CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-406

MEDICAL REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: August 5, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-406
Fortical (calcitonin-salmon) Nasal Spray
Unigene Labs
Treatment of osteoporosis in women > 5 years post-menopause

SUBJECT: NDA review issues and recommended action

Summary of issues

This is the second review cycle for this application for a synthetic salmon calcitonin nasal spray product. The original application was received March 3, 2003 and an "approvable" action was taken by the division on December 31, 2003. Although the biopharmaceutics and clinical efficacy data were sufficient to support approval, relying in part on the agency's previous findings with Miacalcin, there were no immunogenicity data submitted. Additionally, several CMC deficiencies were identified requiring resolution.

Dr. Colman's memo dated December 29, 2003 summarizes the data in support of the efficacy of Fortical in the treatment of osteoporosis, which lead to the conclusion that, with regard to effects on bone, Fortical is clinically indistinguishable from Miacalcin. I concur.

The sponsor submitted a complete response to the action letter on September 16, 2004, which included the requested immunogenicity data based on analyses of stored serum samples from their pivotal 24-week study comparing Fortical to Miacalcin on markers of bone turnover and on change from baseline in bone mineral density by DEXA at selected skeletal sites. Dr. Kehoe has reviewed the immunogenicity data and finds that there were no differences in the immunogenicity of Fortical and Miacalcin. I concur with her conclusion.

Dr. Kehoe has recommended in both of her reviews that consideration be given to exacting a commitment on the part of the sponsor to conduct a phase 4 trial to evaluate the efficacy of Fortical in prevention of fractures in the target population. Dr. Colman addressed this in his memo dated December 31, 2003, stating that such a study should not be required as a condition of approval, and I concur. The issue of the need for fracture efficacy data to support approval of this product has furthermore been addressed in the Agency's response to a Citizen Petition related to Fortical.

The CMC issues have all been resolved.

There are no outstanding scientific or regulatory issues.

Recommendation
Pending final agreement on labeling, this application may be approved.

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/s/

David Orloff
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-406
Submission Code	AZ
Letter Date	Sept 15, 2004
Stamp Date	Sept 16, 2004
PDUFA Goal Date	March 16, 2005
Reviewer Name	Theresa Kehoe
Review Completion Date	Dec 9, 2004
Established Name	Calcitonin-salmon
(Proposed) Trade Name	Fortical
Therapeutic Class	Bone, Mineral Metabolism
Applicant	Unigene, Inc
Priority Designation	S
Formulation	Nasal spray
Dosing Regimen	200IU
Indication	Osteoporosis
Intended Population	Postmenopausal women

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Fortical 200 IU daily be approved for the treatment of osteoporosis in women greater than 5 years post menopause.

1.2 Recommendation on Postmarketing Actions

1.2.2 Required Phase 4 Commitments

This reviewer recommends consideration be given for a company commitment to do a phase IV fracture prevention trial. The company is aware of the need for fracture prevention data with calcitonin nasal spray treatment. To date, an adequate clinical trial evaluating salmon calcitonin's efficacy in fracture prevention has not been conducted.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Unigene Laboratories, Inc. has submitted this 505(b)(2) application for approval of the marketing of a recombinant salmon calcitonin (Fortical®) nasal spray for the treatment of postmenopausal osteoporosis. The initial NDA submission provided data showing pharmacokinetic and pharmacodynamic equivalence to the currently marketed synthetic salmon calcitonin (Miacalcin) nasal spray product. The clinical development program consisted of 3 clinical trials: a pilot pharmacokinetic trial, a pharmacokinetic bioequivalence trial and a larger active-comparator pharmacodynamic equivalence trial. This submission provides the immunogenicity data requested in the initial action letter. Two immunogenicity studies were performed on archived samples from the 24-week study, UGL-N9904.

1.3.2 Efficacy

No new efficacy data were submitted in response to the Approvable Letter. In review of the initial 505(b)(2) submission, conclusions regarding the efficacy of Fortical were based primarily on the Agency's prior approval of Miacalcin Nasal Spray and the results of a 24-week, active-controlled, pharmacodynamic bioequivalence study in which changes in serum levels of β-CTx were similar for women treated with Fortical and Miacalcin.

1.3.3 Safety

No new studies have been conducted with the Fortical nasal spray formulation since submission of the original NDA. In the safety update data from studies with other formulations of rsCT (oral and injectable), no new safety concerns were noted.

The two studies conducted to evaluate Fortical's human immunogenicity profile were performed using archived samples from the 24-week treatment study UGL-N9904. The treatment duration of this 6-month study should be sufficient to allow antibody formation. There were no differences between Fortical and Miacalcin with regard to the ability to cause binding or neutralizing antibody formation. The overall impact of calcitonin antibody formation on therapeutic efficacy remains unclear. Concern regarding anaphylactic reactions to this salmon calcitonin product remain, and labeling should include language regarding allergic reactions similar to the Miacalcin labeling.

1.3.4 Dosing Regimen and Administration

Unigene Laboratories is requesting approval of a single dose of recombinant salmon calcitonin (Fortical) nasal spray: 200 IU daily. The currently marketed synthetic salmon calcitonin nasal spray dose is also 200 IU daily.

1.3.6 Special Populations

Fortical is indicated for the treatment of postmenopausal women with osteoporosis. All of the subjects enrolled in the Fortical trials were women. The efficacy and safety of recombinant salmon calcitonin nasal spray has not been evaluated in the pediatric population. Nearly all subjects in the submitted Fortical studies were Caucasian. Therefore, the effects of race/ethnicity on the safety and efficacy of recombinant salmon calcitonin (Fortical) cannot be assessed.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

In this submission, Unigene Laboratories, Inc. provides a complete response to the deficiencies noted in the Approvable Letter of December 31, 2003.

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. The primary action of calcitonin is regulation of calcium homeostasis principally through inhibition of osteoclastic bone resorption.

2.2 Currently Available Treatment for Indications

In addition to Miacalcin nasal spray (synthetic salmon calcitonin), other medications currently approved for the treatment of postmenopausal osteoporosis include the bisphosphonates alendronate sodium (Fosamax), risedronate sodium (Actonel) and ibandronate sodium (Boniva) as well as raloxifene (Evista) and teriparatide acetate (Forteo).

2.4 Important Issues With Pharmacologically Related Products

Salmon calcitonin (Miacalcin) nasal spray was initially approved in August, 1995 for the treatment of osteoporosis in women more than 5 years post menopause. There were 3 pivotal clinical trials evaluating the safety and efficacy of Miacalcin in the treatment of postmenopausal osteoporosis. After presentation to the Endocrine and Metabolic Advisory Committee, approval was based on bone mineral density and not fracture prevention. Approval was contingent on the completion of a phase IV fracture prevention trial. The fracture prevention trial, known as PROOF, was submitted as a labeling supplement in 1999 and was found not approvable, based on the ambiguous results of the statistical analyses of the fracture data. Other published trials have been conducted evaluating the use of Miacalcin nasal spray for the treatment of corticosteroid induced osteoporosis, treatment of osteoporosis following hip fracture and treatment of osteoporosis in men.

2.5 Presubmission Regulatory Activity

Unigene Laboratories, Inc. submitted a 505(b)(2) application for approval of the marketing of a recombinant salmon calcitonin (Fortical®) nasal spray for the treatment of postmenopausal osteoporosis in March, 2003. The initial application provided data showing pharmacokinetic and pharmacodynamic equivalence to the currently marketed synthetic salmon calcitonin (Miacalcin) nasal spray product. The application was found to be approvable contingent upon completion of adequate human immunogenicity studies. Unigene subsequently submitted a protocol for characterization of Fortical's human immunogenicity profile, in response to the Agency's

request. The protocol methods were found adequately validated and the company was allowed to proceed.

