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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

NPS Pharmaceuticals submitted Natpara, an injected recombinant human parathyroid hormone, for the treatment of long term hypoparathyroidism. Approval is being sought for this treatment based on evaluations of change in oral calcium and vitamin D doses from baseline to Week 24 in hypoparathyroid patients.

1.1 Conclusions and Recommendations

Natpara was effective with respect to a composite endpoint involving oral calcium doses, vitamin D doses, and normalized serum calcium levels was met in a randomized controlled phase 3 efficacy trial. Based on the findings given in this review, Natpara is effective in lowering the necessary dosages of oral calcium and vitamin D in adult hypoparathyroid patients.

1.2 Brief Overview of Clinical Studies

There are a total of 5 efficacy and safety studies in the NPS clinical development program which are described in Table 3 of section 2.1. CL1-11-040 study is listed by the sponsor as the primary registration study and will be the focus for this review. This was a 24-week placebo controlled study which used a dose titration process to achieve a functioning dose for each subject by the end of the treatment period. Due to the low prevalence of hypoparathyroidism, this study had a multicenter and multinational population in order to achieve adequate statistical power. This included a number sites from 8 countries (USA 20, Canada 3, Denmark 3, Hungary 3, Belgium 1, France 1, Italy 1, UK 1) where a total of 29 sites randomized subjects. The primary endpoint was a composite of oral calcium reduction, vitamin D reduction, and normalized serum calcium concentrations. Using the methodology described in section 3.2.2, we found the outcomes were better on Natpara when compared with placebo (Table 1).

Table 1: Primary Endpoint Results

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

All five efficacy and safety studies are listed in Table 3 of section 2.1. The remaining four studies are used to provide evidence of the effectiveness of Natpara for the treatment of hypoparathyroidism as a replacement for the endogenous parathyroid hormone PTH(1-84).

1.3 Statistical Issues and Concerns

- The biggest concern involved the reliability of some of the data in the study. Due to major protocol violations in the data from one of the clinical co-investigators, observations at site 1002 were deemed unreliable. Therefore, parts of the analysis were

rerun excluding patients from this site. There were 10/134 (7.46%) subjects removed from the analysis with response patterns shown in Table 2 below. Results from the analysis done after removing the sites are given in Table 5 and

Table 7 for primary and secondary endpoints. Unless otherwise noted, proportions and statistics are based on the modified dataset with these ten subjects removed in this review.

Table 2: Subjects in Site 1002

	Placebo (N=4)	Natpara (N=6)
	n (%)	n (%)
Non-Responder	4 (100)	4 (66.67)
Responder	0 (0)	2 (33.33)

- Another concern involved a protocol amendment to the primary endpoint changing the third piece of the composite endpoint from having “*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*” to having “*an albumin-corrected total 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.*” Changing this part of the endpoint to have a range of 8-9 mg/dL for serum calcium concentrations for all subjects, I found the proportion of those who had normal serum calcium levels under both the old and new definitions continued to remain non-significant when comparing differences between the two treatment groups. Under the original imputation there were 88.1% of those in Natpara versus 87.5% in placebo ($p=0.92$) with normal levels. This associates with a difference of 0.6% having an asymptotic 95% CI of (-11.8%, 12.1%). When implementing the new 8-9 mg/dL range I found 46.4% versus 52.5% ($p=0.53$) with a difference of -6.1% (-24.9%, 12.7%). Using this in the composite primary endpoint, regardless of which amendment a subject came in under, I found 21/47 (44.7%) of responders became non-responders, but the overall response rate in the Natpara group of 27/84 (32.1%) versus 1/40 (2.5%) in the placebo group remained statistically significant ($<.0001$).
- The composite primary endpoint assesses diagnostic measurements including calcium dosage, vitamin D dosage, and albumin corrected total calcium serum normality. Such measurements are not a direct measure of clinical benefit on how a patient functions or survives.

2 INTRODUCTION

2.1 Overview

There were five efficacy and safety studies, listed in Table 3, which were completed and submitted for review with one study designated as primary containing a placebo control arm.

Table 3: Safety and Efficacy Studies in Hypoparathyroid Subjects for NATPARA (rhPTH[1-84])

	Study Objectives	Study Design and Type of Control	Test Product(s), Number of Subjects	Duration of Treatment
<i>Placebo Controlled Study</i>				
CL1-11-040 (REPLACE)	Efficacy and Safety	Randomized, double-blind, placebo controlled	Varying doses of 50, 75, and 100 µg SC in the thigh of rhPTH[1-84] daily, 90 or Placebo, 44	24 weeks
<i>Dose Comparison Concurrent Controlled Study</i>				
PAR-C10-007 (RELAY)	Efficacy and Tolerability	Randomized, dose-blinded	Fixed doses of 25 or 50 µg SC in the thigh of rhPTH[1-84] daily, 47	8 weeks
<i>Dose Comparison Concurrent Uncontrolled Study</i>				
PAR-C10-008 (RACE)	Safety and Tolerability	Open-Label	Varying doses of 25, 50, 75, and 100 µg SC in the thigh of rhPTH[1-84] daily, 53	12 months + extension Ongoing
<i>Uncontrolled</i>				
PAR-C10-009 (REPEAT)	Safety and Tolerability	Open-Label	Varying doses of 50, 75, and 100 µg SC in the thigh of rhPTH[1-84] daily, 24	24 Weeks
<i>Investigator Initiated Trial</i>				
Bilezikian IIT	Safety and Efficacy	Open-label study, prospective	Varying doses of 50, 75, and 100 mg SC in the thigh of rhPTH[1-84] daily or less than daily, 79	Ongoing

