-16 week screening and stabilization period to ensure a common baseline followed by a 24-week treatment period. The initial dosage was 50 ug daily that could be up-titrated as per the scheme below (Dr. Lowy's review, page 23).

Figure 1 Scheme for Trial 040



During the optimization period, both oral calcium and vitamin D doses were adjusted toward a goal of albumin-corrected total serum calcium of 8.0 to 9.0 mg/dl. Following randomization, subjects underwent staged reductions in calcium and vitamin D while maintaining the pre-dose, albumin-corrected total serum calcium. The primary efficacy endpoint was the percentage of responders at Week 24, based on a composite of three components:

1. At least a 50% reduction from baseline oral calcium supplementation and
2. At least a 50% reduction from baseline active vitamin D dose and
3. 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

There were several secondary efficacy endpoints:

1. Percent change from baseline in calcium supplementation dose at Visit 16 (Week 24) in the NPSP 558 treatment group vs. placebo.
2. Proportion of subjects that achieve independence from supplemental active vitamin D metabolite/analog usage AND a calcium supplementation dose of 500 mg/day, or less by Visit 16 (Week 24) in the NPSP 558 treatment group vs. placebo.
3. The frequency of clinical symptoms of hypocalcemia (including paresthesiae, muscle cramping, tetany, seizures) during Visit 14 (Weeks 16) to visit 16 (Week 24) in the NPSP 558 treatment group vs. placebo.

There were several exploratory endpoints which could demonstrate other salutary effects of PTH such as 24-hour urine calcium excretion, change in bone mineral density, and bone turnover markers.

There was one site that had major protocol violations (8% of data) and it was removed from the full dataset. Below are the results for the primary endpoint of the full data and with the site removed (Dr. Clark's review, page 14).

Table 2: Primary Endpoint Analysis Results For the Modified Dataset

		Placebo (N=40)		Natpara (N=84)		Treatment Difference	
		n (%)	Exact 95% CI	n (%)	Exact 95% CI		P
Primary EP, (MDS)	Non-Responder	39 (97.5)	(0.06, 13.16)	38 (45.24)	(43.52, 65.66)	52.26 (40.57, 63.95)	<.0001
	Responder	1 (2.5)		46 (54.76)			
WCS, (MDS)	Non-Responder	31 (77.5)	(10.84, 38.45)	40 (47.62)	(41.19, 63.40)	29.88 (13.1, 46.66)	0.0019
	Responder	9 (22.5)		44 (52.38)			
Changing Serum CA (8-9), (MDS)	Non-Responder	39 (97.5)	(0.06, 13.16)	57 (67.86)	(22.36, 43.22)	29.64 (18.55, 40.74)	<.0001
	Responder	1 (2.5)		27 (32.14)			

Table 3: Primary Endpoint Analysis Results for the Full Dataset

		Placebo (N=44)		Natpara (N=90)		Treatment Difference	
		n (%)	Exact 95% CI	n (%)	Exact 95% CI		P
LOCF, Full Dataset (FDS)	Non-Responder	43 (97.7)	(0.06, 12.02)	42 (46.7)	(42.51, 63.93)	51.06 (39.85, 62.27)	<.0001
	Responder	1 (2.3)		48 (53.3)			
WCS, (FDS)	Non-Responder	35 (79.6)	(0.10, 0.35)	44 (48.9)	(0.4, 0.62)	30.66 (14.89, 46.43)	0.0007
	Responder	9 (20.5)		46 (51.1)			
Changing Serum CA range to be 8-9, (FDS)	Non-Responder	43 (97.7)	(0.06, 12.02)	63 (70)	(20.79, 40.57)	27.73 (17.29, 38.17)	<.0001
	Responder	1 (2.27)		27 (30)			

The worst comparison scenario imputes all placebo incompleters as responders and all Natpara incompleters as non-responders

P-value results based on a two-sided Fisher's Exact Test

Exact 95% CI based on Exact CI calculations for each treatment group

Treatment Differences and CI based on LS Means using a binomial model

Results for secondary endpoints are listed in the table below (Dr. Clark's review, page 15).