2.6 Other Relevant Background Information

A Citizen's Petition was submitted in January 2004 requesting that FDA not approve the Unigene NDA for Fortical, or any other NDA in which recombinant salmon calcitonin is the active ingredient, that contains only biochemical markers of bone turnover or bone mineral density data as proof of efficacy. As discussed above, data submitted from the PROOF trial was insufficient to allow labeling for osteoporosis fracture prevention.

It should also be noted that Miacalcin is approved and labeled for increasing bone mineral density in postmenopausal women, not for reduction of fracture risk. Fortical is recombinant salmon calcitonin and has the same primary, secondary, and tertiary chemical structures as Miacalcin, a synthetic salmon calcitonin product. This submission is based on the 505(b)(2) regulations and Fortical has adequately demonstrated non-inferior pharmacodynamic effects on bone resorption and bone mineral density when compared to Miacalcin (previously submitted and reviewed studies).

In all of the studies submitted and reviewed, there is no evidence to suggest that Fortical is different from Miacalcin with regard to effectiveness or safety, including immunogenicity.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see Dr. Yang's review for complete details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Unigene submitted the agreed upon studies to evaluate the human immunogenicity characteristics of this recombinant salmon calcitonin product. No new clinical efficacy data were submitted.

4.3 Review Strategy

This review concentrates on the submitted immunogenicity data as well as updated safety information from studies of the oral and injectable formulations of Fortical.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) was not consulted for this NDA.

4.5 Compliance with Good Clinical Practices

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

4.6 Financial Disclosures

No new financial disclosure information was submitted.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Review of the immunogenicity studies is the focus of this review. Additional safety data from the updated safety report was also reviewed. No new studies have been conducted with the Fortical nasal spray formulation since submission of the original NDA.

Safety data from the seven studies which used the oral rsCT formulation (IND 59,459) and the injectable rsCT formulation (IND 50,747) were reviewed. A total of 139 subjects were treated with the oral rsCT formulation in the four oral studies, and a total of 88 subjects were treated with the injectable formulation in three studies. There were no deaths or serious adverse events reported in these seven studies. Adverse events and withdrawals rates were similar to the studies previously reviewed. No new safety concerns for rsCT with either formulation were noted.

Injectable (intravenous, subcutaneous or intramuscular injection) Forcaltonin (a different formulation utilizing a different production strain) was approved for treatment of Paget's disease and hypercalcemia of malignancy in January, 1999 in the European Union and was available from October, 1999 to July, 2002 in the United Kingdom only. Distribution was suspended in July, 2002 due to the closure of the only approved European manufacturing facility. The marketing authorization for Forcaltonin was suspended in January, 2004 pending validation of a new manufacturing site. Post marketing data from the use of in the United Kingdom indicate approximately 499 patient exposures occurred in the 3 years of availability.

7.1.10 Immunogenicity

Unigene, Inc. utilized a two step process to characterize Fortical's human immunogenicity profile. The first step employed ELISA methodology for antibody screening with archived samples from the 24-week study UGL-N9904 in which subjects were treated with Fortical (rsCT) or Miacalcin (ssCT) Nasal Spray 200 IU daily. The second step utilized an in vitro bioassay with CHO-K1 (Chinese Hamster Ovary-K1) cells to determine if neutralizing antibody was present in those with antibody detected on screening. The company has adequately validated the direct ELISA methods for detection of rsCT antibody.

Study UGLIMMPF0402: Determination of Human Anti-sCT Antibodies from a Tolerability Study Comparing Fortical Nasal Spray and Miacalcin Nasal Spray in Postmenopausal Osteoporotic Women

Study Procedure: Baseline and Week 24 archived samples from study UGL-N9904 were analyzed by direct ELISA for the presence of antibody to rsCT. Samples were initially screened against rsCT coated wells or against buffer coated wells. Positive samples (those with a signal/noise ratio ≥ 1.20) underwent further analysis with comparisons made to the time 0 sample. If a sample showed a signal to noise ratio of rsCT treated wells to bicarbonate treated wells of < 1.20 and a ratio of signals at time Week 24 to time 0 also < 1.20, then the sample was considered a false positive. All true positive samples underwent dilution to determine antibody titer. The positive control for the ELISA assay was a polyclonal rabbit antibody to rsCT (R35). This ELISA assay was validated using normal human donor serum in study MV-091: Direct ELISA to Identify Anti-sCT Antibodies in Human Serum.

Results: Samples from 118 of the 134 subjects enrolled in study UGL-N9904 were evaluated. The other 16 subjects were terminated early in the study and therefore were not evaluated. Fifty-eight subjects had screened positive on the initial ELISA testing. Upon further evaluation as outlined above, 29 samples were found to be true positives. Of the 29 positives, 13 occurred in Miacalcin-treated subjects and 16 in Fortical-treated subjects. Five subjects (2 treated with Fortical and 3 treated with Miacalcin) had samples with high antibody titers, defined as still positive at 1:500 dilution. As outlined in the table below, comparison of the two treatment groups showed no statistical difference in the mean signal to noise ratio for either rsCT to bicarbonate buffer (p=0.808) or Week 24 time point to Week 0 time point (p=0.973).

Comparison of Fortical and Miacalcin Treated Positive Samples				
Treatment	**Fortical (rsCT)**		**Miacalcin (ssCT)**	
Signal to Noise Ratio	**rsCT to Buffer**	**24 week to 0 week**	**rsCT to Buffer**	**24 week to 0 week**
Mean	1.44	1.64	1.50	1.63
SD	0.810	1.152	0.618	0.548
% CV	56.34	70.33	51.28	33.70
SEM	0.196	0.288	0.150	0.146

Medical Officer Conclusions: The formation of antibodies during treatment with heterologous biopharmaceutical proteins is common. Prior studies evaluating the antibody response of treatment with salmon calcitonin show that antibody formation occurs in 40 – 70% of subjects treated for more than 4 months[1]. Subjects in study UGL-N9904 were treated with nasal salmon calcitonin (Fortical or Miacalcin) for 24 weeks. At the end of this study, approximately 25% of subjects tested positive for antibodies. While the proportion of patients with positive antibody formation is lower than what has been reported in the literature, most published reports are based on the subcutaneous injection formulation of salmon calcitonin which would be expected to elicit a higher degree of antibody formation than the nasal spray. When evaluated by the proportion of subjects who developed antibodies or by the development of high antibody titers, there appears to be no difference between Fortical and Miacalcin.

Study UGLIMMBA0403: Neutralizing Antibody Study: Determination of the Ability of Human Anti-sCT Antibodies from a Tolerability Study Comparing Fortical Nasal Spray and Miacalcin Nasal Spray in Postmenopausal Osteoporotic Women to Neutralize rsCT Activity Measured by a Cell-Based Bioassay

Study Procedure: Samples from the 29 subjects with positive anti-rsCT antibodies from study UGLIMMPF0402 underwent further analysis to detect if the antibody had neutralizing ability, defined as the ability to compete for sCT receptor binding. Both baseline (Week 0) and Week 24 samples were analyzed for neutralizing ability. A novel cell-based assay using cultured CHO-K1 cells and analysis of cAMP response was developed by the sponsor. Salmon calcitonin (sCT) binding to specific G-protein coupled receptors on the cell membrane elicits a dose-dependent intracellular accumulation of cAMP. The company used cultured Chinese Hamster Ovary (CHO-K1) cells and measured dose-response curves for cAMP accumulation. Cyclic AMP was measured by RIA. All samples were diluted 1:20 with assay buffer (a 1:50 dilution was used for the positive control, the R35 antibody). The percent maximal cAMP response was determined by setting the control rsCT standard at 100%. Duplicate bioassays were performed with positive and negative controls. Based on statistical analysis of the assay validation procedures, the assay cut point was set at 84% of maximal cAMP response.