2.1.1 Class and Indication

Natpara is an injected recombinant human parathyroid hormone developed by NPS Pharmaceuticals. The proposed indication is a replacement for endogenous parathyroid hormone for the long term treatment of hypoparathyroidism. In addition to efficacy and safety, this submission examines the tolerability of varying doses at 25, 50, 75, and 100 µg injected daily. Based on findings of improvement in oral calcium dose, active vitamin D dose, normalization of albumin corrected total serum calcium concentration.

2.1.2 History of Drug Development

The active pharmaceutical ingredient is a strain of E. coli modified by rDNA technology. Initially, rhPTH(1-84) started as a treatment for osteoporosis in postmenopausal women. On January 31, 1995 NPS submitted an IND (b)(4) to the FDA for the investigation of rhPTH(1-84). This was followed by NDA (b)(4) on May 10, 2005 under the proprietary name Preos with

the therapeutic indication of “Treatment of postmenopausal women with osteoporosis”. On March 9, 2006 the NDA received an approvable letter with key issues relating to safety associated with hypercalcemia and reliability of the delivery device used in the clinical trials. (b) (4)

[REDACTED] This was withdrawn without prejudice on March 24, 2011.

The sponsor pursued continued development of rhPTH(1-84) for treatment of hypoparathyroidism and the development of a new pen injector system, choosing NPSP558 as the designation for rhPTH(1-84) to distinguish it from the previous development program for osteoporosis. NPSP558 for hypoparathyroidism was given an Orphan Drug Designation in 2007. On December 17, 2007 a pre-IND meeting was held with the FDA and IND 076514 was submitted on September 19, 2008 to conduct the pivotal trial CL1-11-040.

A type C advice meeting with the FDA was held on September 26, 2011 after the completion of the main trial. It was agreed that the marketing application for this indication would rely on NPS’s sponsored multinational efficacy and safety studies in hypoparathyroidism along with safety data from clinical trials and postmarketing experience in patients with osteoporosis.

A different type C advice meeting on July 6, 2010 concluded that the submission of NPSP558 would be submitted as a drug-device combination with a bridging strategy for the transition from the device initially used in the hypoparathyroidism clinical trials to the intended US commercial mixing device and pen injector. The sponsor subsequently completed the bridging program between the injectors and has added the intended commercial devices and corresponding instruction in the ongoing PAR-C10-008 study.

On May 23, 2014 a teleconference was held between the sponsor and the FDA to discuss major issues concerning protocol violations at one of the main study sites. As a result, much of the analysis was rerun without subjects contained in this site.

2.2 Data Sources

Data and final study report were submitted electronically and archived under the network path location <\\cdsesub1\bla\CTD_Submissions\STN125511>. The information needed for this review was contained in Module 1 FDA Regional Information (cover letter, meeting correspondence, and labeling), Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Report. This review focuses on documents submitted to serial number 0000.

An independent investigator initiated trial not listed in Table 3 was run in Denmark with results published in the *Journal of Bone and Mineral Research* in October of 2011. The results of this study are given by Sikjaer et al. in “The Effect of Adding PTH(1-84) to Conventional Treatment of Hypoparathyroidism: A Randomized, Placebo-Controlled Study.”

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This submission is in the electronic common technical document (eCTD) format with an xml backbone. All required documents that are necessary for statistical review were submitted. Study datasets were provided as SAS XPORT transport files. No additional information request was made for the statistical review.

