

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-406

STATISTICAL REVIEW(S)

NDA 21-406

Fortical (salmon calcitonin) Nasal Spray

This is a 505(b)(2) application.

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Fortical (salmon calcitonin) Nasal Spray

Not applicable at this time because the application is a 505(b)(2) and does not contain a new active ingredient, new dosage form, new indication, new routes of administration, or new dosing regimen.

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 5, 2004

From: J. Todd Sahlroot, Ph.D. (HFD-715)

To: Theresa Kehoe, M.D. (HFD-510)

Subject: Labelling Review of Fortical (NDA 21-406, recombinant salmon calcitonin) in Study 9904 in women with postmenopausal osteoporosis

Introduction

The sponsor submitted data from Study 9904, a randomized, active-controlled Phase 2/3 trial at 2 UK and 3 US sites to assess the pharmacologic response and tolerability to Fortical nasal spray in women with postmenopausal osteoporosis. This study randomized patients to 24 weeks of treatment with Fortical 200 IU nasal spray (n=67) or Miacalcin (chemically synthesized salmon calcitonin) 200 IU nasal spray (n=67). Patients also received a daily supplement containing calcium and Vitamin D.

The primary endpoint was change from baseline in β -CTx, a biochemical marker of bone resorption, at 12 weeks. Other bone markers studied included NTX, urinary DPD, BSAP, serum osteocalcin and PTH. β -CTx, NTX and urinary DPD were measured at baseline and weeks 4, 8 and 12. BSAP, serum osteocalcin and PTH were measured at baseline and week 12.

BMD of the AP spine, lateral spine and femur were measured at baseline and week 24. No fracture data were collected.

This statistical review is not a comprehensive review of the data from the trial but rather meant to address aspects of the proposed label that are not specifically covered by Dr. Qiu in her clinical pharmacology (biopharm) review. Her review will address the comparability of Fortical and Miacalcin with respect to the pharmacodynamic (PD) endpoints mentioned above. Comparability will be assessed by bioequivalence methods typically applied to pharmacokinetic (PK) data. This statistical review will examine BMD endpoints and specific analysis

results for PD endpoints, e.g., changes from baseline, mentioned in the proposed label but not covered in the biopharm review.

Results

Table 1 shows this reviewer's summary data for PD endpoints at 12 weeks. The change from baseline results in Table 1 agree with data from the sponsor's Final Study Report. The sponsor also calculated % changes from baseline in the label for 3 of the 6 PD endpoints (β -CTx, NTX and urinary DPD) in the Fortical group only. These % changes (-40%, -18% and -12%, respectively) differ from the results in Table 1 (-36%, -15% and -8%).

Table 1. Bone marker (PD) endpoints at week 12 (ITT LOCF)

Bone marker	Fortical	Miacalcin
<u>β-CTx</u>	(n=59)	(n=59)
Baseline ¹ mean	0.61	.055
Mean change from baseline	-0.22	-0.23
Mean % change from baseline	-36%	-43%
<u>NTX</u>	(n=59)	(n=59)
Baseline ¹ mean	14.8	13.8
Mean change from baseline	-2.5	-2.4
Mean % change from baseline	-15%	-17%
<u>Urinary DPD</u>	(n=59)	(n=59)
Baseline ¹ mean	9.1	8.1
Mean change from baseline	-1.0	-0.6
Mean % change from baseline	-8%	-6%
<u>BSAP</u>	(n=56)	(n=58)
Baseline ¹ mean	29.0	26.2
Mean change from baseline	-2.6	-2.6
Mean % change from baseline	-9%	-9%
<u>Serum osteocalcin</u>	(n=56)	(n=58)
Baseline ¹ mean	32.8	30.2
Mean change from baseline	-5.8	-6.0
Mean % change from baseline	-18%	-19%
<u>PTH</u>	(n=56)	(n=58)
Baseline ¹ mean	37.9	39.4
Mean change from baseline	-1.1	-4.9
Mean % change from baseline	-2%	-11%

¹ Each patient's baseline was the mean of two pre-treatment values taken approximately one week apart.

Per protocol, treatment groups were to be compared on the primary endpoint using ANOVA with terms for treatment group and center. A 2-sided 95% confidence interval (CI) for the difference in least square means was to be calculated using the standard errors from the ANOVA. The upper bound of the CI (representing a "worst case" for Fortical) was compared to $\pm 35\%$ of the mean of β -CTx at baseline. Dr. Choudhury of the statistical reviewing team raised the issue that the margin may be too liberal by comparison with the observed standard error. The clinical significance of the margin is ultimately a decision for the Medical Officer (see paragraph below).

Table 2 shows analysis results for β -CTx. The difference in least square means for the change in baseline was +0.01 with 95% CI = (-0.05, +0.07). The baseline mean was 0.58 giving reference limits of ± 0.20 ($\pm 35\%$ of 0.58). The lower and upper limits of the 95% CI fall within the pre-specified reference limits.