Results: Initial bioassay screening identified 6 subjects with non-neutralizing antibodies, 11 subjects with neutralizing antibodies and 12 subjects that required further investigation because of positive cut point in baseline samples. These 12 subjects were retested at a higher dilution (1:50). At the higher dilution, satisfactory results were achieved in all subjects - 5 with neutralizing antibodies and 7 with non-neutralizing antibodies. Overall, of the 29 subjects with positive ELISA antibody titers, 16 (8 treated with Fortical and 8 treated with Miacalcin) were positive for neutralizing ability. The mean neutralizing activity was 56.36% maximal cAMP response in the Fortical-treated subjects and 59.84% maximal cAMP response in the Miacalcin-treated subjects (p=0.618). All 5 subjects (2 treated with Fortical and 3 treated with Miacalcin) with high ELISA antibody titers had neutralizing antibodies.

Evaluation of bone mineral density and biochemical markers of bone turnover in response to study drug in subjects who developed high titer neutralizing antibodies showed no clear pattern indicating that these patients had a reduced pharmacodynamic response to Fortical or Miacalcin

when compared with patients who did not develop antibodies. As outlined in the table below, the two subjects treated with Fortical decreased β-CTx by 2% and 44%, while the 3 subjects treated with Miacalcin had β-CTx changes ranging from -78% to +293%. Changes in bone mineral density at both the spine and hip were minuscule for all subjects. Fortical-treated subjects with no documented antibody formation had a mean change in β-CTx of -37% (SD ±25.8, range -76% to +29%); a mean change in spine BMD of 0.01% (SD ±0.03, range -0.05% to +0.09%) and a mean change in hip BMD of 0.01% (SD ±0.027, range -0.05% to +0.08%). Miacalcin-treated subjects with no documented antibody formation had a mean change in β-CTx of -49% (SD ±28.0, range -84% to +21%); a mean change in spine BMD of 0.02% (SD ±0.03, range -0.03% to +0.06%) and a mean change in hip BMD of 0.01% (SD ±0.022, range -0.04% to +0.04%).

Study UGL-9904: Patients with High Neutralizing Antibody Titers				
Treatment	PtId	% Change β-CTx (Week 12)	% Change Spine BMD (Week 24)	% Change Hip BMD (Week 24)
Fortical	228	-44	-0.008	-0.01
	236	-1.8	-0.033	0.17
Miacalcin	109	-50	0.018	-0.009
	215	-78	0.022	0.005
	227	293	0.056	-0.012

Medical Officer Conclusions: Antibody formation to therapeutic proteins used as drugs is common but frequently without clinical significance. In theory, the presence of neutralizing antibodies may reduce the long term effectiveness of the drug therapy. Of the 29 subjects in study UGL-N9904 with positive ELISA antibodies (13 in the Fortical-treated group and 16 in the Miacalcin-treated group), 16 exhibited antibodies with neutralizing effects (8 in the Fortical-treated group and 8 in the Miacalcin-treated group), including all 5 subjects with high antibody titers (2 in the Fortical-treated group and 3 in the Miacalcin-treated group). When evaluated by changes in β-CTx and bone mineral density, there was no evidence that these 16 patients had a reduced response to treatment with Fortical or Miacalcin.

Review of the literature indicates that the ability of calcitonin antibodies to impart drug resistance are mixed. Therefore, the development of neutralizing antibodies is similar when Fortical treatment is compared to Miacalcin treatment. The clinical significance of these antibodies is uncertain.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The two studies conducted to evaluate Fortical's human immunogenicity profile used archived samples from the 24-week treatment study UGL-N9904. The duration of this study should provide a sufficient amount of time for antibody formation. Both the screening immunogenicity study and the in-vitro bioassay appear adequately validated and controlled. Results indicate that there is no difference between Fortical and Miacalcin with regard to the ability to induce antibody formation. As well, the neutralizing capacity of the antibodies formed was no different

between the two salmon calcitonin agents. The overall impact of calcitonin antibody formation on therapeutic efficacy remains unclear, although analysis of changes of β-CTx and bone density do not suggest that these antibodies interfered with Fortical's inhibition of bone resorption.

While data from this NDA do not indicate that neutralizing antibodies will diminish Fortical's effectiveness, concern remains regarding anaphylactic reactions to this salmon calcitonin product remain. Language regarding this potential adverse event should be included in the Fortical labeling, as it is for the Miacalcin labeling.

9 OVERALL ASSESSMENT

9.1 Conclusions

There is no difference in binding or neutralizing antibody formation with Fortical (recombinant salmon calcitonin) nasal spray when compared to Miacalcin (synthetic salmon calcitonin) nasal spray. The prior efficacy review found that based on biochemical markers of bone formation and bone mineral density, Fortical was pharmacodynamically equivalent to Miacalcin. No significant safety issues were raised by my prior review although the small sample size of the trials would have required a large difference in event incidence between groups before any conclusions could be made regarding safety differences between Fortical and Miacalcin.

9.2 Recommendation on Regulatory Action

This reviewer recommends that Fortical 200 IU daily be approved for the treatment of osteoporosis in women greater than 5 years post menopause.

9.3 Recommendation on Postmarketing Actions

9.3.2 Required Phase 4 Commitments

This reviewer recommends consideration be given for a company commitment to do a phase IV fracture prevention trial. The company is aware of the need for fracture prevention data with calcitonin nasal spray treatment. To date, the Division does not believe that an adequate clinical trial has been conducted to demonstrate that calcitonin reduces the risk of osteoporotic fracture.

9.4 Labeling Review

The Fortical package insert was compared to the Miacalcin package insert with the intent to provide a parallel label, see Appendix 10.2.

10 APPENDICES

10.2 Line-by-Line Labeling Review

See separate document. Given the 505(b)2 status of the application, the Fortical label will replicate the current Miacalcin label.

REFERENCES

[1] Grauer A, et. al. Clinical significance of antibodies against calcitonin. Exp Clin Endocrinol 103: 345 – 351. 1995.

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Theresa Kehoe
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MEDICAL REVIEW OF IMMUNOGENICITY PROTOCOL

NDA: 21-406

DRUG: Calcitonin-salmon (rDNA) Nasal Spray, Fortical®

INDICATION: Treatment of osteoporosis in women greater than 5 years post menopause.

COMPANY: Unigene, Inc.

DATE OF SUBMISSION: April 26, 2004

DATE OF REVIEW: June 14, 2004

Unigene, Inc. has submitted the protocol for characterization of Fortical's human immunogenicity profile, in response to the Agency's request. The protocol is devised as a two step process. The first step utilizes ELISA methodology for antibody screening. The second step utilizes an in vitro bioassay to determine if neutralizing antibody is present in those with antibody detected on screening. The company will utilize archived samples from the 24 week study UGL-N9904 in which subjects were treated with Fortical (rsCT) or Miacalcin (ssCT) Nasal Spray 200 IU daily.

The company has adequately validated the direct ELISA methods for detection of rsCT antibody. This study can proceed. Please refer to Dr. Yang's review of the ELISA methodology.

The company intends to use a bioassay with CHO-K1 (Chinese Hamster Ovary-K1) cells in order to detect neutralizing antibodies to rsCT. This assay as not been adequately validated and Unigene will need to supply further information for validation, as outlined in Dr. Yang's review.

Recommendation:

1. The company may proceed with the direct ELISA screening for antibody to rsCT.
2. Further information and validation of the in vitro bioassay with CHO-K1 cells is needed prior to implementation of this study.

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TEAM LEADER MEMORANDUM

NDA: 20-406

DRUG: Recombinant salmon calcitonin nasal spray (Fortical)

INDICATION: Treatment of postmenopausal osteoporosis

COMPANY: Unigene

PRIMARY REVIEWER: Theresa Kehoe, MD

DATE OF MEMO: 29 December 2003

I. BACKGROUND

Unigene Laboratories has submitted a NDA under the 505(b)(2) regulations for a recombinant salmon calcitonin nasal spray, which they hope to market under the trade name Fortical. Reference is made to the Agency's prior approval of Miacalcin Nasal Spray, a synthetic salmon calcitonin product. In addition to being a recombinant product, Fortical differs from Miacalcin in that it contains Tween 80, sodium hydroxide, citric acid, phenylethyl alcohol, and benzyl alcohol, whereas Miacalcin does not. And while Miacalcin contains nitrogen and benzalkonium chloride, Fortical does not.