Table 4: Results for Key Secondary Endpoints

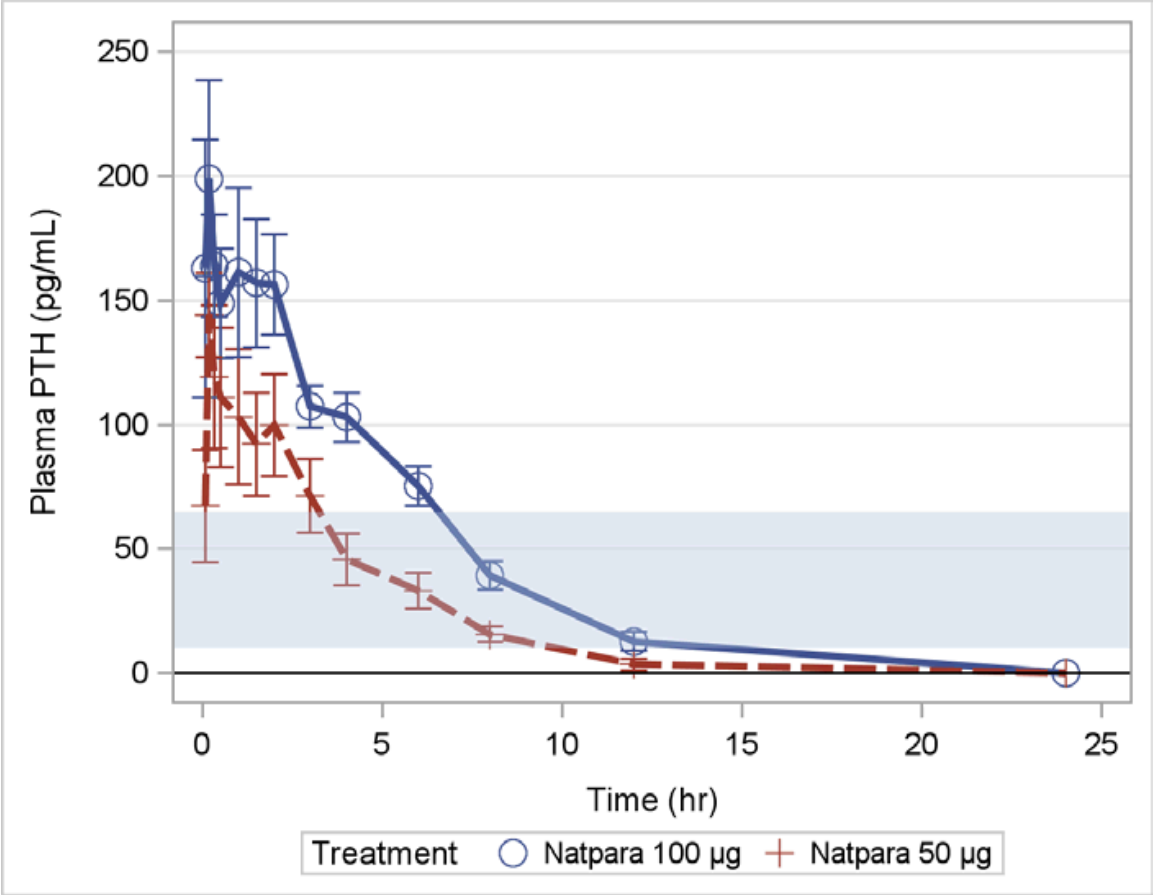
		Placebo (N_{FDS}=44) (N_{MDS}=40)	Natpara (N_{FDS}=90) (N_{MDS}=84)	Difference in Means/OR* (95% CI)	P**
Endpoint 1: Percent Change from Baseline in CA Supplementation					
	CA Reduction ≥ 50%, n(%)	3 (6.8)	61 (67.8)	28.8 (8.2, 100.6)	<.0001
LOCF, FDS	% Reduction from Baseline CA, Mean (SD)	-8.9 (39.4)	51.3 (44.7)	59.9 (44.2, 75.7)	<.0001¤
	Absolute Reduction from Baseline CA, Mean (SD)	-117.1 (533)	1124.2 (1208.2)	1147.5(856.7, 1438.4)	<.0001
	CA Reduction ≥ 50%, n(%)	3 (7.5)	58 (69.1)	27.5(7.8, 97.4)	<.0001
LOCF, MDS	% Reduction from Baseline CA, Mean (SD)	-6.56 (38.5)	51.80 (44.6)	58 (41.8, 74.2)	<.0001
	Absolute Reduction from Baseline CA, Mean (SD)	-85 (536.3)	1152 (1219)	1135.8 (838.6, 1433)	<.0001

