CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-406

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-406	Submission Date(s): March 05, 2003; April 3, 2003, and May 12, 2003
Brand Name	Fortical®
Generic Name	Calcitonin-salmon
Reviewer	Wei Qiu, Ph.D.; Jaya Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Division of Metabolic and Endocrine Drug Products
Sponsor	Unigene Laboratories, Inc.
Relevant IND(s)	59,664
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Nasal spray in 3.5 mL fill
Indication	Treatment of postmenopausal osteoporosis

1 Executive Summary

Unigene Laboratories, Inc. submitted a 505(b)(2) application under NDA 21-406 for Fortical® (calcitonin-salmon) nasal spray in 3.5 mL fill for the treatment of postmenopausal osteoporosis on March 05, 2003, April 3, 2003, and May 12, 2003. Fortical® contains recombinant salmon calcitonin (rsCT) as the active ingredient.

Calcitonin (CT) is a 32-amino acid, carboxyl-terminal amidated polypeptide hormone secreted from thyroid gland. Calcitonin is barely detectable in the peripheral plasma of normal subjects under basal conditions. Calcitonin regulates calcium homeostasis primarily by inhibiting osteoclastic bone resorption.

The sponsor conducted three clinical studies to demonstrate comparable pharmacokinetic and pharmacodynamic properties for Fortical® Nasal Spray and the Reference Listed Drug (RLD), Miacalcin® Nasal Spray (calcitonin-salmon) approved for the treatment of postmenopausal osteoporosis in 1995. Miacalcin® contains synthetic salmon calcitonin (ssCT) as the active ingredient. The ssCT is currently available for subcutaneous (SC), intramuscular (IM), intravenous (IV), and intranasal (IN) administration.

The following three clinical studies were included in this NDA:

UGL-N9901---A pilot pharmacokinetic study conducted in 12 healthy volunteers to confirm the suitability of the multi-dose administration regimen for the assessment of pharmacokinetic parameters.

UGL-N9903---A single-blind, multi-dose, crossover bioequivalence study comparing Fortical® Nasal Spray with Miacalcin® Nasal Spray in normal volunteers

UGL-N9904---A phase II/III comparator-controlled study in 134 patients with postmenopausal osteoporosis to evaluate pharmacological equivalence in terms of biochemical markers of bone turnover

Pharmacokinetics study results showed that the to-be-marketed Fortical® formulation had 18% higher $C_{max100-120}$ and 24% higher $AUC_{100-120}$ values than the Miacalcin® Nasal Spray. Strict bioequivalence was not established between Fortical® Nasal Spray and Miacalcin® Nasal Spray.

Fortical® Nasal Spray and Miacalcin® Nasal Spray demonstrated a comparable pharmacological effect in terms of decrease in serum beta-CTx from baseline following 12-week treatment. Ratio (Fortical® Nasal Spray/ Miacalcin® Nasal Spray) of least square means of the decrease in serum beta-CTx from baseline was 98.76% and the 90% confidence interval was between 75.57% and 124.43%.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-406 submitted on March 05, 2003, April 3, 2003, and May 12, 2003 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

Not applicable.

2 Table of Contents

3 Summary of CPB Findings

Relative Bioavailability of Fortical® Nasal Spray Compared to Miacalcin® Nasal Spray:

Relative bioavailability of Fortical® Nasal Spray compared with Miacalcin® Nasal Spray was examined in a multi-dose regimen due to the low bioavailability of sCT given intranasally. This regimen allows for the achievement of blood levels of sCT, which can be accurately measured and characterized. The Fortical® Nasal Spray exhibited 18% higher $C_{max100-120}$ and 24% higher $AUC_{100-120}$ values than Miacalcin® Nasal Spray.

Following six doses of 400 IU Fortical® or Miacalcin® Nasal Spray at 20 minute interval, the 90% confidence intervals of ratios (Fortical®:Miacalcin® Nasal Spray) of geometric means for AUC_{100-}

$_{120}$ and $Cmax_{100-120}$ of sCT were 108.91 - 142.27% and 104.44 - 133.65%, respectively. Since the 90% confidence intervals of $AUC_{100-120}$ and $Cmax_{100-120}$ ratios were outside the 80% - 125% range, it was concluded that the rate and extent of absorption of Fortical® Nasal Spray and Miacalcin® Nasal Spray were not equivalent.

Relative Pharmacological Response of Fortical® Nasal Spray Compared to Miacalcin® Nasal Spray:

Decreases in serum beta-CTx from baseline, the primary pharmacodynamic endpoint, were comparable following 12-week treatments of Fortical® or Miacalcin® Nasal Spray. Ratio (Fortical® Nasal Spray/ Miacalcin® Nasal Spray) of least square means of the decrease in serum beta-CTx from baseline was 98.76% with 90% confidence interval between 75.57% and 124.43%. Besides serum beta-CTx, other biochemical markers of bone resorption including serum N-terminal telopeptide of collagen type I (NTx) and urinary deoxypyridinoline (DPD) were also assessed. Significant difference was not detected between treatments for either decrease in NTx or decrease in urinary DPD.

4 QBR

4.1 General Attributes

Q. What is the to-be-marketed formulation of Fortical® Nasal Spray?

Fortical® Nasal Spray contains recombinant salmon calcitonin as the active ingredient.