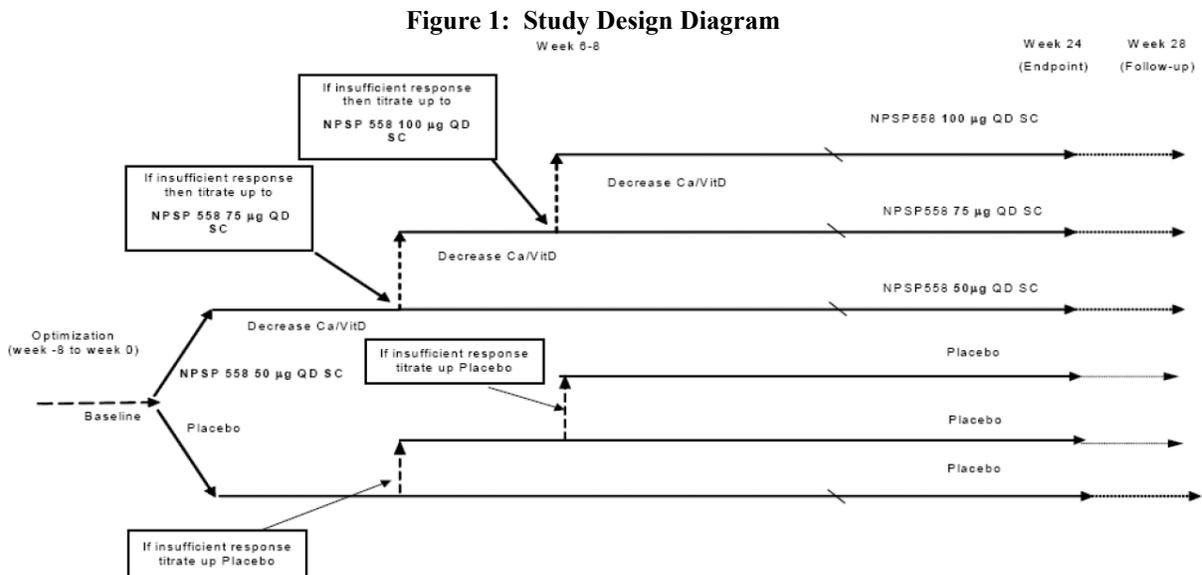
A statistical analysis plan was submitted and reviewed for the main study and all primary and key secondary efficacy endpoints were reproduced from the submitted data. No sponsor code was submitted or reviewed in this application, but the define.xml provided enough detail to understand the data and run appropriate analyses.

The Office of Scientific Investigations (OSI) inspected several clinical sites. This turned up several protocol violations leading to the questionability of some of the data in one of the clinical sites as described in section 1.3. For further information on these violations please see the review submitted by Cynthia Kleppinger in the OSI.

3.2 Evaluation of Efficacy.

3.2.1 Study Design and Endpoints

The main study was a 6-month, multicenter, double-blind, randomized, placebo-controlled study. Since the study included one primary and three secondary efficacy endpoints, a fixed sequence test procedure was used to control the Type I error starting with the primary efficacy endpoint and then proceeding to the secondary endpoints in a pre-specified order, if any hypothesis was found to be non-significant with $p < .05$ level then any subsequent tests were not executed. Figure 1 gives an applicant created schematic of this study design.



Baseline was defined as the last available pre-dose value. An optimization period was implemented so that all subjects were brought to a common baseline in order to ensure that subjects in both arms of the study began treatment at the same levels of calcium control; this controlled for comparisons between treatment arms. Randomization followed by a 24-week treatment period came next. This started with 50mg daily and up-titration options in increments of 25 mg every two weeks up to a maximum of 100 mg and down-titration anytime to a min of 50 mg. The sponsor enrolled 134 adult subjects with hypoparathyroidism with a 2:1 randomization of treatment to placebo in 29 investigative sites internationally. Of the 134 eligible subjects, 90 were randomized to NPS558 and 44 to placebo. All 134 were included in the Intent-to-Treat (ITT) and safety analyses and 115 were included in the Per Protocol (PP) analysis. Thirteen subjects discontinued prior to the end of treatment. Of the six in the treatment arm, three were due to AEs, one unspecified subject decision, one lost to follow-up and one investigator decision. In the control group there were seven who discontinued: three were investigator's decision due to noncompliance with study procedures, three were personal decisions, and one was due to unspecified noncompliance.

3.2.1.1 Primary Endpoint

The primary efficacy endpoint in the main CL1-11-040 study was the percentage of responders at Week 24, based on investigator-prescribed data relating to a composite endpoint of three components,

1. At least a 50% reduction from the baseline oral calcium dose
2. At least a 50% reduction from the baseline active vitamin D dose. It should be noted that adjustments were made to the baseline doses so the two different types of vitamin D (calcitriol and alphacalcidol) administered in the study would be equivalent (2 doses of alphacalcido = 1 dose of calcitriol)
3. An albumin corrected total serum calcium concentration that was maintained or normalized compared to the baseline value (≥ 7.5 mg/dL) and did not exceed the upper limit of the laboratory normal range.

The applicant rationale for why these criteria were used was given as following: the first two components were chosen to provide a large and clinically significant decrease in reliance on supplements when compared to placebo so that a treatment effect would be clearly differentiated; the third component served two purposes, 1) it ensures that any reduction in supplements would not be at the expense of worsening baseline serum calcium concentrations, 2) it did not allow serum calcium levels to go above the upper limit of normal at week 24. This endpoint mandated that only subjects who had clinically significant decreases in their reliance on supplements and had continued stable or improved serum calcium when compared with baseline standard of care could be responders.