In discussions held during early phases of development, the Division requested that the company conduct a pharmacodynamic study to compare the effects of Fortical and Miacalcin Nasal Spray on markers of bone turnover. This study was considered necessary because reliance on traditional bioequivalency studies was not feasible due to the extremely low bioavailability of calcitonin following clinical doses (i.e., 200 IU per day). A high-dose bioequivalency study was conducted and provides ancillary support for approval of Fortical.

Miacalcin Nasal Spray was approved in August, 1995. The drug is "indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Miacalcin (calcitonin-salmon) Nasal Spray should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated."

Unlike Fosamax, Evista, Actonel, Forteo, and Boniva, Miacalcin's approval was based solely on changes in bone mineral density (BMD) not fracture data. A phase-4 fracture study known as PROOF was conducted by Novartis and the results were submitted as a supplemental NDA

requesting that the drug be indicated to reduce the risk for osteoporotic fracture. The Division believed that the trial failed to adequately demonstrate that Miacalcin 200 IU per day significantly reduced the risk for morphometric vertebral fracture relative to placebo, and the supplement was not approved in July, 1999.

Dr. Kehoe has recommended that Fortical receive an Approvable Letter, with Approval contingent upon submission of human immunogenicity data (discussed below). She is also recommending that Unigene consider conducting a phase-4 fracture study. I agree with her recommendation for immunogenicity data, but do not believe that the company should be required to conduct a phase-4 fracture trial. Given that the Fortical Nasal Spray NDA was submitted as a 505(b)(2) application, with reference to Miacalcin Nasal Spray, there is no regulatory basis to require that Unigene conduct a fracture study. When approved, the Fortical labeling will reflect, to the extent considered reasonable, the labeling for Miacalcin. The labeling for Miacalcin makes it clear that the drug's approval was based on BMD, not fracture data. The Fortical labeling will do the same[1].

II. PHARMACODYNAMIC EFFECTS OF FORTICAL AND MIACALCIN

Evidence of Fortical's pharmacodynamic equivalency to Miacalcin was shown in a 24-week, randomized, double-blind[2], active-controlled study of 134 postmenopausal women. Sixty-seven women were randomized to Fortical 200 IU per day and 67 to Miacalcin 200 IU per day. There was no placebo group in the study. All subjects received supplemental calcium and vitamin D. The primary efficacy outcome was the change from baseline to Week 12 in serum levels of ß-CTx, a marker of bone resorption. To be considered equivalent to Miacalcin, the 95% confidence interval for the difference between groups in the mean change from baseline to Week 12 in ß-CTx had to be within the prespecified equivalence margin of ± 0.20 ng/ml. Since there were no placebo-controlled data of Miacalcin Nasal Spray's effect on ß-CTx, the equivalence margin was determined by taking ±35% of the mean baseline ß-CTx value.

The groups were well matched for baseline characteristics. The mean age of the participants was 66 years, 97% of the subjects were Caucasian, and the average LS BMD was 0.800 gm/cm^2 (approximate T-score of -2.53). A total of 59 women in each group completed the first 12 weeks of the study.

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[1] It is worth noting that the results of the PROOF trial were published in the *American Journal of Medicine* in 2000;

-reviewed journal, albeit a

[2] Because the two drugs were presented in bottles that differed in size and color it is possible that the trial was not, strictly speaking, conducted under double-blind conditions. Even if this was the case, the objective endpoint of the trial would not likely be influenced by a subject's or investigator's knowledge of drug assignment.

In the primary analysis of efficacy, the 95% confidence interval for the difference between treatment groups in the mean change from baseline to Week 12 in ß-CTx was -0.08 to 0.06 ng/ml, well within the prespecified margin of ± 0.20 ng/ml. The point estimate for the difference between groups was 0.01 ng/ml.

In secondary analyses, the changes from baseline to Week 12 in serum levels of ß-CTx within the Fortical and Miacalcin groups were -36% and -43%, respectively ($p<0.001$). In addition, the changes from baseline to Week 24 in lumbar spine and hip BMD were evaluated by DEXA. The mean changes in LS BMD were 1.3% in the Fortical group and 1.5% in the Miacalcin group. The mean changes in femoral hip BMD were 1.3% and 1.0% in the Fortical and Miacalcin groups, respectively.

These results indicate that the pharmacodynamic effects of Fortical and Miacalcin on bone are equivalent.

No significant safety issues were noted during the conduct of this study - in particular, the safety profiles of the two formulations on the nasal mucosa were similar.

III. BIOAVAILABILITY STUDY

The relative bioavailability of Fortical was compared with Miacalcin in a multi-dose, crossover study of 47 healthy female volunteers. On each day of dosing, subjects received a total of 2400 IU of Fortical or Miacalcin over a 100 minute period. The C_{max} and AUC values for Fortical were 56 pg/ml and 891 pg.min/ml and 47 pg/ml and 716 pg.min/ml for Miacalcin. Because the upper bounds of the 90% confidence intervals for the differences between Fortical and Miacalcin were above 125, the standard upper bound for bioequivalence, Fortical is not, by regulatory standards, bioequivalent to Miacalcin. But because Fortical was slightly more bioavailable than Miacalcin, this difference is not clinically significant.

IV. FINANCIAL DISCLOSURE

Dr. Kehoe has reviewed the financial disclosure information provided in the NDA and only one investigator had significant equity interest in Unigene.

V. DSI INSPECTION

The Division of Scientific Investigation was not consulted for this application.

VI. COMMENT

The results of the pharmacodynamic and bioavailability studies indicate that Fortical Nasal Spray is clinically equivalent to Miacalcin Nasal Spray. Before the drug is approved, the following issues need to be addressed:

1) On more than one occasion during the development of Fortical, the Division told Unigene that they would need to characterize the human immunogenetic profile of their drug. Because the NDA does not contain any information about the immunogenicity of Fortical, this deficiency should be addressed before the drug is approved.
2) The Chemistry reviewer, Dr. Yang, is requesting that the following information be provided prior to approval: 1) A satisfactory response to the deficiencies delineated in the Draft List of Deficiencies and Information Request (in the CMC reviews for NDA 21-406, [redacted]), and 2) An overall acceptable cGMP recommendation from the Office of Compliance that was delayed due to a change in a testing facility submitted by the applicant one month before the due date.
3) Because this NDA was submitted under the 505(b)(2) regulations, with reference to approval of Miacalcin Nasal Spray in 1995, the labeling for Fortical should, to the extent possible, mirror the labeling for Miacalcin. Details of the labeling will be addressed during the second review cycle.

V. REGULATORY RECOMMENDATION

Approvable

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

/s/

Eric Colman
12/31/03 12:20:27 PM
MEDICAL OFFICER

Eric Colman
12/31/03 12:22:52 PM
MEDICAL OFFICER
Eric Colman for David Orloff

CLINICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: NDA 20-406
Application Type: 505 (b)(2) NDA
Sponsor: Unigene Laboratories, Inc
Proprietary Name: Fortical
Pharmaceutical Category: Recombinant salmon calcitonin
Route of Administration: Nasal Spray
Indication: Treatment of Postmenopausal Osteoporosis
Dosage: 200 IU daily
Reviewer: Theresa Kehoe, MD
Date Review Completed: December 22, 2003
Chemistry Reviewer: Yvonne Yang, Ph.D.
Pharmacology Reviewer: Gemma Kuijpers, Ph.D.
Biopharmaceutics Reviewers: Wei Qiu, Ph.D., Jaya Vaidyanathan, Ph.D.
Statistical Reviewer: Todd Sahlroot, Ph.D.