Table 2. Treatment difference and 95% CI for β -CTx change from baseline

	Fortical (n=59)	Miacalcin (n=59)
LS [†] mean change from baseline	-0.19	-0.20
Treatment difference (F minus M)		
LS [†] mean	+0.01	
95% CI	(-0.05, +0.07)	
Margin ($\pm 35\%$ of the mean of β -CTx at baseline)	± 0.20 ($\pm 35\%$ of 0.58)	

[†] Least square

The sponsor was asked at the Pre-NDA meeting to characterize the miacalcin vs placebo effect size from historical data, and from this construct a meaningful non-inferiority margin. There are apparently no data (assuming the sponsor examined all potential sources) that can provide such an estimate¹. Since the reference limits may be too wide, the MO should independently consider whether the upper limit of the 95% CI excludes all values that represent clinically significant treatment differences. If so, Fortical can be considered to be non-inferior to Miacalcin.

Table 3 shows this reviewer's summary data for BMD endpoints at the AP spine, lateral spine and femur. Changes from baseline in Table 3 agree with the

¹ The PROOF study, a randomized comparison of miacalcin and placebo, comes closest to providing an estimate of the miacalcin-placebo effect for β -CTx. However, β -CTx was measured only at yearly intervals so 12-week data were unavailable. The sponsor also performed a meta-analysis of data from 7 trials with controls receiving calcium and / or Vitamin D to estimate the placebo effect at 3 months. However, the estimate provided is likely to underestimate the true placebo rate since some groups did not receive vitamin D.

sponsors results. The sponsor calculated percent change from baseline for the AP spine only. Both BMD endpoints, change from baseline and % change from baseline, are included in the Table since the latter is the usual primary endpoint in trials for the prevention of postmenopausal osteoporosis.

Table 3 also shows median changes in addition to means. The median is especially relevant for the lateral spine due to the small sample size (n=13/group) and the skewness of the distributions, particularly Fortical. LOCF results were equivalent to completer results since there was only one BMD measurement after screening.

Table 3. BMD endpoints at week 24 (ITT LOCF)

BMD endpoint	Fortical	Miacalcin
<u>AP spine</u>	(n=58)	(n=57)
Baseline ¹ mean	0.800	0.825
Change from baseline		
Mean	+0.010	+0.012
Median	+0.005	+0.011
% change from baseline		
Mean	+1.3%	+1.5%
Median	+0.7%	+1.3%
<u>Lateral spine</u>	(n=13)	(n=13)
Baseline ¹ mean	0.597	0.609
Change from baseline		
Mean	+0.031	+0.026
Median	+0.012	+0.013
% change from baseline		
Mean	+6.0%	+4.7%
Median	+2.2%	+2.3%
<u>Femur</u>	(n=58)	(n=57)
Baseline ¹ mean	0.569	0.572
Change from baseline		
Mean	+0.006	+0.003
Median	+0.005	+0.002
% change from baseline		
Mean	+1.3	+1.0%
Median	+0.9	+0.4%

¹ Baseline consisted of a single measurement for each patient

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Blinding

The sponsor has referred to the trial as double-blind. The following text from page 13 of the Final Report, however, describes what seems to be a lack of full blinding for the drug product:

"...Because the two products were presented in bottles that differed in size and color, the patients were requested not to discuss the bottles with the study personnel. Questions regarding the bottles were to be addressed to study pharmacist or designee, who was not blinded and who was able to answer such questions without breaking the blind. Each study site had designated a qualified staff member for this purpose."

The situation described above is similar to so-called "A/B blinding" in which treatment assignments are not known explicitly but each drug is identified by the same letter code or number. A/B blinding can lead quickly to unblinding of the entire trial since all patients are unblinded as soon as any one patient is unblinded.

I do not think the lack of adequate blinding in Study 9904 calls the results into question. There is no reason to believe that the randomization of patients to treatment was adversely affected, i.e., there is no evidence of selection bias. Blinded assessment is probably not critical due to the objective nature of the endpoints. However, it is disingenuous to call the trial double-blind.

Suggestions for labelling

- The label should present results from the actual study design which was a comparison between Fortical and Miacalcin. This should include, at a minimum, the difference in treatment means for the primary endpoint and 90% confidence limits (or 95%, depending on the level of uncertainty that is considered appropriate).
- The label has several statements about statistically significant changes from baseline for PD endpoints (except PTH). The statements refer primarily to the Fortical group and one or all of the 1, 2 and 3-month time points. A table format would provide a better presentation of the data and should include % changes from baseline at 12 weeks for clinically important PD endpoints. The Table should include data from both treatment groups, without statements about statistical significance.

-- The effect of Fortical for PD endpoints measured at weeks 4 and 8 could reference the Figure for β -CTX in the proposed label with a statement that effects seen at 4 weeks persisted during the entire 12 week observation period similar to the time course shown in the Figure.

-- The differences between my results and the sponsor's for % change in β -CTX, NTX and urinary DPD will need to be resolved for any endpoints that are labelled.

- Any labeled BMD results can be treated as in the bullet above, i.e. in a Table showing % changes from baseline at 24 weeks in both groups for appropriate BMD endpoints.
- The trial should not be described as double-blind
- The Clinical Pharmacology section of the label cites fracture data from PROOF. These data were reviewed in a previous submission but not labelled. The fracture data should be removed from the label.

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Todd Sahlroot
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