The primary efficacy endpoint occurred at week 24. If an ITT subject dropped out early or didn't have assessments at Week 24, then the last efficacy assessments were carried forward (LOCF). Subjects were considered non-responders if they did not have sufficient drug exposure (discontinued treatment before Visit 14 (Week 16)). If a subject was enrolled before protocol amendment 7.0 then the primary endpoint was subject to slight modifications regarding the albumin corrected total serum calcium concentration. These differences, however, made

little difference in the results for pre and post-amendment 7 results with one subject in the Natpara group that would have been considered a responder had she come in after amendment 7.0, but was considered a non-responder due to her entry under amendment 4.

The primary endpoint for all 3 NPS sponsored efficacy studies supporting the main study were also similar composites as shown below in the applicant generated table below (Table 4).

Table 4: Applicant’s Table of Composite Endpoints for NPS Sponsored Efficacy Studies

Study	CL1-11-040	PAR-C10-007	PAR-C10-008	PAR-C10-009
Duration at Endpoint	24 weeks	8 weeks	52 weeks	24 weeks
Response Criteria^a				
Oral Calcium	≥ 50% reduction from baseline	Reduction to ≤ 500 mg/day	≥ 50% reduction from baseline OR Dose of ≤ 500 mg	≥ 50% reduction from baseline OR Dose of ≤ 500 mg
Calcitriol/Alphacalcidol	≥ 50% reduction from baseline	Reduction to ≤ 0.25 µg/day (calcitriol)	≥ 50% reduction from baseline OR Dose of ≤ 0.25 µg/day (calcitriol)	≥ 50% reduction from baseline OR Dose of ≤ 0.25 µg/day (calcitriol) or ≤ 0.50 µg/day (alphacalcidol)
Serum ACSC ^b	Maintained or normalized compared to baseline value (≥ 7.5 mg/dL) and did not exceed the laboratory ULN	Between 7.5 mg/dL and the ULN for the central laboratory	Between 7.5 mg/dL and the ULN for the central laboratory	Normalized or maintained compared to the baseline value and did not exceed the ULN of the central laboratory

ACSC = albumin-corrected total serum calcium concentration; ITT = Intent-to-treat; ULN = upper limit of normal

In order to meet the definition of a responder, all 3 criteria had to be met at the same time.

^a Response criteria was based on ITT population using investigator-prescribed dosing data.

^b Total serum calcium was response criterion for Study PAR-C10-009

Source: Table 4-7 in the Integrated Summary of Efficacy report

3.2.1.2 Secondary Endpoints

Secondary efficacy endpoints for the pivotal trial consisted of:

1. Percent change from baseline in calcium supplementation dose at Visit 16 (Week 24) in the NPS 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 NPS 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 NPS 558 treatment group vs. placebo.

In order to create a response rate for the third secondary endpoint, I used the sponsor list of adverse event preferred terms for hypocalcemia symptoms. The AEs listed for ‘hypocalcemia’ and ‘hypocalcemia symptoms’ were used in my calculations which did not match up with the sponsors although they were found to be equally non-significant.

3.2.2 Statistical Methodologies

A fixed sequence testing procedure was used to control the Type I Error. If the primary endpoint was found to be significant then the first secondary endpoint was tested. This step-down procedure was used as described in Section 3.2.1.

The primary analysis was conducted using all randomized subjects receiving at least one dose and having at least one post-baseline efficacy measurement. The 2-sided Fisher's Exact test was used to test for responder rate difference between Natpara and placebo. Additional sensitivity analyses, including Cochran-Mantel-Haenszel method, and MMRM were specified by the applicant to determine the robustness of the primary efficacy analysis.

The first secondary endpoint, percentage change from baseline in calcium supplementation dose at Visit 16 (Week 24) in the investigator prescribed data, compared treatment group differences using an ANCOVA model with treatment as a factor and baseline calcium as a covariate. In addition to the ANCOVA results, the least squares means, standard error, and 95% confidence intervals for each treatment were also calculated along with the least squares mean difference between the treatments along with the appropriate standard error and 95% confidence interval for the difference.

The next secondary endpoint, 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), the proportions meeting this endpoint were compared between the two treatment groups using a CMH test along with an odds ratio and 95% confidence interval based on the investigator prescribed data.

The last secondary endpoint, the frequency of clinical symptoms of hypocalcemia during Visit 14 (Weeks 16) to visit 16 (Week 24), was tested using a CMH test to compare proportions between the two treatment groups. In addition to the CMH results, an odds ratio with 95% confidence interval was also run.

Prospectively defined subgroup analyses were conducted, including age, gender, and prescribed active vitamin D at baseline subgroups. Descriptive statistics, including number of subjects, mean, median, SD, max, and min, were run for continuous variables. Statistical summaries using number of subjects and percentages were run on categorical variables.