WCS Sensitivity Analysis, FDS	CA Reduction ≥ 50%, n(%)	10 (22.7)	57 (63.3)	5.9 (2.6, 13.4)	<.0001
	% Reduction from Baseline CA, Mean (SD)	-4.75 (36.3)	47.6 (46.3)	52.1 (36.3, 67.9)	<.0001
	Absolute Reduction from Baseline CA, Mean (SD)	-48.9 (475.3)	1040.6 (1219.7)	999.8 (700.3, 1299.3)	<.0001
Endpoint 2: Independence from Supplemental Active Vitamin D metabolite/analog and CA supplementation dose ≤ 500 mg/day by Week 24					
LOCF, FDS	Achieved Secondary Endpoint 2	1 (2.3)	37 (41.11)	30 (4, 227.8)	<.0001¤
LOCF, MDS	Achieved Secondary Endpoint 2	1 (2.5)	35 (41.7)	27.9 (3.7, 212.5)	<.0001
WCS, FDS	Achieved Secondary Endpoint 2	6 (13.6)	35 (38.9)	4.03 (1.5, 10.5)	0.0028
Endpoint 3: Frequency of hypocalcemia symptoms between Weeks 16 and 24 (Comparing proportions with symptoms)					
Subjects with Clinical symptoms of Hypocalcemia during Week 16 to 24, FDS		14 (31.8)	31 (34.4)	1.126 (0.5, 2.4)	0.8467¤
MDS		12 (30)	30 (35.7)	1.3 (0.6, 2.9)	0.6851

*Odds Ratio calculated for binary variables, differences and CI calculated for continuous based on ANCOVA model
**P-values based on Fisher's Exact test for binary variables, and ANCOVA adjusting for baseline with continuous variables
¤ Primary Variable specified for secondary analysis endpoint

Urine calcium amounts (> 300 mg/dl) are of clinical interest in patients with hypoparathyroidism. There is data in Study CL09-002 regarding PD markers of interest in patients with hypoparathyroidism that are relevant to this issue. The PK in patients with hypoparathyroidism is presented below (Dr. Roman's review, page 12).

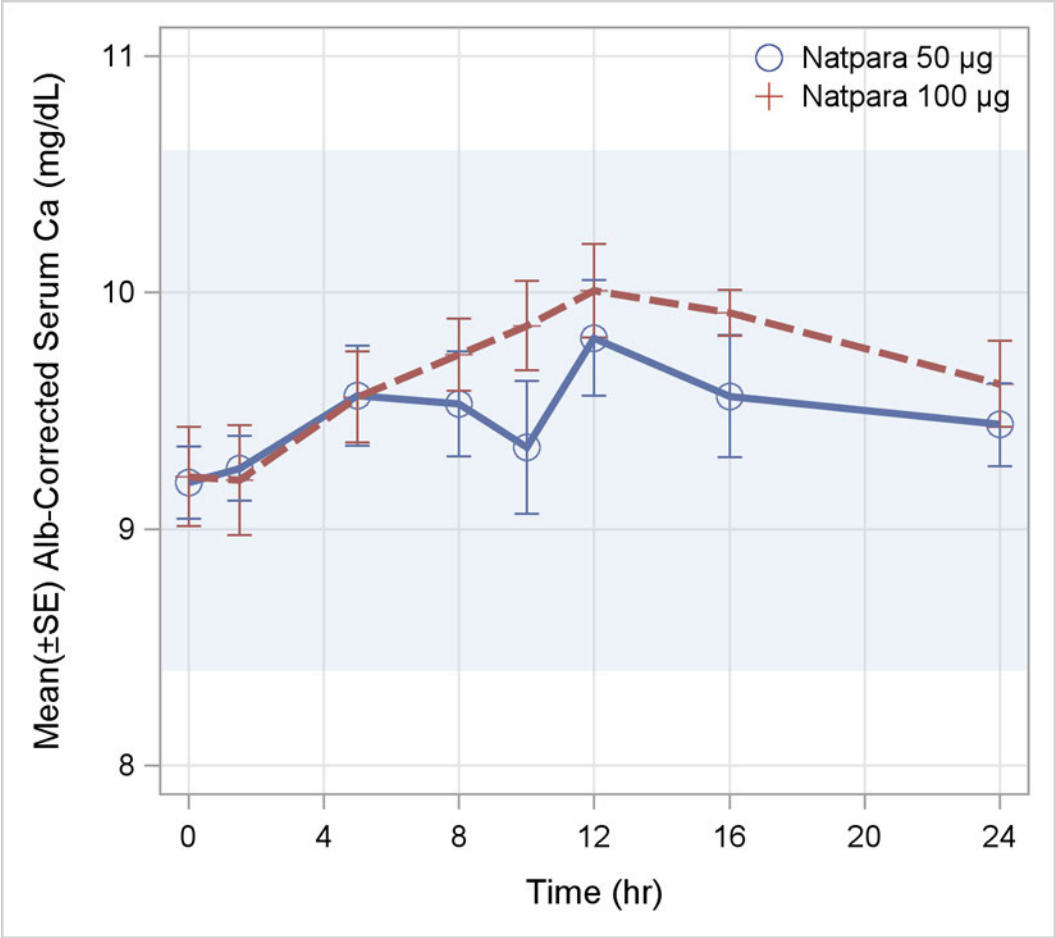
Figure 7 Mean plasma concentration versus time profile of Natpara (single 50 and 100 µg SC doses in the thigh of same subjects, minimum 7 days washout between 2 periods).