REVIEW SUMMARY:
See executive summary

OUTSTANDING ISSUE:
See executive summary

RECOMMENDED REGULATORY ACTION:
N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**
NDA, Efficacy/Label supplement: XX **Approvable** _____ **Not Approvable**
_____ **Approve**

SIGNATURES:
Medical Reviewer: Theresa Kehoe, M.D. **Date:** December 22, 2003.

Medical Team Leader: Eric Colman, M.D. **Date:** _____.

CLINICAL REVIEW

Table of Contents

Clinical Review for NDA 20- —

Executive Summary

I. Recommendations

A. Recommendation on Approvability

This reviewer recommends that Fortical 200 IU daily for the treatment of osteoporosis in women greater than 5 years post menopause be deemed approvable. Approval is contingent upon completion of adequate human immunogenicity studies.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

This reviewer recommends consideration be given for a company commitment to do a phase IV fracture prevention trial. The company is aware of the need for fracture prevention data with calcitonin nasal spray treatment. To date, an adequate clinical trial evaluating calcitonin's efficacy in fracture prevention has not been conducted.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Unigene Laboratories, Inc. has submitted this 505(b)(2) application for approval of the marketing of a recombinant salmon calcitonin (Fortical®) nasal spray for the treatment of postmenopausal osteoporosis. This application provides data showing pharmacokinetic and pharmacodynamic equivalence to the currently marketed synthetic salmon calcitonin (Miacalcin) nasal spray product. The clinical development program consisted of 3 clinical trials: a pilot pharmacokinetic trial, a pharmacokinetic bioequivalence trial and a larger active-comparator pharmacodynamic equivalence trial.

B. Efficacy

In this 505(b)(2) submission, conclusions regarding the efficacy of Fortical were based primarily on the Agency's prior approval of Miacalcin Nasal Spray and the results of a 24-week, active-controlled, equivalence study comparing changes in bone markers in Fortical- vs. Miacalcin-treated postmenopausal women. Supportive data came from a bioequivalence study.

In the 24-week active-controlled study, treatment with Fortical or Miacalcin for 12 weeks resulted in statistically significant decreases in bone turnover markers. In evaluation of the primary efficacy endpoint, β-CTx, Fortical resulted in a 36% decrease compared with baseline ($p < 0.001$) and treatment with Miacalcin resulted in a 43% decrease compared with baseline ($p < 0.001$). The two drugs were deemed equivalent because the 95% confidence interval for the difference between groups in the mean change from baseline to Week 12 in ß-CTx was –0.08 to 0.06 ng/ml, which is within the prespecified

equivalence margin of ± 0.20 ng/ml. At 24 weeks of therapy, treatment with Fortical or Miacalcin resulted in a significant increase in bone mineral density at the AP spine. In comparison to Miacalcin, Fortical appears pharmacodynamically equivalent for the treatment of osteoporosis in women greater than 5 years post menopause.

C. Safety

There were no new safety signals noted with Fortical treatment. In the studies utilizing high dose salmon calcitonin, nasal symptoms and dizziness were more commonly experienced with the recombinant (Fortical) formulations in the small phase 1 study, however in the larger bioequivalence study, nasal symptoms were equally distributed among the treatment groups. The occurrence of nasal adverse events was equally distributed between the Fortical and Miacalcin treatment groups in the 24-week pharmacodynamic equivalency study. Events noted in the high-dose pharmacokinetic trials (nausea, dizziness, postural hypotension) were not seen in this trial. There were no clinically significant laboratory or ECG changes noted in any of the trials. No fractures were noted in the trials, although morphometric fractures were not evaluated.

D. Dosing

Sufficient evidence has been provided that a 200 IU daily dose of recombinant salmon calcitonin (Fortical) nasal spray is pharmacodynamically equivalent and as safe as the currently marketed synthetic salmon calcitonin (Miacalcin) nasal spray dose of 200 IU daily.

E. Special Populations

Fortical is intended for the treatment of postmenopausal women with osteoporosis. All of the subjects enrolled in these trials were women.

Clinical Review

I. Introduction and Background

I.A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Unigene Laboratories, Inc. has submitted this 505(b)(2) application for approval of marketing of a recombinant salmon calcitonin (Fortical®) nasal spray for the treatment of postmenopausal osteoporosis. This application provides data on pharmacokinetic and pharmacodynamic equivalence to a currently marketed synthetic salmon calcitonin (Miacalcin) nasal spray product.

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. The primary action of calcitonin is regulation of calcium homeostasis primarily through inhibition of osteoclastic bone resorption.

I.B. State of Armamentarium for Indication(s)

In addition to Miacalcin nasal spray (synthetic salmon calcitonin), other medications currently approved for the treatment of postmenopausal osteoporosis include the bisphosphonates alendronate sodium (Fosamax), risedronate sodium (Actonel) and ibandronate sodium (Boniva) as well as raloxifene (Evista) and teriparatide acetate (Forteo).

I.C. Important Milestones in Product Development

The Fortical clinical development program consists of 3 clinical trials: a pilot pharmacokinetic trial, a pharmacokinetic/bioequivalence trial and a larger active-comparator pharmacodynamic equivalence trial. Interactions with the FDA include:

October 7, 1999 — A pre-IND meeting was held and based on the agreements reached at that meeting, the company submitted studies UGLN9903 and UGL-N9904 with the objectives of demonstrating the therapeutic and safety equivalence of Fortical Nasal Spray with the innovator product, Miacalcin Nasal Spray. A follow-up teleconference with the company on 10/19/1999 was held in order to stress the importance of human antigenicity studies.

February 10, 2000 — A teleconference was held with FDA regarding the protocol for study UGL-N9904. The Agency suggested that one or two primary variables of efficacy be chosen. The Company selected serum β-CTx because of the availability of historical data for this biochemical marker of bone turnover, and because the assay for β-CTx had high reproducibility and low intra-sample variability. To establish pharmacodynamic equivalence, the Agency required that both the reference and test drugs should produce a significant change from baseline for the chosen primary biochemical variable, β-CTx. Therefore, the company decided that in study UGL-N9904, the patient population would be restricted to those who had evidence of high bone turnover defined as two pretreatment serum β-CTx measurements, taken on two separate occasions approximately 1 week apart, that were both above 0.24 ng/mL. In addition, the Agency required that the respective responses to the two drugs should not be statistically different. That is, the two drugs were to be considered equivalent if the 95% confidence interval for the difference between groups in the mean change from baseline to Week 12 in ß-CTx was within the prespecified equivalence margin of ± 0.20 ng/ml. The sample size calculations were based on analysis of historical data for osteoporotic patients, supplied by [redacted]. The study was therefore designed to fulfill both of the Agency's requirements for pharmacologic equivalence.

June 12, 2001 — A pre-NDA meeting was held. The pivotal study (UGL-N9904) was designed to analyzed a change in serum β-CTx levels as the primary efficacy variable. Patients in this study received calcium and vitamin D supplementation during treatment, and the proposed labeling for Fortical

Nasal Spray will suggest that patients take similar supplements along with Fortical Nasal Spray. The study did not contain a supplement-only control arm, and in light of the fact that and calcium supplementation alone has been shown in some studies to have a modest effect on bone turnover, the company was asked by the Agency to conduct a review and meta-analysis of the published literature concerning the effects of calcium and vitamin D on serum β -CTx. The sponsor has therefore performed a meta-analysis of published clinical trials in osteoporosis patients which analyzed serum CTx at the appropriate time points, and which included a calcium-only or calcium-plus-vitamin D placebo arm. The meta-analysis was conducted in order to estimate the quantitative contribution of the dietary supplements to the total pharmacological effect observed in the Fortical and Miacalcin groups.

December, 2003 — Inquiry was made to the company regarding human immunogenicity studies. The company stated that rat immunogenicity studies had been performed, but there had never been a request or agreement to perform human immunogenicity studies. The company felt that since authenticity with Miacalcin had been demonstrated, there would not be a need for such a study. Upon further discussion, the company stated that they have 6 month samples for study UGL-N9904 participants archived should a need for human immunogenicity studies be determined.