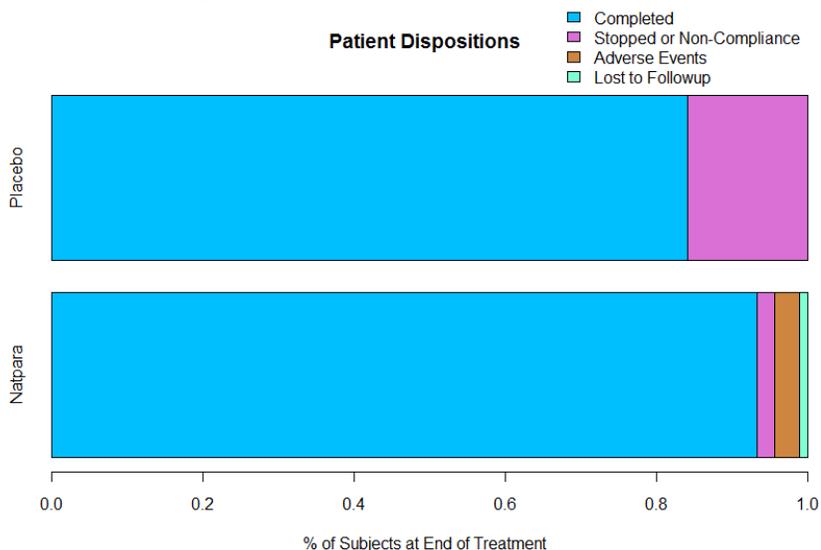
I also ran a worst comparison scenario (WCS) sensitivity analysis for all primary and key secondary endpoints wherein all non-completers were considered responders if they were under placebo and non-responders under Natpara. For secondary endpoints measuring change from baseline, the highest level of supplementation observed over the course of the study was imputed for those in the Natpara arm and the lowest level for those under placebo.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were 196 subjects screened for this trial in 33 sites over 8 countries. Of these, 134 in 29 sites were randomized to one of two study arms. All 134 subjects were included in the ITT population used for the analysis, and 115 were considered to be a part of the per protocol population. Within the ITT population 13 subjects discontinued before the end of treatment at visit 16, 6 (6.7%) being treated with Natpara and 7 (15.9%) from placebo. There was one additional subject in the placebo group who completed the treatment but did not complete the study (completed visit 16 for the endpoint but not follow-up visit 18). Figure 2 illustrates the

percentage of completers/non-completers and reasons for not completing based on the full dataset (N=134). It does appear that while subjects receiving Natpara are more likely to drop out due to an adverse event (hypertension, CVA), those on placebo were more likely to drop out due to subject (concerns over increased CA in urine, subject relocation, noncompliance) or investigator decision (noncompliance).

Figure 2: Completion status at Week 16



Descriptive table generated based off these populations which can be found in the Appendix matched with Table 11-2 of the sponsor’s clinical study report.

3.2.4 Results and Conclusions

For the primary analysis, a statistically significant difference ($p < 0.001$) was found for responder rates in the ITT population when comparing treatment (54.8%) to placebo (2.5%). With a treatment difference of 52.3%, there seems to be a benefit in terms of efficacy based on this composite endpoint. There were a total of 44 responders that were recorded at week 24 and two responders which were imputed by the applicant using a LOCF method. A worst comparison scenario (WCS) imputation analysis was also run wherein all those with missing endpoints in the Natpara arm were imputed as non-responders and those in the placebo arm were imputed as responders. Results also remained significant across the WCS indicating that these results will remain statistically significant under other less stringent imputation methods with this particular endpoint. Due to clinical concern on what may be considered stable for serum calcium, the primary endpoint analysis was also redone based on the endpoint revisions described in section 1.3, Statistical Issues and Concerns. Under this scenario there were a total of 26 observed responders at week 24 and one responder imputed using LOCF to create a total of 27 responders in the Natpara treatment arm. Although there was a substantial drop in the response rate with this new endpoint, it remained statistically significant showing a difference in response rate from placebo. Results for the primary endpoint were calculated using both the full dataset (FDS) and modified dataset (MDS) which removes the site with major protocol violations described in

Section 1.3. Table 5 and Table 6, given below, show results using the LOCF method, the WCS imputation for non-completers, and the revised serum calcium primary endpoint for both the FDS and MDS.

Table 5: Primary Endpoint Analysis Results For the Modified Dataset

		Placebo (N=40)		Natpara (N=84)		Treatment Difference	P
		n (%)	Exact 95% CI	n (%)	Exact 95% CI		
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 6: Primary Endpoint Analysis Results for the Full Dataset

		Placebo (N=44)		Natpara (N=90)		Treatment Difference	P
		n (%)	Exact 95% CI	n (%)	Exact 95% CI		
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