Table 1. Composition of Fortical® Nasal Spray

Component	Fortical® Nasal Spray
sCT (IU/mL)	
Sodium Chloride	
Tween 80	
Hydrochloric acid	
Sodium hydroxide	
Citric acid	
Phenylethyl alcohol	
Benzyl alcohol	

4.2 General Biopharmaceutics

Q. Is the Fortical® nasal spray bioequivalent to the currently marketed Miacalcin® nasal spray in normal volunteers? (Reviewed by Dr. Jaya Vaidyanathan)

Unigene has developed this recombinant salmon calcitonin (rsCT), which is identical to the chemically synthesized salmon calcitonin (ssCT), the active ingredient of currently marketed Miacalcin®, manufactured by Novartis. These differ in composition with respect to preservatives and buffer system. In order to develop a nasal formulation of rsCT, the sponsor has assessed the bioavailability of their formulation in comparison with nasal Miacalcin® ssCT product. Table 2 shows the composition of the salmon calcitonin nasal spray formulations used in the study UGL N9903.

Table 2. Composition of the salmon calcitonin nasal spray formulations.

Component	Fortical A	Fortical B	Miacalcin
sCT(IU/ml)			
Sodium chloride			
Tween 80			
Hydrochloric acid			
Sodium hydroxide			
Nitrogen			
Citric acid			
Phenylethyl alcohol			
Benzyl alcohol			
Benzylkonium chloride			

The bioequivalence study was done with repeated doses of Fortical A nasal spray, Fortical B nasal spray and Miacalcin nasal spray. To test the bioequivalence, a single blind, randomized three-way crossover Latin square design study was conducted in 47 healthy female volunteers. The three treatment periods were 1-week apart and involved administration of six intranasal doses of either, Fortical A, Fortical B, or Miacalcin®. On each dosing day the subjects received six 400-IU doses (200 IU per nostril) of Fortical A, Fortical B or Miacalcin, at 20-min intervals , for a total of 2400 IU over 100 min. Since the sponsor has indicated that the formulation of Fortical B used in this study is identical to that of the product intended for marketing, Fortical® nasal spray, the review will primarily focus on bioequivalence of Fortical B and the reference product. Summary of the pharmacokinetic analysis and statistical results are shown in **Tables 3** and **4** and the plasma concentration vs. time profiles shown in **Figure 1**.

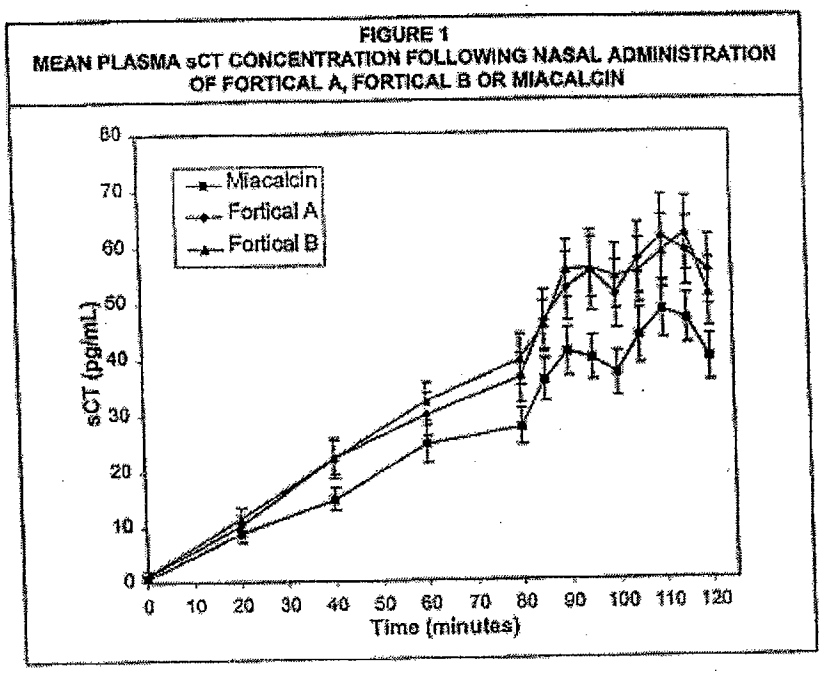
Table 3: Summary of calcitonin-salmon pharmacokinetic parameters (N= 47).

PK parameter	Arithmetic mean (± SD)	
	Miacalcin® nasal spray (reference)	Fortical B nasal spray (test)
$C_{min}60$ (pg/ml)	23.6 (22.6)	31.6 (23.4)
$C_{min}80$ (pg/ml)	27.0 (21.4)	39.0 (30.4)
$C_{min}100$ (pg/ml)	36.9 (25.8)	54.1 (37.4)
$C_{min}120$ (pg/ml)	39.4 (27.5)	50.8 (41.0)
$C_{max\ 80\text{-}100}$ (pg/ml)	45.7 (29.4)	61.3 (40.5)
$C_{max\ 100\text{-}120}$ (pg/ml)	54.1 (34.7)	67.3 (47.1)
$T_{max\ 80\text{-}100}$ (min)	91.6 (5.2)	93.3 (4.8)
$T_{max\ 100\text{-}120}$ (min)	110.8 (5.0)	110.1 (6.6)
$AUC_{80\text{-}100}$ (pg.min/ml)	836 (462)	1061 (627)
$AUC_{100\text{-}120}$ (pg.min/ml)	977 (545)	1160 (777)

Table 4. Statistical Analysis of Calcitonin-Salmon pharmacokinetic parameters (Statistical analysis were performed using Winnonlin by the reviewer)

	Parameter	Geometric mean		Point Estimate (%)	90%CI
Fortical B (Test)	$C_{max\ 100\text{-}120}$ (pg/ml)	55.98	Test vs Reference	118.14	(104.44, 133.65)
	$AUC_{100\text{-}120}$ (pg.min/ml)	890.96		124.48	(108.91, 142.27)
Miacalcin (Reference)	$C_{max\ 100\text{-}120}$ (pg/ml)	47.39			
	$AUC_{100\text{-}120}$ (pg.min/ml)	715.75			

Figure 1. Mean Calcitonin-salmon plasma concentration vs. time profiles.