I.D. Important Issues with Pharmacologically Related Agents

Salmon calcitonin (Miacalcin) nasal spray was initially approved for the treatment of osteoporosis in women more than 5 years post menopause in August, 1995. There were 3 pivotal clinical trials evaluating the safety and efficacy of Miacalcin in the treatment of postmenopausal osteoporosis. After presentation to the Endocrine and Metabolic Advisory Committee, approval was based on bone mineral density and not fracture prevention. Approval was contingent on the completion of a phase IV fracture prevention trial. The fracture prevention trial was submitted as a labeling supplement in 1999 and was found not approvable, based on the ambiguous results of the statistical analysis. Other published trials have been conducted evaluating the use of Miacalcin nasal spray for the treatment of corticosteroid induced osteoporosis, treatment of osteoporosis following hip fracture and treatment of osteoporosis in men.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

II.A. Chemistry

(Please see Dr. Yang's reviews for complete details) The drug product is recombinant Salmon Calcitonin, rsCT, as the active pharmaceutical ingredient.

Fortical Nasal Spray is an aqueous solution of rsCT in a — amber glass vial with a — metering spray pump. Each actuation of the pump delivers a spray containing 200 IU of rsCT. The nasal spray product will deliver — doses, which is a — day supply. A new manufacturing site was submitted to the agency in November, 2003. At this time, full inspection of this site is pending.

II.B. Animal Pharmacology and Toxicology
(Please see Dr. Kuijpers' review for complete details)

II.C. Biopharmaceutics
(Please see Drs. Qiu and Vaidyanathan's review for complete details)

II.D. Statistics
(Please see Dr. Sahlroot's review for complete details) A discussion of the pertinent findings has been incorporated into the appropriate sections of the efficacy review.

III. Human Pharmacokinetics and Pharmacodynamics

III.A. Pharmacokinetics
The pharmacokinetics of Fortical nasal spray was evaluated in studies UGL-N9901 and UGL-N9903. 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 a higher bioavailability 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) of geometric means for $AUC_{100\text{-}120}$ and $Cmax_{100\text{-}120}$ of sCT were 108.91 - 142.27% and 104.44 - 133.65%, respectively. Since the 90% confidence intervals of $AUC_{100\text{-}120}$ and $Cmax_{100\text{-}120}$ 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 strictly equivalent. Please see Drs. Qiu and Vaidyanathan's review for complete details.

III.B. Pharmacodynamics
Study UGL-N9904 examined the pharmacodynamic effects of Fortical in terms of 3 month biomarkers of bone turnover and 6 month bone mineral density data. These data are reviewed in depth in the clinical efficacy section of this review.

IV. Description of Clinical Data and Sources

IV.A. Overall Data

The Fortical clinical development program consists of 3 clinical trials: a pilot pharmacokinetic trial, a pharmacokinetic/bioequivalence trial and a larger active-comparator pharmacodynamic equivalence trial.

IV.B. Tables Listing the Clinical Trials

Fortical Nasal Spray Studies					
		Subjects enrolled (completed)	Age	Study Duration	Endpoint
UGL-N9901	Forcaltonin A	14 (13)	23.6 years	3 weeks	Pharmacokinetics
	Forcaltonin B	14 (12)			
	Miacalcin	14 (14)			
UGL-N9903	Fortical A	47 (45)	29.4 years	3 weeks	Bioequivalence
	Fortical B	47 (46)			
	Miacalcin	47 (46)			
UGL-N9904	total	134 (118)	45-87 years	24 weeks	Biochemical markers of bone turnover
	Fortical (B) 200IU	67 (59)			
	Miacalcin 200IU	67 (59)			

IV.C. Postmarketing Experience

There are no postmarketing data available for the recombinant salmon calcitonin nasal spray product since the drug is not approved in any part of the world. For Miacalcin, the synthetic salmon calcitonin product, a query of the AERS database revealed 933 adverse event reports dating from February 1995 to June 2003. The age range of the patients from these reports was 15 years to 94 years. The most common adverse event reports were related to the nervous (280), body as a whole (219) and gastrointestinal (206) systems. Upper respiratory and nasal adverse events accounted for 157 reports. No new safety signals are suggested by these reports.

IV.D. Literature Review

An extensive literature review was conducted by the company and references were provided. Of note, the company cites the publication of the PROOF trial[1] and places heavy significance on the results of this study in their proposed label. This study is fraught with an extremely high drop out rate, missing data and lack of a clear dose response.

[1] Chestnut CH, et.al. A Randomized Trial of Nasal Spray Salmon Calcitonin in Postmenopausal Women with Established Osteoporosis: the Prevent Recurrence of Osteoporotic Fractures Study. 2000. Am J Med 109:267-276.

V. Clinical Review Methods

V.A. How the Review was Conducted

This review focuses on the pharmacodynamic trial UGL-N9904 for efficacy evaluation and all three trials (UGL-N9901, UGL-N9903 and UGL-N9904) utilizing the nasal spray formulation(s) for safety evaluation.

V.A. Overview of Materials Consulted in Review

This review was conducted utilizing data in the electronic submission of the NDA. All trials were conducted under IND 59,664 (nasal spray). This product has also been evaluated in a subcutaneous injection formulation, under IND 50,747.

V.B. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigation (DSI) was not consulted for this NDA.

V.C. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

V.D. Evaluation of Financial Disclosure

Financial disclosure information was provided by the sponsor and reviewed by this reviewer. One principal investigator stated that he has significant equity interest in Unigene Laboratories, Inc. Appropriate steps were taken by the company to minimize any bias.

VI. Integrated Review of Efficacy

VI.A. Brief Statement of Conclusions

Fortical nasal spray is pharmacodynamically equivalent to Miacalcin nasal spray for the treatment of women with osteoporosis greater than 5 years post menopause.

VI.B. General Approach to Review of the Efficacy of the Drug

Study UGL-N9904 was reviewed in depth for efficacy, based on the biomarker and bone mineral density data. The pharmacokinetic studies, UGL-N9903 and UGL-N9901 have been reviewed in depth by Drs. Qiu and Vaidyanathan. Please refer to their review for a full report.

VI.C. Detailed Review of Trials by Indication

VI.C.1. Study UGL-N9904: 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.

Objectives: The objective of this study was to monitor the biologic response to Fortical nasal spray with Miacalcin nasal spray in postmenopausal osteoporotic women, using biochemical markers of bone turnover, over 12 weeks of treatment. The tolerability of Fortical and Miacalcin following administration of a dose of 200 IU per day was compared over an additional 12-week period.

Study Design: This was a randomized, double-blind, multiple-dose, parallel-group study. This study was conducted at 5 sites, three in the United States and two in the United Kingdom. The 24-week treatment period was preceded by a 4-week screening period. All subjects were instructed in how to administer the nasal spray. For the duration of the study, each subject took two Caltrate tabs, for a daily total of 1200mg calcium and 400 IU Vitamin D.

Population: Women with osteoporosis, confirmed by BMD, who were at least 1 year post menopause were eligible for this study.

Inclusion Criteria

- Must be female and age 45 or over
- Must have undergone the onset of spontaneous or surgical menopause and be amenorrheic for at least one year prior to the start of screening. Spontaneous menopause is defines as the natural cessation of ovarian function. Surgical menopause is defined as bilateral oophorectomy.
- Must have a diagnosis of osteoporosis on the basis of a hip or spine BMD, which was equal to or greater than 2.5 SD below the mean for premenopausal women
- Must have a weight between 45 and 85 kg and a body mass index (BMI) of not greater than 32 (BMI= weight [kg]/height $[m]^2$)
- Must have no clinically significant abnormal findings in the medical history, physical exam or nasal exam
- Must have no clinically significant abnormal laboratory values at the screening assessment
- Must demonstrate an elevated rate of bone turnover as assessed by two pre-treatment serum β-CTx values above 0.24 ng/ml.