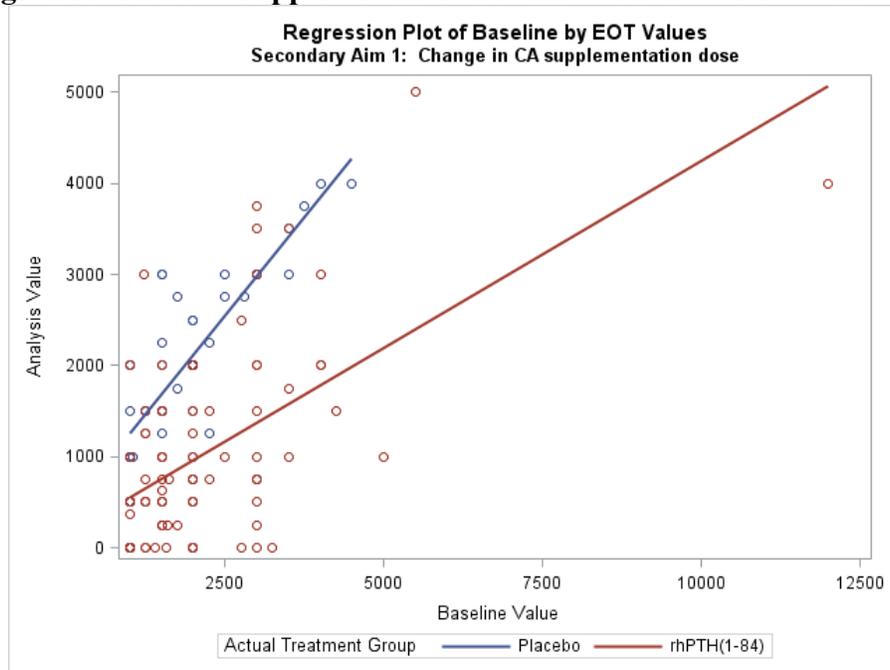
P-value results based on a two-sided Fisher's Exact Test

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

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

Since the primary endpoint was significant it was appropriate to proceed with testing procedures for the secondary endpoints. The first secondary endpoint indicated a statistically significant reduction ($p < 0.001$) from baseline in supplemental calcium dose for the Natpara group (51.8% mean reduction), when compared with placebo (-6.56%). Figure 3 shows a scatter plot of the calcium supplementation at baseline and at end of treatment with regression lines drawn for each treatment arm. The figure illustrates the difference between placebo and Natpara in calcium supplementation by the end of treatment.

Figure 3: Calcium Supplementation at Baseline and End of Treatment



The next secondary endpoint shows a statistically significant difference ($p < .0001$) in response between Natpara and placebo for the proportion of subjects (41.67% vs. 2.5%) who achieved independence from supplemental active vitamin D and reduced their calcium supplementation dose to ≤ 500 mg daily ($p < 0.001$).

In the last secondary endpoint, which concerned safety on the frequency of clinical symptoms of hypocalcemia during Visit 14 (Weeks 16) to visit 16 (Week 24), I was unable to reproduce the applicant's numbers exactly based on what was submitted. Table 11-7 in the clinical study report listed 30/90 (33.3%) subjects in the Natpara arm and 18/44 (40.9%) of subjects on placebo with symptoms of hypocalcemia during this time period. This led to non-significant findings ($p = 0.39$) when testing for a difference between the two arms. In trying to reproduce this endpoint I found a non-significant difference ($p = 0.69$) between the proportion of subjects exhibiting symptoms of hypocalcemia with Natpara (35.7%) when compared with placebo (30%).

Results for all key secondary endpoints are shown in

Table 7 using both the LOCF methodology as well as the WCS imputation. Statistical significance remains robust to the applied imputation methodology.

Table 7: 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					
LOCF, FDS	CA Reduction ≥ 50%, n(%)	3 (6.8)	61 (67.8)	28.8 (8.2, 100.6)	<.0001
	% 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
LOCF, MDS	CA Reduction ≥ 50%, n(%)	3 (7.5)	58 (69.1)	27.5(7.8, 97.4)	<.0001
	% 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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses done for the primary efficacy endpoint were pre-specified by the sponsor. The baseline intrinsic factors considered for analysis were:

- Age (<65)
- Gender
- Geographic Region (North America)
(North America includes Canada and the United States. Other countries in the study include: France, Italy, Belgium, Denmark, the United Kingdom, and Hungary.)

The disease-related factors specified for subgroup analyses were:

- Prescribed active vitamin D metabolite/analog at baseline (high dose, medium dose, and low dose. For calcitriol: low Dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day; for alphacalcidol: low dose 0-0.50 µg/day, medium dose >0.50-1.0 µg/day, high dose >1.0 µg/day) (Note: These ranges are given for the raw, unadjusted baseline doses)
- Prescribed calcium at baseline (0-2000 mg/day, >2000 mg/day)
- Duration of hypoparathyroidism (≤5 years, >5-10 years, >10 years)

Fisher’s exact test was also run within each strata to test for differences.

Testing for subgroups based on race was neither pre-specified nor performed by the sponsor but was included in this review. Since the overall subject population in the FAS was predominantly white (95.52%), this was analyzed as a binary variable with those in the ‘other’ category including those of black, Asian, and Hawaiian/Pacific Islander descent.

As there was only one response in the placebo group, tests for interaction effects were not performed.