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

The graph below indicates that following natpara injection, there is a dose-related increase in serum total calcium levels lasting for up to 24-hours with maximum changes occurring at 12 hours (Dr. Roman's review, page 13).

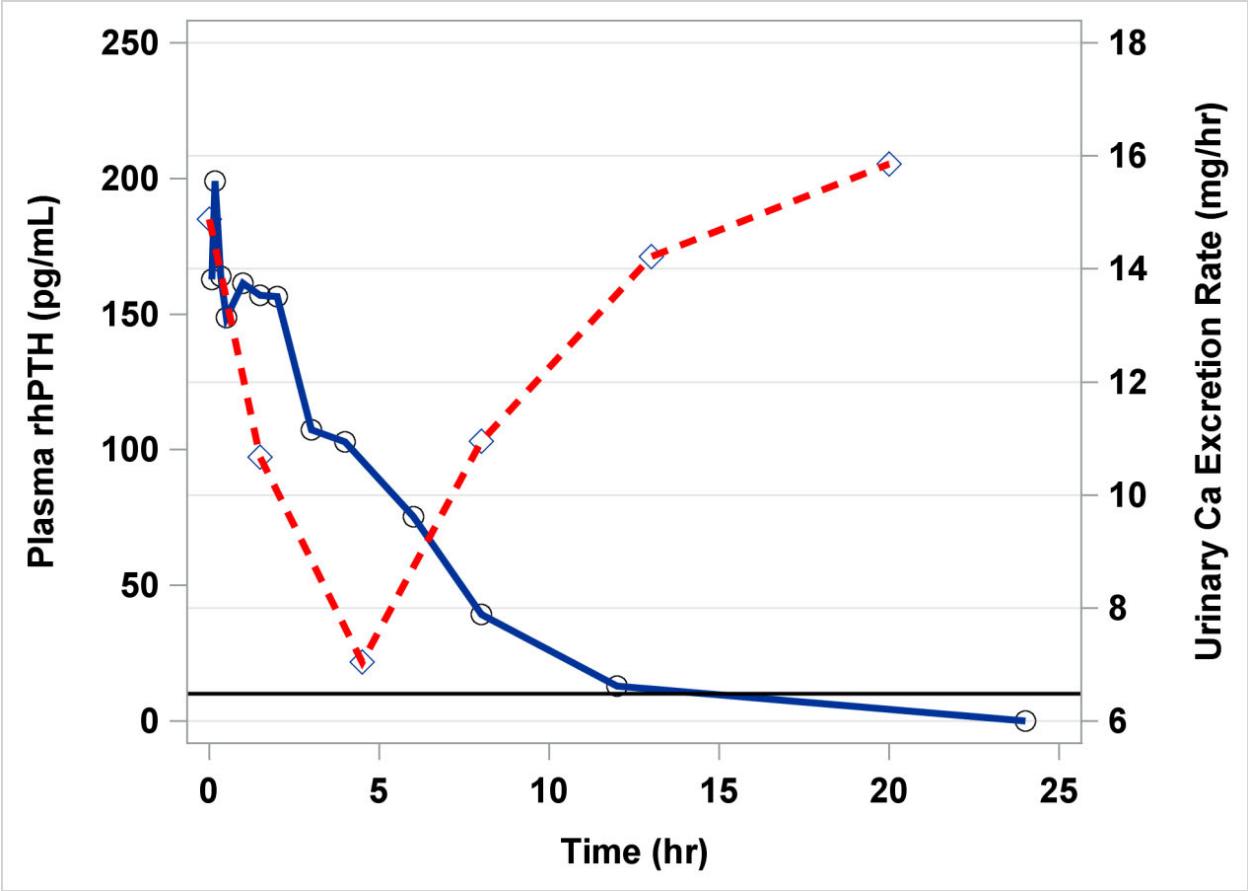
Dose-Related Increase in Serum Calcium with Natpara