Exclusion Criteria

- Have a history of severe allergic disease
- Use of bisphosphonates in the preceding 6 months
- Chronic systemic treatment with glucocorticoids, hormone replacement therapy, calcitonin, or any other medication with the previous 3 months which, in the opinion of then investigator, would interfere with the study
- Clinically relevant abnormal history, physical findings or laboratory values at the pre-study screening assessment that could interfere with the objectives of the study of the safety of the patient.
- Presence of acute or chronic illness or history of chronic illness which, , in the opinion of then investigator, made participation in the study medically inappropriate

- Uncontrolled hypertension, significant gastrointestinal abnormalities, uncontrolled diabetes mellitus, significant coronary artery disease, any psychotic mental illness, chronic allergic rhinitis, asthma, uncorrected endocrine dysfunction, or significantly impaired hepatic, respiratory or renal function
- Use of prescription medicine during the 28 days before the study or use of an over-the-counter medication during the 7 days before the study that would, in the opinion of then investigator, interfere with the outcome of the study
- Participation in any other clinical study of a new chemical entity or a prescription medicine within the previous month
- Participation in any other clinical study of a new chemical entity or a prescription medicine within the previous 3 months unless, in the opinion of then investigator, such participation would not interfere with the outcome of the present study
- History of drug or alcohol abuse, or intake of more than 30 units of alcohol weekly
- Possibility that the patient will not cooperate with the requirements of the protocol
- Any nasal abnormality, such as nasal polyps, that, in the opinion of then investigator, could interfere with the absorption of intranasally administered test drug
- Known sensitivity to the excipients of either Fortical nasal spray or Miacalcin nasal spray

COMMENT: Vitamin D status was not assessed as part of entry criteria or laboratory evaluation for this study.

Study Medication: Subjects were assigned to receive one of the two investigational drugs, each having a dose of 200 IU salmon calcitonin, plus two oral Caltrate tabs (1200mg calcium and 400 IU Vitamin D total) per day. The Miacalcin nasal spray was supplied in the manufacturer's original 2-mL clear glass bottle, over-labeled for blinding purposes. The Fortical (B formulation) nasal spray was supplied in an amber 3.5-mL glass bottle. 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.

COMMENT: The study was technically double-blind, in that neither the patients nor the study personnel knew which of the two treatments each subject was receiving. However, the containers for the two study drugs were different in size and color. Although such differences could have easily lead to unblinding, it is unlikely that the container difference affected the principal efficacy results.

Efficacy Measures

Primary: The primary efficacy endpoint was a change in β-CTx after twelve weeks of treatment

Secondary: The secondary efficacy parameters included urinary free deoxypyridinoline (DPD) crosslinks, serum N-terminal telopeptide of collagen type I (NTx), serum bone specific alkaline phosphatase (BSAP), osteocalcin, parathyroid hormone levels, bone mineral density and bone markers measured in sweat.

Safety Measures: Included adverse events, laboratory evaluations, physical examination, including detailed nasal exam, ECG and vital signs. Safety results are discussed in detail in the Integrated Summary of Safety.

Study Methods: Serum and second void urine samples were collected at baseline, 4, 8 and 12 weeks for assessment of urinary free deoxypyridinoline (DPD) crosslinks, serum N-terminal telopeptide of collagen type I (NTx) and serum C-terminal telopeptide of collagen type I (β-CTx). Serum bone specific alkaline phosphatase (BSAP), osteocalcin and parathyroid hormone levels were also measured at 12 weeks. For all biomarkers, baseline values represent the average of two pre-treatment samples, collected one week apart. Bone mineral density was measured by DEXA at screening and 24 weeks in completer subjects. All DEXA equipment was cross-calibrated using a standardized phantom. The ——— sweat collection device was used to collect sweat for the possible future analysis of pyridinoline and deoxypyridinoline levels. Two patches were worn for 5 days during screening and at the ends of weeks 4, 8 and 12.

Physical exam, chemistry panel, hematology panel and urinalysis were performed at screening, weeks 12 and 24. A detailed nasal exam was performed by an otolaryngologist at screening, weeks 12 and 24; and by the principal investigator at weeks 4 and 18. Adverse event assessment and recording were performed at screening, 4, 8, 12, 18 and 24 weeks.

Withdrawal criteria: Subjects could withdraw from the study at any time. Investigators could withdraw subjects for medical reasons such as intolerance to study medication, intercurrent illness, the need for medication which was contraindicated, or withdrawal of consent.

Statistical Analyses: A modified ITT patient population was used for the analysis of the primary variable. This population was defined as all subjects who received treatment and had at least one follow-up β-CTx measurement value. the data were analyzed using the analysis of variance. The 95% confidence interval for the difference in the mean change from baseline was determined. The protocol specified that the confidence interval must be contained with ± 35% of the mean baseline β-CTx value in order for the treatment groups to be declared biologically equivalent.

Protocol Amendments: There were no amendments to this protocol.

Results

Patient Disposition: Two hundred and five subjects were screened for enrollment into this study, with 134 subjects enrolled. One hundred eighteen subjects completed the study.

Study UGL-N9904: Patient Disposition		
	Miacalcin	Fortical
Enrolled	67	67
Included in ITT	59	59
Withdrew - Safety	7	7
Withdrew - Nonsafety	1	1
Deaths	0	0
Completed	59	59

Protocol Violations: Screening entry criteria violations occurred in seven subjects. Other protocol violations occurred in 125 subjects. Most violations occurred because nasal examinations performed by the ENT physician were done outside the allowed 3 day time window.

COMMENT: Although there were numerous protocol violations, the numbers and types of violations were evenly distributed across the two groups. It is very unlikely that the protocol violations affected the principal efficacy or safety results.

Demographics: The two groups were well matched for baseline demographic characteristics (Table below). The mean age of the participants was 66 years, 97% of the subjects were Caucasian, and the average LS BMD was 0.800 gm/cm^2 (approximate T-score of -2.53). The presence of prevalent vertebral fractures was not assessed.

Study UGL-N9904: Patient Demographics			
	Fortical	Miacalcin	P value
N	67	67	
Age (yrs.)	66.3	65.7	0.635
Time since last menses (years)	19.3	19.8	0.785
Body Weight (kg)	63.7	64.1	0.197
Body Height (m)	1.59	1.61	0.090
BMI (kg/m2)	25.2	24.7	0.385
Race			
Caucasian	65 (97.0)	66 (98.5)	
Black	1 (1.5)	0	
Hispanic	1 (1.5)	0	
Indian	0	1 (1.5)	

COMMENT: Miacalcin is currently indicated for treatment of osteoporosis in women greater than 5 years post menopause. This study enrolled osteoporotic women who were at least 1 year without menses. However, the average time since last menses is approximately 19 years and only 8 enrolled subjects had cessation of menses less than 5 years prior to study enrollment. Therefore, the study population can be considered comparable to the patient populations seen in prior Miacalcin studies.

Primary Efficacy Outcomes

Change in β-CTx: As outlined in the table below, the mean baseline β-CTx level was lower in the Miacalcin-treated group (p = 0.069). Both Fortical and Miacalcin treated subjects had statistically significant decreases in β-CTx levels at twelve weeks of therapy (-0.22 in the Fortical-treated group and -0.23 in the Miacalcin-treated group).

Study UGL-N9904: β-CTx Results		
	Fortical	Miacalcin
	(n=59)	(n=59)
Baseline [1] mean (SD) ng/mL	0.61 ± 0.25	.055 ± 0.21

Study UGL-N9904: β-CTx Results		
	Fortical	Miacalcin
Final mean (SD) ng/mL	0.38 ± 0.21	0.32 ± 0.23
Mean change from baseline	-0.22 ± 0.18	-0.23 ± 0.18
Mean % change from baseline	-36%	-43%
p value	< 0.001	< 0.001
p value, between treatment groups	0.828	
[1] Each patient's baseline was the mean of two pre-treatment values taken approximately one week apart.		