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The Fortical B formulation had a higher $C_{max100\text{-}120}$ and $AUC_{100\text{-}120}$ values than the Miacalcin® Nasal Spray formulation. The 90% CI for the ratio of geometric means of Fortical B and the reference product $C_{max100\text{-}120}$ was (90.23, 129.17) and that for $AUC_{100\text{-}120}$ was (96.56, 129.31). The reviewer repeated the statistical analysis using WinNonlin and obtained the 90% CI for the ratio of geometric means of $C_{max100\text{-}120}$ to be (104.44, 133.65) and that for $AUC_{100\text{-}120}$ to be (108.91, 142.27). Since the upper 90% confidence interval for the geometric mean for both C_{max} and AUC fell outside the bioequivalence goal post of 80-125%, the Fortical nasal spray is not bioequivalent to the commercial product.

Q. What was the relative pharmacological response of Fortical® Nasal Spray compared to Miacalcin® Nasal Spray?

Fortical® Nasal Spray and Miacalcin® Nasal Spray demonstrated comparable pharmacological response in terms of decreases in serum beta-CTx from baseline following 12-week treatment. Ratio (Fortical® Nasal Spray/ Miacalcin® Nasal Spray) of least square means of the decrease in serum beta-CTx from baseline was 98.76% with the 90% confidence interval between 75.57% and 124.43%.

The pharmacodynamics of the to-be-marketed formation of Fortical® Nasal Spray and Miacalcin® Nasal Spray were compared in a controlled double-blind, randomized study in postmenopausal osteoporosis patients (UGL-N9904). One hundred and thirty four patients were enrolled and 118 completed the study. This study was conducted at three sites in the US and two sites in the UK. Each subject was given either product 200 IU per day, for 6 months. The selected dose is the recommended dose for Miacalcin® Nasal Spray. The patients also received a daily supplement of 1200 mg calcium and 400 IU vitamin D.

Biochemical markers of bone resorption including serum beta-CTx, N-terminal telopeptide of collagen type I (NTx) and urinary deoxypyridinoline (DPD) were assessed after 4, 8, and 12 week treatment. The primary pharmacodynamic endpoint is the decrease in serum beta-CTx values from baseline following 12 weeks of treatment. Although biochemical markers of bone formation including serum bone specific alkaline phosphatase (BSAP), serum osteocalcin, and serum parathyroid hormone (PTH) were assayed at 12 weeks, they were not treated as secondary endpoints. The sponsor agreed that it was unlikely to see anything at 3 months in this study.

Serum beta-CTx

The serum beta-CTx data are summarized in **Table 5** and **Figure 2**. On average, change in serum beta-CTx from baseline to final time-point was -0.22 ng/mL for the Fortical® Nasal Spray treated patients and -0.23 ng/mL for the Miacalcin® Nasal Spray treated patients, respectively. The serum beta-CTx data obtained from both treatments were highly variable with CV% approximately 100%.

Table 5. Summary of Serum beta-CTx

Time-Point	Mean (SD) Observed Response (ng/mL)		Mean (SD) Change from Baseline (ng/mL)	
	Fortical® Nasal Spray	Miacalcin® Nasal Spray	Fortical® Nasal Spray	Miacalcin® Nasal Spray
Baseline	0.61 (0.25)	0.55 (0.21)	--	--
Week 4	0.39 (0.25)	0.33 (0.23)	-0.21 (0.20)	-0.22 (0.19)
Week 8	0.35 (0.24)	0.32 (0.20)	-0.25 (0.18)	-0.22 (0.18)
Week 12	0.38 (0.21)	0.29 (0.22)	-0.23 (0.18)	-0.24 (0.18)
Final	0.38 (0.21)	0.32 (0.23)	-0.22 (0.18)	-0.23 (0.18)

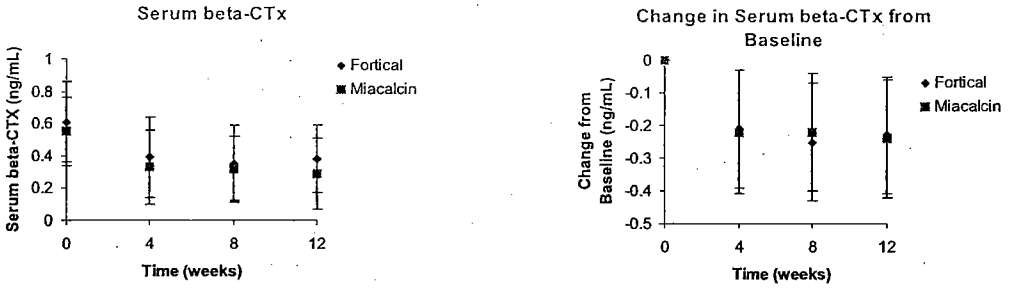

Figure 2. Mean (SD) serum beta-CTx (left panel) and mean (SD) change in serum beta-CTx (right panel) following treatment with Fortical® or Miacalcin® Nasal Spray

This reviewer utilized the bioequivalence approach to test the change in serum beta-CTx from baseline to final time-point. Ratio (Fortical® Nasal Spray/ Miacalcin® Nasal Spray) of Least Square Means for the change in serum beta-CTx from baseline to final time-point was 98.76% and the 90% confidence interval was between 75.57% and 124.43% (**Table 6**).