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 (red dotted line) were of shorter duration as serum PTH decreases (blue solid line) as indicated in the graph below (Dr. Roman's review, page 14).

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



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

The clinical pharmacology review has modeling (please refer to their review) that hypothesizes 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. An example of one of the many modeling simulations performed is presented below (Dr. Khurana's review, page 49).

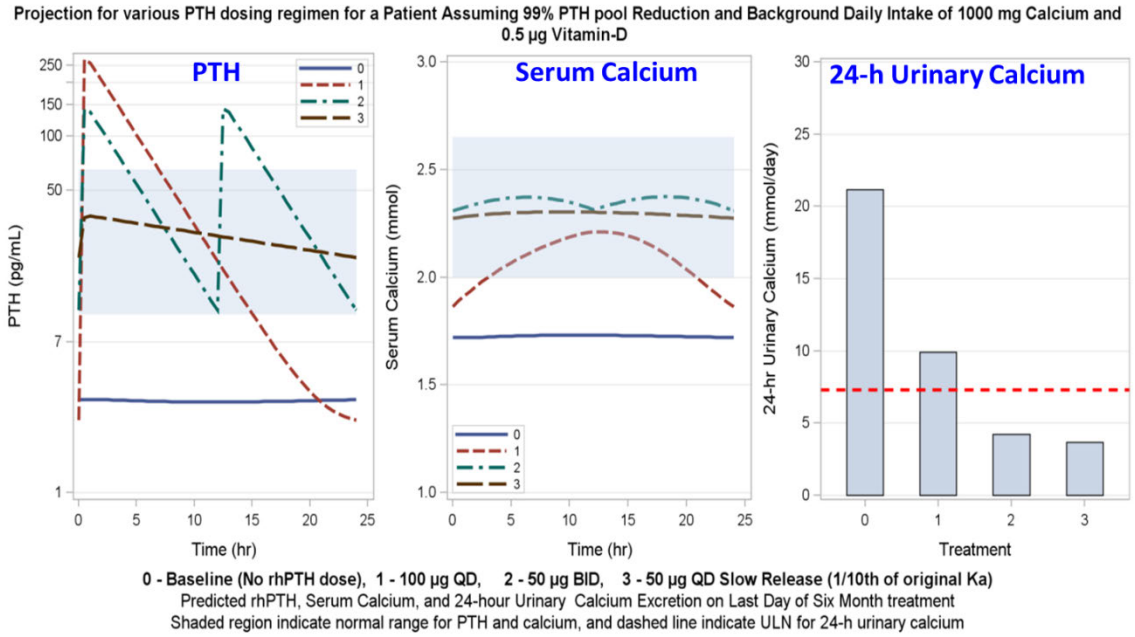


Figure 2 Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 1000 mg oral Calcium and 0.5 µg Vitamin D in a patient representing 99% PTH pool reduction

The above would seem quite possible, as it would be expected, that the closer the dosing of Natpara to physiological the more the salutary effects would be expressed.