4.1 Subgroup Results

Results for the primary endpoint in each subgroup are shown in Table 8 below. In general, the subgroup analysis results remained consistent with the overall efficacy results presented in Section 3.2.4.

The CMH test for general association indicates that there is an association between treatment arm and response for at least one stratum in each subgroup. The exact test results show which strata appear to have the most significant association within each subgroup, because of the post-hoc nature of this analysis and the lack of control for Type I error these results should be interpreted with caution. With just a couple of exceptions, which could be due to power issues, all strata appear to have at least a borderline (<0.1) association with treatment. The failure to see a statistically significant difference in all groups is most likely due to sample size and power issues that is typical in subgroup analyses. Due to these issues and the fact that the sponsor is not seeking any labeling claims based on these specialized populations, no further analyses were performed for these subgroups.

Table 8: Subgroup Analysis Results

			Placebo (N=40)	RhPTH(1-84) (N=84)	
			n (%)	n (%)	Exact P
Age	<65 Years	Non-Responder	35 (97.2%)	38 (47.5%)	<.001
		Responder	1 (2.8%)	42 (52.5%)	
	≥65 Year	Non-Responder	4 (100%)	0 (0%)	0.029
		Responder	0 (0%)	4 (100%)	
Gender	Male	Non-Responder	7 (100%)	9 (47.4%)	0.023
		Responder	0 (0%)	10 (52.6%)	
	Female	Non-Responder	32 (97%)	29 (44.6%)	<.001
		Responder	1 (3%)	36 (55.38%)	
Baseline Active Vitamin D	Low Dose	Non-Responder	2 (66.7%)	1 (16.7%)	0.226

		Responder	1 (33.3%)	5 (83.3%)	
		Non-Responder	12 (100%)	11 (50%)	
	Medium Dose	Responder	0 (0%)	11 (50%)	0.003
		Non-Responder	25 (100%)	26 (46.4%)	
	High Dose	Responder	0 (0%)	30 (53.6%)	<.001
	Baseline CA ≤ 2000 mg	Non-Responder	28 (96.6%)	22 (38.6%)	
		Responder	1 (3.5%)	35 (61.4%)	<.001
	Baseline CA > 2000 mg	Non-Responder	11 (100%)	16 (59.3%)	
		Responder	0 (0%)	11 (40.7%)	0.016
	≤ 5 Years	Non-Responder	9 (90%)	3 (20%)	
	Hypoparathyroidism	Responder	1 (10%)	12 (80%)	<.001
	5-10 Years	Non-Responder	13 (100%)	10 (37%)	
	Hypoparathyroidism	Responder	0 (0%)	17 (63%)	<.001
	>10 Years	Non-Responder	17 (100%)	25 (59.5%)	
	Hypoparathyroidism	Responder	0 (0%)	17 (40.5%)	0.001
	North America	Non-Responder	20 (95.2%)	17 (39.5%)	
		Responder	1 (4.8%)	26 (60.5%)	<.001
	Europe	Non-Responder	19 (100%)	21 (51.2%)	
		Responder	0 (0%)	20 (48.8%)	<.001
	White	Non-Responder	38 (97.4%)	35 (43.8%)	
		Responder	1 (2.6%)	45 (56.3%)	<.001
	Other	Non-Responder	1 (100%)	3 (75%)	
		Responder	0 (0%)	1 (25%)	1

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

One clinical site which accounts for almost 8% of the data was excluded from the analysis due to major protocol violations. Since the head of this site was also one of the two head investigators for the entire study it does cast doubtfulness as to how reliable the rest of the data are. Various imputation methods and exclusion tactics have been implemented in this review to see how well the findings stand up to missing data problems and known protocol violations. However, if there is an underlying flaw in the methodology or clinical practices used when collecting the data then

the findings presented here will reflect these biases and faults and may not be indicative of what would happen in a real-world setting.

5.2 Collective Evidence

Due to its orphan drug status, only one main study for Natpara was required for this NDA submission. A major issue that was not fully resolved for this trial had to do with the primary efficacy endpoint and how the sponsor defined ‘normal’ for serum calcium levels. After recalculating this endpoint based on new criteria (see Section 1.3) I found a much lower response rate for those being treated with Natpara (see Table 5) with the response dropping from 53.3% to 30%. However, the difference when compared to the placebo arm under this new definition remained statistically significant. Secondary endpoints for reduction in calcium supplementation and independence from supplemental active vitamin D and calcium were also statistically significant and remained so under very stringent imputation methods for missing data.

5.3 Conclusions and Recommendations

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.

5.4 Labeling Recommendations

(b) (4)

(b) (4)

(b) (4)

All numbers based on the data from the main study should be changed to reflect the exclusion of the ten subjects from the site described in section 1.3.