Table 6. Analysis of Bioequivalence Approach

PD parameter	LSM (SE)		Ratio of LSM (%)	90% CI (%)
	Fortical® Nasal Spray	Miacalcin® Nasal Spray		
Change in Serum beta-CTx (ng/mL)	-0.2231 (0.0235)	-0.2259 (0.0235)	**98.76**	**75.57-124.43**

Taking the high variability of serum beta-CTx into consideration, it was concluded that Fortical® Nasal Spray and Miacalcin® Nasal Spray had comparable pharmacological activity.

Serum NTx

The serum NTx response is summarized in **Table 7** and **Figure 3**. The mean decrease from baseline with treatment of Fortical® and Miacalcin® Nasal Spray were 2.48 and 2.42 nM BCE, respectively. Ratio (Fortical® Nasal Spray/Miacalcin® Nasal Spray) of least square mean for the decrease in serum NTx from baseline was 1.03. The 90% confidence interval was between 69.61% to 130.39%. The serum NTx data were also highly variable with CV% more than 100%.

Table 7. Summary of Serum NTx

Time-Point	Mean (SD) Observed Response (nM BCE)		Mean (SD) Change from Baseline (nM BCE)	
	Fortical® Nasal Spray	Miacalcin® Nasal Spray	Fortical® Nasal Spray	Miacalcin® Nasal Spray
Baseline	14.75 (4.02)	13.81 (3.68)	--	--
Week 4	12.34 (3.80)	11.78 (3.87)	-2.47 (3.16)	-1.98 (2.97)
Week 8	12.23 (3.41)	11.38 (3.47)	-2.47 (2.47)	-2.31 (2.49)
Week 12	12.37 (3.63)	11.06 (3.45)	-2.45 (2.55)	-2.69 (2.03)
Final	12.35 (3.52)	11.30 (3.51)	-2.48 (2.52)	-2.42 (2.23)

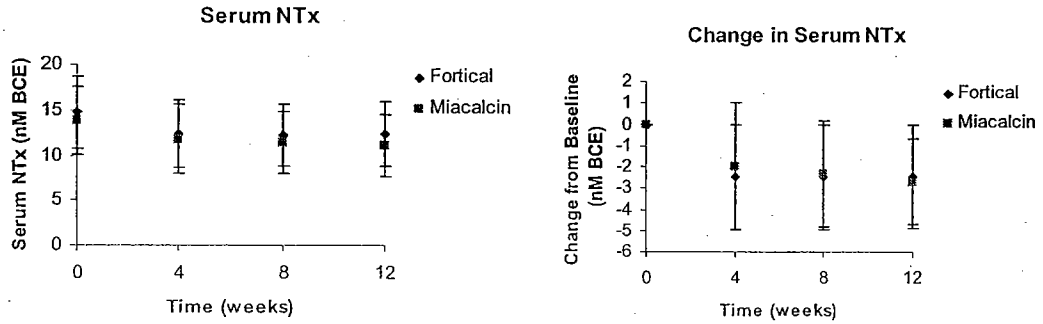

Figure 3. Mean (SD) serum NTx (left panel) and mean (SD) change in serum NTx (right panel) following treatment with Fortical® or Miacalcin® Nasal Spray

Urinary DPD

The urinary DPD response is summarized in **Table 8** and **Figure 4**. The mean decrease from baseline with treatment of Fortical® and Miacalcin® Nasal Spray were 0.97 and 0.58 nM/mM, respectively. Ratio (Fortical® Nasal Spray/Miacalcin® Nasal Spray) of least square mean for the decrease in urinary DPD from baseline was 1.68. The 90% confidence interval was between -72.44% and 272.44%. The urinary DPD data is highly variable with CV% more than 200%.

Table 8. Summary of Urinary DPD

Time-Point	Mean (SD) Observed Response (nM/mM creatinine)		Mean (SD) Change from Baseline (nM/mM creatinine)	
	Fortical® Nasal Spray	Miacalcin® Nasal Spray	Fortical® Nasal Spray	Miacalcin® Nasal Spray
Baseline	9.02 (3.07)	8.09 (2.68)	--	--
Week 4	8.13 (3.00)	7.12 (2.71)	-0.75 (2.18)	-0.97 (2.42)
Week 8	8.01 (2.74)	7.34 (2.35)	-0.94 (2.33)	-0.80 (1.79)
Week 12	7.75 (2.90)	7.36 (2.75)	-1.22 (2.11)	-0.78 (2.03)
Final	7.91 (2.86)	7.51 (3.27)	-0.97 (2.38)	-0.58 (2.66)