The efficacy data demonstrate that Natpara doses of 50-100 mcg daily can maintain serum calcium while decreasing the use of calcium supplements and Vitamin D. However, Natpara did not decrease overall (24 hour) calcium renal excretion. This likely is due to the clinical pharmacological effect described above due to non-physiological dosing. Other salutary effects on bone and quality of life remain speculative.

Safety

Compared to the standard of care, Natpara had similar amounts of serious adverse events and treatment emergent adverse events and there did not appear to be immunogenicity concerns. Changing from standard of care to Natpara may result in episodes of hypo- or hypercalcemia until appropriate titration levels are achieved.

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, so it should not be a surprise given their similarity.

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.

In summary, there were no unexpected adverse events with most events anticipated based on the known effects of PTH. Observations in animal studies raise the concern of a potential risk of osteosarcoma.

Advisory Committee Meeting

An AC meeting was held on September 12, 2014. Members voted 8 in favor and 5 against approval of Natpara. Most voting against approval felt that the dose could be better optimized to closer mimic physiological levels, resulting in more salutary effects. Most voting for, and against, approval indicated that it was a difficult decision for them. There were some very moving testimonials from patients regarding how Natpara use resulted in improvement of the 'brain fog' that is associated with this disease.

Panel members indicated they would like some type of registry or other system to monitor for osteosarcoma but were unclear on the extent of how aggressive they expected regulation in this regard. They also seem to desire a post marketing risk management plan, but were unclear on the goals.

Conclusions and Recommendations

The sponsor has demonstrated that Natpara does have some effects of PTH even when not given in a physiologic manner. They have also demonstrated that when not given in a physiologic manner, there can be adverse effects, incomplete effects, and at least in animal studies, severe concerns. Modeling by our clinical pharmacology colleagues has generated hypothesis that a relatively minor change in dosing interval, and perhaps dose, could more closely simulate physiologic 24 hour serum PTH levels. While twice a day dosing doubles the frequency and number of injections, the potential payoff, if the modeling is accurate, could be quite substantial. Viewing the inconvenience of twice a day (or perhaps more) injections could be considered in the context of those taking insulin for diabetes where frequent daily dosing (and even pump infusion) occurs and this seems a small price to pay if there was normalization of urine calcium and normal bone metabolism. As noted by many on the Advisory Committee, there is disappointment that efficacy analyses that evaluated clinical benefit beyond dose reduction of supplemental calcium/Vitamin D were not robust. Some felt that without a demonstrated benefit on hypercalciuria reduction, Natpara, even though a normally excreted hormone that is missing, did not demonstrate any advantage over standard of care treatment. This observation along with the animal findings of osteosarcoma is a cause of concern. It cannot be overstated that normal hormones given in non-physiologic doses carry risks and cause adverse events. Such is the case with thyroid hormone, corticosteroids, growth hormone, insulin and others.

There were many patients that testified at the open public session that Natpara had changed their lives for the better. Most described lifting of 'brain fog' in their moving testimonials. Unfortunately, this was not captured/demonstrated in evaluations of the trials, so it is hard to tell if this was a select subpopulation or if the instrument of evaluation was not sensitive.

In any event, it is clear that Natpara does maintain serum calcium while decreasing the burden of oral calcium intake. This in and of itself can be very important to those requiring substantial replacement or those who cannot maintain control with available therapies. As such, I believe that Natpara should be approved. However, I am not as sure that it should be considered, in its present dosage recommendations, as standard care for all patients with PTH deficits in light of its unknown long term risks and in the absence of a demonstrated advantage over available therapies. I think the sponsor did a very inadequate job of dose exploration and the present dosage and dosing interval carry safety concerns that may be easily remedied with further pharmacologic evaluation. As such, as part of a PMR, we will require timely further dose exploration to decrease the potential risk of osteosarcoma (by perhaps decreasing Cmax and AUC) and decrease urinary calcium excretion. A REMS will also be required to inform physicians and patients of the potential limitations of this new hormone replacement therapy. Hopefully then this drug will be available for those truly in need, but not for those that could wait until, and if, better dosing becomes available.

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/s/

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01/23/2015