Table 9: Descriptive Statistics for Study CL1-11-040

Characteristic	Category	Placebo (N=40)	NPSP558 (N=84)	All
Age Groups	<45 years	13 (32.50%)	35 (41.67%)	48 (38.71%)
	45 to 64 years	23 (57.50%)	45 (53.57%)	68 (54.84%)
	≥65 years	4 (10.00%)	4 (4.76%)	8 (6.45%)
Sex	Female	33 (82.50%)	65 (77.38%)	98 (79.03%)
	Male	7 (17.50%)	19 (22.62%)	26 (20.97%)
Race	White	39 (97.50%)	80 (95.24%)	119 (95.97%)
	Black	0 (0.00%)	1 (1.19%)	1 (0.81%)
	Asian	1 (2.50%)	1 (1.19%)	2 (1.61%)
	Hawaiian/Pacific Islander	0 (0.00%)	1 (1.19%)	1 (0.81%)
	Other	0 (0.00%)	1 (1.19%)	1 (0.81%)
Ethnicity	Hispanic or Latino	0 (0.00%)	2 (2.38%)	2 (1.61%)
	Not Hispanic or Latino	40 (100.00%)	82 (97.62%)	122 (98.39%)
Region	Central and Eastern Europe	7 (17.50%)	16 (19.05%)	23 (18.55%)
	North America	21 (52.50%)	43 (51.19%)	64 (51.61%)
	Western Europe	12 (30.00%)	25 (29.76%)	37 (29.84%)
Prescribed Active Vitamin D at Baseline	Low Dose	3 (7.50%)	6 (7.14%)	9 (7.26%)
	Medium Dose	12 (30.00%)	22 (26.19%)	34 (27.42%)
	High Dose	25 (62.50%)	56 (66.67%)	81 (65.32%)
Prescribed Calcium at Baseline	0-2000 mg/day	29 (72.50%)	57 (67.86%)	86 (69.35%)
	>2000 mg/day	11 (27.50%)	27 (32.14%)	38 (30.65%)
Duration of Hypoparathyroidism Groups	≤5 years	10 (25.00%)	15 (17.86%)	25 (20.16%)
	> 10 years	17 (42.50%)	42 (50.00%)	59 (47.58%)
	>5-10 years	13 (32.50%)	27 (32.14%)	40 (32.26%)
Country	BEL	2 (5.00%)	3 (3.57%)	5 (4.03%)

Characteristic	Category	Placebo (N=40)	NPSP558 (N=84)	All
	CAN	1 (2.50%)	4 (4.76%)	5 (4.03%)
	DNK	4 (10.00%)	9 (10.71%)	13 (10.48%)
	FRA	1 (2.50%)	1 (1.19%)	2 (1.61%)
	GBR	3 (7.50%)	6 (7.14%)	9 (7.26%)
	HUN	7 (17.50%)	16 (19.05%)	23 (18.55%)
	ITA	2 (5.00%)	6 (7.14%)	8 (6.45%)
	USA	20 (50.00%)	39 (46.43%)	59 (47.58%)
Age	N	40.0	84.0	124.0
	Mean	48.9	46.6	47.3
	SD	13.8	12.2	12.7
	Median	52.0	47.0	48.5
	Min	21.0	19.0	19.0
	Max	73.0	74.0	74.0
	Duration of Hypoparathyroidism	N	40.0	84.0
	Mean	11.6	14.6	13.6
	SD	8.1	11.2	10.3
	Median	8.5	10.5	9.0
	Min	2.0	2.0	2.0
	Max	38.0	50.0	50.0
Baseline Height (cm)	N	40.0	84.0	124.0
	Mean	165.0	167.4	166.7
	SD	8.3	8.8	8.7
	Median	166.0	167.8	166.8
	Min	147.3	147.0	147.0
	Max	190.5	190.5	190.5
	Baseline Weight (kg)	N	40.0	84.0
Mean		78.9	82.1	81.1
SD		16.4	18.6	17.9
Median		76.0	82.5	80.0
Min		52.6	50.3	50.3

Characteristic	Category	Placebo (N=40)	NPSP558 (N=84)	All
	Max	115.9	140.0	140.0
Baseline Body Mass Index (kg/m ²)	N	40.0	84.0	124.0
	Mean	28.9	29.3	29.2
	SD	5.3	6.4	6.1
	Median	29.6	29.1	29.2
	Min	18.2	18.9	18.2
	Max	38.8	48.4	48.4

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/s/

JENNIFER J CLARK
06/26/2014

THOMAS J PERMUTT
06/26/2014
I concur.

MARK D ROTHMANN
06/26/2014
I concur

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125511

Applicant: NPS Pharmaceuticals

Stamp Date: 10/24/2013

Drug Name: NPSP558

NDA/BLA Type: Original-1

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	None planned or done
Appropriate references for novel statistical methodology (if present) are included.			X	None used
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

File name: Statistics Filing Checklist for a New BLA 125511

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician Date

Supervisor/Team Leader Date

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/s/

JENNIFER J CLARK
01/08/2014

MARK D ROTHMANN
01/08/2014
concur