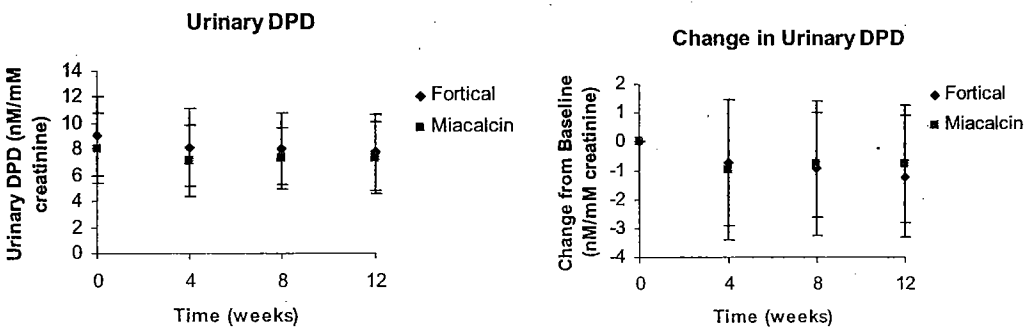

Figure 4. Mean (SD) Urinary DPD (left panel) and mean (SD) change in urinary DPD (right panel) following treatment with Fortical® or Miacalcin® Nasal Spray

Bone Formation Markers: Serum BSAP, Osteocalcin, and PTH

The serum BSAP, osteocalcin, and PTH data are summarized in **Table 9**. The mean decrease in serum BSAP with treatment of Fortical® and Miacalcin® Nasal Spray was 2.60 and 2.63 U/L, respectively. The mean decrease in serum osteocalcin with treatments of Fortical® and Miacalcin® Nasal Spray was 5.80 and 6.00 ng/mL, respectively. The mean decrease in serum PTH with treatment of Fortical® and Miacalcin® Nasal Spray was 1.15 and 4.95 pg/mL, respectively. Since 12 week is too short to examine bone formation markers adequately, these results are not conclusive. These bone formation markers exhibited even higher variability than bone resorption markers.

Table 9. Summary of Serum BSAP, Osteocalcin, and PTH

Time-Point	Mean (SD) Observed Response		Mean (SD) Change from Baseline	
	Fortical® Nasal Spray	Miacalcin® Nasal Spray	Fortical® Nasal Spray	Miacalcin® Nasal Spray
	Serum BSAP (U/L)			
Baseline	28.78 (9.77)	26.09 (7.27)	--	--
Week 12	25.86 (8.42)	24.54 (7.33)	-2.48 (4.14)	-2.73 (3.40)
Final	26.28 (8.88)	24.74 (7.88)	-2.60 (4.08)	-2.63 (3.41)
	Serum Osteocalcin (ng/mL)			
Baseline	32.41 (10.64)	30.05 (9.41)	--	--
Week 12	27.10 (9.92)	24.28 (7.28)	-5.67 (4.79)	-6.08 (4.56)
Final	27.05 (9.71)	24.76 (7.75)	-5.80 (4.86)	-6.00 (4.48)
	Serum PTH (pg/mL)			
Baseline	38.80 (15.00)	38.93 (11.81)	--	--
Week 12	36.59 (14.42)	35.59 (16.18)	-1.06 (8.14)	-5.27 (10.54)
Final	36.19 (14.28)	35.87 (15.90)	-1.15 (8.19)	-4.95 (10.48)

4.3 Analytical

Q. Was the analytical assay for the calcitonin-salmon plasma concentration validated?

To determine the concentration of sCT in human plasma after dosing with sCT, a commercially available sCT ELISA (ultra-sensitive salmon calcitonin ELISA,) was adapted and optimized for the quantitative determination of sCT in human plasma. The lower limit of quantitation (LLQ) of the radioiummunoassay for determining sCT in plasma was 10 pg/ml. For calculation of all AUC values, concentrations below the LLQ were assigned a value of zero, if they occurred at the beginning or end of the profile. The criteria for

acceptance of the assay included r squared values of standard curves ≥ 0.98; the %CV of the OD readings of standards and QC samples was ≤ 25%. The linearity of the method was evaluated by analysis of seven rsCT standards from 10.0 to 160.0 pg/ml in normal human plasma. The results indicated an inter-assay precision of < 14% and inter-assay accuracy between 95 and 103%.

5 Labeling

Under **CLINICAL PHARMACOLOGY** Section

The information below, describing the clinical pharmacology of calcitonin, has been derived from studies with *injectable* calcitonin. The mean bioavailability of commercially available calcitonin-salmon product following nasal spray administration is approximately 3% of that of injectable calcitonin in normal subjects. Therefore, the conclusions concerning the CLINICAL PHARMACOLOGY of this preparation may be different.

Under **CLINICAL PHARMACOLOGY**

Pharmacokinetics and Drug Metabolism

The pharmacokinetic parameters of Fortical® Nasal Spray were obtained after multiple dose administration by the nasal route in normal volunteers. Fortical® (calcitonin-salmon) is rapidly absorbed by the nasal mucosa. Peak plasma concentrations of drug appear approximately 10 minutes after nasal administration. The half-life (t1/2) of elimination of calcitonin-salmon is calculated to be 22.8 minutes. Absorption of nasally administered calcitonin has not been studied in postmenopausal women.

Under **CLINICAL PHARMACOLOGY** Section **Pharmacodynamics** Subsection
(Since Miacalcin® Nasal Spray labeling does not have this section, the inclusion of this section may cause misleading. Therefore, the whole section is recommended to be deleted.)

6 Appendix

6.1 proposed labeling

19 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

6.2 Individual Study Reviews

STUDY SYNOPSIS

Name of Sponsor:	Unigene Laboratories, Inc.
Name of Finished Product:	Forcaltonin A and Forcaltonin B Nasal Spray
Name of Active Ingredient:	recombinant salmon calcitonin (rsCT)
Study Title:	Safety tolerability and pharmacokinetics of repeated intranasal doses of Forcaltonin, a recombinant salmon calcitonin, compared with Miacalcin, an established synthetic salmon calcitonin (UGL-N9901)
Principal Investigator:	Steve Warrington MA MD FRCP FFPM
Study Center:	Hammersmith Medicines Research, Central Middlesex Hospital, Acton Lane, London NW10 7NS
Publication (reference):	None
Study Period:	Phase of Development: 1 February - March, 2000
Objectives:	To evaluate the pharmacokinetics of 2 formulations of rsCT, Forcaltonin A and B, and a currently marketed synthetic salmon calcitonin (ssCT), Miacalcin, after repeated doses of 400 IU each, and to assess bioequivalence of the 3 formulations
Methodology:	During each of three treatment periods in this three-way crossover study, each subject received five 400-IU doses of test drug at 20-minute intervals, a total of 2000 IU over a period of 80 minutes. Blood samples were collected at regular intervals after each dose
No. of Subjects (planned and completed):	12 subjects were planned and 12 subjects completed the study
Diagnosis and Main Criteria for Inclusion:	Subjects were healthy female volunteers, between the ages of 18 and 45 years, with a body mass index in the range 19-30
Test Article, Dose and Mode of Administration, Lot no:	Five 400-IU doses, of each of the following test drugs, administered nasally: • Forcaltonin A Nasal Spray, (Unigene), Lot no. CTM0001 • Forcaltonin B Nasal Spray, (Unigene), Lot no. CTM0002
Treatment Duration:	Subjects received five treatments over 80 minutes during each of three treatment phases

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STUDY SYNOPSIS (cont'd)

Name of Sponsor:	Unigene Laboratories, Inc.
Name of Finished Product:	Forcaltonin A and Forcaltonin B Nasal Spray
Name of Active Ingredient:	recombinant salmon calcitonin (rsCT)
Reference therapy, Dose and Mode of Administration, Lot. No:	Miacalcin® (Novartis, formerly Sandoz), five 400-IU doses, administered nasally, Lot no. 339 A 6994
Criteria for Evaluation Serum sCT Concentration: Pharmacokinetic Analysis: Safety:	 sCT was measured in the serum at various timepoints by radioimmunoassay. A population pharmacokinetic program (P. Pharm) was used to determine pharmacokinetic parameters of Clearance (CL), Absorption Rate (Ka), Volume of Distribution (VC) and half-life ($t_{1/2}$). Adverse events, clinical laboratory evaluations, physical exam/ECG findings and vital sign assessments.
Results and Conclusions sCT Concentrations: Pharmacokinetic Conclusions: Safety Results:	 Mean AUC_{80-100} values calculated from the sCT profiles for Forcaltonin A, Forcaltonin B and Miacalcin were 666, 733 and 872 pg*min/mL, respectively. Mean $C_{max, 80-100}$ values for the three treatments were 38.6, 43.2 and 49.7 pg/mL, respectively. Pharmacokinetic modeling was used to verify that the multiple-dose treatment regimen resulted in a steady state serum concentration for sCT after the fifth dose. The $t_{1/2}$ was determined to be 22.8 minutes. The most frequently reported treatment-related AEs were nausea, rhinitis and dizziness. A few clinically-significant changes in hemoglobin or HCT values were observed and were attributable to the volume of blood withdrawn for sampling. All other safety assessments, including physical examinations, vital sign assessments and ECGs, were within normal limits.

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STUDY SYNOPSIS

Name of Sponsor:	Unigene Laboratories, Inc.
Name of Finished Product:	Fortical A and Fortical B Nasal Spray
Name of Active Ingredient:	recombinant salmon calcitonin (rsCT)
Study Title:	A single-blind, multi-dose, crossover bioequivalence study comparing Fortical® Nasal Spray with Miacalcin® Nasal Spray in normal volunteers (UGL-N9903)
Principal Investigator:	David Hoelscher, MD
Study Center:	PPD Development Clinical Lab, 706A Ben White Blvd West, Austin, TX 78704-7016
Publication (reference):	None
Study Period:	Phase of Development: 1 February - March, 2000
Objectives:	To evaluate the pharmacokinetics of 2 formulations of rsCT, Fortical A and B, and a currently marketed synthetic salmon calcitonin (ssCT), Miacalcin, after repeated doses of 400 IU each, and to assess bioequivalence of the 3 formulations.
Methodology:	During each of three treatment periods in this three-way crossover study, each subject received six 400-IU doses of test drug at 20-minute intervals, a total of 2400 IU over a period of 100 minutes. Blood samples were collected at regular intervals after each dose.
No. of Subjects (planned, enrolled and completed):	48 subjects were planned, 47 were enrolled and 45 completed the study.
Diagnosis and Main Criteria for Inclusion:	Subjects were healthy female volunteers, between the ages of 18 and 45 years, with a body mass index in the range 19-30.
Test Article, Dose and Mode of Administration, Lot no:	Six 400-IU doses, of each of the following test drugs, administered nasally: • Fortical A Nasal Spray, (Unigene), Lot no. CTM0010 • Fortical B Nasal Spray, (Unigene), Lot no. CTM0011
Treatment Duration:	Subjects received six treatments over 100 minutes during each of three treatment phases.

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STUDY SYNOPSIS (cont'd)

Name of Sponsor:	Unigene Laboratories, Inc.
Name of Finished Product:	Fortical A and Fortical B Nasal Spray
Name of Active Ingredient:	recombinant salmon calcitonin (rsCT)
Reference therapy, Dose and Mode of Administration, Lot. No:	Miacalcin® (Novartis, formerly Sandoz), six 400-IU doses, administered nasally, Lot No. 379B2540
Criteria for Evaluation Plasma sCT Concentration: Pharmacokinetic Analysis: Safety:	 sCT measured in the plasma at several time-points by ELISA. Plasma sCT profiles used to determine AUC and C_{max} at steady-state for the three treatments. Adverse events, clinical laboratory evaluations, physical exam, nasal exam, ECG findings and vital sign assessments.
Results and Conclusions sCT Concentrations: Pharmacokinetic Conclusions: Safety Results:	 $AUC_{100\text{-}120}$ was 1155, 1160 and 977 pg•min/mL for Fortical A, Fortical B and Miacalcin, respectively. $C_{max100\text{-}120}$ was 69.0, 67.3 and 54.1 pg/mL for Fortical A, Fortical B and Miacalcin, respectively. The pharmacokinetics of all three formulations were highly variable, with confidence intervals of 60 to 90%. Not all subject profiles contained enough data to calculate half-life. Half-life values for Fortical A, Fortical B and Miacalcin were 30.1 (N=20), 25.4 (N=22) and 25.7 (N=26) for Fortical A, Fortical B and Miacalcin, respectively. There were no severe AEs and no serious or unexpected AEs reported. There were no withdrawals due to AEs. No significant differences were found between the three formulations with regard to the incidence of AEs. The most common AEs were nausea, rhinitis, vomiting and headache.

STUDY SYNOPSIS

Name of Sponsor:	**Unigene Laboratories, Inc.**
Name of Finished Product:	**Fortical® Nasal Spray**
Name of Active Ingredient:	**recombinant salmon calcitonin (rsCT)**
Study Title:	Pharmacologic response and tolerability to Fortical® Nasal Spray and Miacalcin® Nasal Spray in postmenopausal osteoporotic women: A phase II/III, double-blind, multiple dose, parallel study
Principal Investigators and Study Sites:	Dr. Devapriya Dev Synexus Manchester Manchester, UK Dr. Jean Fraser Synexus Wrightington Wigan, UK Dr. Robert Lang The Osteoporosis Diagnostic and Treatment Center Hamden, CT, USA Madison, CT, USA Dr. John F. Aloia Bone Mineral Research Center Mineola, NY, USA
Phase of Development:	2/3
Study Period:	March 10, 2000 – May 23, 2001
Objectives:	To demonstrate pharmacological equivalence of Fortical Nasal Spray with Miacalcin® Nasal Spray in postmenopausal osteoporotic women, using biochemical markers of bone resorption, and to assess the tolerability of the two formulations.
Methodology:	Randomized, parallel-group, double blind study.
No. of Subjects (planned, enrolled and completed):	134 subjects were planned, 134 were enrolled and 118 subjects completed the study.
Diagnosis and Main Criteria for Inclusion:	Women with postmenopausal osteoporosis (T score of at least -2.5 SD), with an accelerated rate of bone turnover as indicated by an elevated level of serum C-terminal telopeptide of collagen type-I (β-CTx).
Test Article, Dose and Mode of Administration, Lot no:	**Fortical Nasal Spray, 200 IU per day, intranasally, Lot no. CTM0011**
Treatment Duration:	**24 weeks**
Reference Therapy, Dose and Mode of Administration, Lot no:	**Miacalcin Nasal Spray (Novartis), 200 IU per day, intranasally, Lot no. 399B3525**

STUDY SYNOPSIS (cont'd)

Name of Sponsor:	Unigene Laboratories, Inc.
Name of Finished Product:	Fortical Nasal Spray
Name of Active Ingredient:	recombinant salmon calcitonin (rsCT)
Criteria for Evaluation	
Efficacy:	Primary efficacy criterion was a change in β-CTx after 12 weeks of treatment. Other biochemical indices of bone turnover, as well as BMD before and after treatment, were also measured.
Safety:	Adverse events, clinical laboratory evaluations, physical exam, nasal exam, ECG findings and vital sign assessments.
Results and Conclusions	
Efficacy:	Both treatment groups had statistically significant reductions in serum β-CTx, NTx, BSAP and osteocalcin, at urinary DPD, at all measured time-points. The between-group difference in mean change in serum β-CTx was 0.01 ng/mL, which is contained within the boundries of the 95% confidence interval. Thus, Fortical and Miacalcin are shown to have equivalent pharmacologic activity with regard to the suppression of bone turnover, as indicated by the reduction in serum β-CTx. BMD increased significantly after 24 weeks of treatment in both treatment groups for AP spine ($p \leq 0.006$). In the Fortical and Miacalcin groups, the increase in BMD at this site was 1.3% and 1.4%, respectively. For the lateral spine, the increases in BMD were not statistically significant for either treatment group. For the femur, the increase was significant in the Fortical group only.
Safety Results:	Fortical Nasal Spray and Miacalcin Nasal Spray were clinically safe and reasonably well-tolerated in this study. The AEs seen are consistent with the known effects of calcitonin nasal spray. The most common treatment-related AEs for both treatment groups were rhinitis, headache, epistaxis, nausea, and rash. There were no statistically significant differences between treatment groups in the number of patients reporting any AE. There were no deaths and no treatment-related serious AEs reported during this study for either Fortical or Miacalcin Nasal Spray.

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/s/

Wei Qiu
12/11/03 09:53:58 AM
BIOPHARMACEUTICS

Hae-Young Ahn
12/17/03 04:58:33 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	21-406	Brand Name	FORTICAL®
OCPB Division	II	Generic Name	calcitonin-salmon (recombinant)
Medical Division	DMEDP, HFD-510	Drug Class	hormone
OCPB Reviewer	S.W. Johnny Lau	Indication(s)	treat postmenopausal osteoporosis
OCPB Team Leader	Hae-Young Ahn	Dosage Form	nasal spray
		Dosing Regimen	200 IU/day
Date of Submission	3/5/2003	Route of Administration	nasal
Estimated Due Date of OCPB Review		Sponsor	Unigene Laboratories, Inc.
PDUFA Due Date	1/5/2004	Priority Classification	standard
Division Due Date	12/5/2003		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	x	1		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				

solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; multi dose:	x	1		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?		The sponsor should: • state whether the formulation tested in Study UGL-N9904 was identical to the to-be-marketed formulation Clinical Pharmacology and Biopharmaceutics reviewer will phone the sponsor for this information.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS	
NDA:	**21-406 (reference IND 59,664)**
Compound:	recombinant calcitonin-salmon (FORTICAL®, 200 IU/nasal spray)
Sponsor:	Unigene Laboratories, inc.
Submission Date:	March 5, 2003
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

NDA 21-406 is a 505 (b)(2) NDA seeking approval for the 200 IU recombinant calcitonin-salmon/0.09 mL nasal spray (FORTICAL®) once daily to treat osteoporosis in postmenopausal women. Synthetic calcitonin-salmon (200 IU/0.09 mL) is marketed as Miacalcin® for the same indication. These 2 products differ in preservative and buffer system. Per the Division of Metabolic and Endocrine Drug Products' February 6, 2001 letter to the sponsor, FORTICAL® nasal spray will not receive an AB rating due to non-bioequivalence to Miacalcin®.

Findings

- The sponsor conducted 2 clinical pharmacology and biopharmaceutics studies to support the Human Pharmacokinetics and Bioavailability section (Section 6) of this NDA (see Attachment).
- Study UGL-N9901 was a pilot to study multi-dose PK and citric acid's effect on the nasal absorption of recombinant calcitonin-salmon in 12 healthy volunteers.
- Study UGL-N9903 was a multi-dose bioequivalence study between the recombinant calcitonin-salmon nasal spray and Miacalcin® Nasal Spray in 47 volunteers.
- The sponsor conducted a Phase 2/3 comparator-controlled study (UGL-N9904) for 24 weeks in 134 postmenopausal osteoporosis patients. This study measured the treatment effect and safety profiles of Fortical® or Miacalcin® on serum and urine bone turnover markers and bone mineral density (BMD; screening and 24-week). Per April 16, 2003 filing meeting, Dr. Bruce Schneider, medical reviewer, will review the BMD and safety data for this study. The clinical pharmacology and biopharmaceutics review team will review the serum and urine bone turnover markers data for Study UGL-N9004. This study's electronic data in SAS transport files are in the electronic document room but the hard study reports are not in Section 6.
- One of the 2 formulations tested in Study UGL-9903 (Fortical B®) was identical to the to-be-marketed formulation.
- Study reports, bioanalytical reports, and validation reports for studies UGL-N9901 and UGL-9903 were provided.
- The sponsor provided annotated proposed labeling for review.
- The sponsor also provided 3 study reports ( ) comparing the subcutaneous injections of Fortical™ to Miacalcic® in the addendum of Section 6.

Comment

The sponsor should:

- state whether the formulation tested in Study UGL-N9904 was identical to the to-be-marketed formulation

Attachment starts here.

TABLE 3F-1
SUMMARY OF HUMAN PHARMACOKINETIC STUDIES

Study No.	Title / Dose & Study Population	Analytical Method and Body Fluid Used	Test Products	Location of Full Study Report
UGL-N9901	"Safety tolerability and pharmacokinetics of repeated intranasal doses of Forcaltonin™, a recombinant salmon calcitonin (rsCT), compared with Miacalcin®, an established synthetic salmon calcitonin (ssCT)" 400 IU intranasal dose (200 IU in each nostril) every 20 minutes x 5 doses (over 80 minutes) in 12 healthy female volunteers, aged 18 to 45 years, with a body weight between 45 to 75 kg, and a body mass index 19 to 30 kg/m^2	Salmon Calcitonin Radioimmunoassay Kit ( ) Human Serum	Forcaltonin A	Volume 24, Page 030
			Forcaltonin B	
			Miacalcin	
UGL-N9903	"A single-blind, multi-dose, crossover bioequivalence study comparing Fortical Nasal Spray with Miacalcin® Nasal Spray in normal volunteers" 400 IU intranasal dose (200 IU in each nostril) every 20 minutes x 6 doses (over 100 minutes) in 47 healthy female volunteers, aged 18 to 45 years, with a body weight between 45 to 75 kg, and a body mass index 19 to 30 kg/m^2	Salmon Calcitonin ELISA ( ) Human Plasma	Fortical A	Volume 26, Page 001
			Fortical B*	
			Miacalcin	

* Fortical B used in this study is identical to Fortical Nasal Spray, the product intended for marketing

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/s/

S.W. Johnny Lau
4/16/03 03:46:50 PM
BIOPHARMACEUTICS

Hae-Young Ahn
4/17/03 09:18:00 AM
BIOPHARMACEUTICS

NDA 21-406
Fortical (salmon calcitonin) Nasal Spray

No DSI audits were requested.