The equivalency margin for the comparison of Fortical and Miacalcin was defined as ± 35% of the mean baseline β-CTx levels for all subjects, which was 0.58 ng/mL. Therefore, the 95% confidence interval of the treatment difference needed to be within ± 0.20ng/mL. As the table below outlines, the treatment difference 95% confidence interval is well within the non-inferiority margin.

UGL-N9904: Treatment difference and 95% CI for β-CTx change from baseline		
	Fortical (n=59)	Miacalcin (n=59)
LS [1] mean change from baseline	-0.19	-0.20
Treatment difference (Fortical minus Miacalcin) LS [1] mean 95% CI	+0.01 (-0.05, +0.07)	
Margin (±35% of the mean of β-CTx at baseline)	±0.20 (±35% of 0.58)	
[1] Least square		

Secondary Efficacy Outcomes

Change in Markers of Bone Turnover: The table below displays the endpoint results for all other measured markers of bone turnover, including bone resorption markers serum NTx and urinary DPD and bone formation markers BSAP and osteocalcin.

Serum NTx: Serum NTx values were not significantly different between the two treatment groups at baseline. There was a 15% decrease from baseline ($p < 0.001$) in the Fortical treated group and a 17% decrease from baseline in the Miacalcin treated group ($p < 0.001$). There was no significant treatment difference between the groups.

Urinary DPD: Urinary DPD values were not significantly different between the two treatment groups at baseline. There was an 8% decrease from baseline ($p = 0.003$) in the Fortical treated group and a 6% decrease from baseline in the Miacalcin treated group ($p = 0.099$). There was no significant treatment difference between the two groups.

BSAP: BSAP was lower in the Miacalcin group, compared with the Fortical group at baseline ($p = 0.093$). There was a 9% decrease from baseline in both treatment groups ($p < 0.001$). There were no significant treatment difference between the two groups at study end.

Osteocalcin: Osteocalcin levels were not significantly different between the two treatment groups at baseline. There was an 18% decrease from baseline in the Fortical treated group ($p < 0.001$) and a 19% decrease from baseline in the Miacalcin treated group ($p < 0.001$). There was no significant treatment difference between the two groups at study end.

PTH: PTH levels were not significantly different between the two treatment groups at baseline. There was a non-significant 2% decrease from baseline in the Fortical treated group ($p=0.298$) and an 11% decrease for baseline in the Miacalcin treated group ($p <0.001$). There was a significant treatment difference between the two groups ($p = 0.018$).

COMMENT: Without Vitamin D levels to assist in the evaluation of the PTH levels, it is difficult to fully interpret the trends seen.

Study UGL-N9904, Biochemical Markers of Bone Turnover		
	Fortical	Miacalcin
NTX	(n=59)	(n=59)
Baseline [1] mean (SD) ng/mL	14.8 ± 4.0	13.8 ± 3.7
Final mean (SD) ng/mL	12.4 ± 3.5	11.3 ± 3.5
Mean change from baseline	-2.48 ± 2.52	-2.42 ± 2.23
Mean % change from baseline	-15%	-17%
p value	< 0.001	< 0.001
p value, between treatment groups	0.995	
Urinary DPD	(n=59)	(n=59)
Baseline [1] mean (SD) ng/mL	9.03 ± 3.07	8.09 ± 2.68
Final mean (SD) ng/mL	7.91 ± 2.86	7.51 ± 3.28
Mean change from baseline	-0.98 ± 2.34	-0.58 ± 2.66
Mean % change from baseline	-8%	-6%
p value	0.003	0.099
p value, between treatment groups	0.407	
BSAP	(n=56)	(n=58)
Baseline [1] mean (SD) ng/mL	28.78 ± 9.77	26.09 ± 7.27
Final mean (SD) ng/mL	26.28 ± 8.88	24.74 ± 7.88
Mean change from baseline	-2.60 ± 4.08	-2.63 ± 3.41
Mean % change from baseline	-9%	-9%
p value	< 0.001	< 0.001
p value, between treatment groups	0.962	
Osteocalcin	(n=56)	(n=58)
Baseline [1] mean (SD) ng/mL	32.41 ± 10.64	30.05 ± 9.41
Final mean (SD) ng/mL	27.05 ± 9.71	24.76 ± 7.75
Mean change from baseline	-5.80 ± 4.86	-6.00 ± 4.48
Mean % change from baseline	-18%	-19%
p value	< 0.001	< 0.001
p value, between treatment groups	0.848	
	Fortical	Miacalcin
PTH	(n=56)	(n=58)
Baseline [1] mean (SD) ng/mL	38.80 ± 15.00	38.93 ± 11.81
Final mean (SD) ng/mL	36.19 ± 14.28	35.87 ± 15.90
Mean change from baseline	-1.15 ± 8.19	-4.95 ± 10.48
Mean % change from baseline	-2%	-11%
p value	0.298	0.001
p value, between treatment groups	0.018	

Bone Mineral Density: Change in bone mineral density at the AP spine, lateral spine and femur was assessed at 24 weeks for subjects who completed treatment. BMD at the AP spine was significantly increased from baseline in both treatment groups. The was no treatment difference

noted between the two groups. As one would have expected, the largest increase in bone mineral density occurred at the lateral spine where there is the highest percentage of trabecular bone present. In this study, the sample size for lateral spine measurements is small (n = 13) and skewed, rendering adequate interpretation difficult.

Study UGL-N9904: Bone Mineral Density		
BMD endpoint	Fortical	Miacalcin
AP spine	(n=58)	(n=57)
Baseline [1] mean	0.800	0.825
Change from baseline		
Mean	+0.010	+0.012
Median	+0.005	+0.011
p value	0.006	0.001
p value, between groups	0.914	
% change from baseline		
Mean	+1.3%	+1.5%
Median	+0.7%	+1.3%
Lateral spine	(n=13)	(n=13)
Baseline [1] mean	0.597	0.609
Change from baseline		
Mean	+0.031	+0.026
Median	+0.012	+0.013
p value	1.152	0.074
p value, between groups	0.808	
% change from baseline		
Mean	+6.0%	+4.7%
Median	+2.2%	+2.3%
Femur	(n=58)	(n=57)
Baseline [1] mean	0.569	0.572
Change from baseline		
Mean	+0.006	+0.003
Median	+0.005	+0.002
p value	0.047	0.316
p value, between groups	0.582	
% change from baseline		
Mean	+1.3	+1.0%
Median	+0.9	+0.4%

Medical Officer's Conclusions: Treatment with Fortical or Miacalcin for 12 weeks resulted in statistically significant decreases in bone turnover markers. For the primary efficacy endpoint, β-CTx, treatment with Fortical resulted in a 36% decrease compared with baseline ($p < 0.001$) and treatment with Miacalcin resulted in a 43% decrease compared with baseline ($p < 0.001$). There was not a placebo group in this study. Data from placebo groups from prior studies with Miacalcin cannot be used for comparison for several reasons: 1) serum β-CTx was not evaluated in previous studies and 2) the earliest time point of any biomarker evaluation was 12 months. At 24 weeks of therapy, treatment with Fortical or Miacalcin resulted in a significant increase in bone mineral density at the AP spine [+1.3% in the Fortical-treated group ($p=0.006$) and +1.5% in the Miacalcin-treated group ($p=0.001$)]. In comparison to Miacalcin, Fortical appears pharmacodynamically equivalent for the treatment of osteoporosis in women greater than 5 years post menopause.

VI.D. Efficacy Conclusions

The efficacy of Fortical Nasal Spray was based primarily on the prior approval of Miacalcin Nasal Spray and the results of a 24-week, active-controlled, equivalence study comparing changes in bone markers in Fortical- vs. Miacalcin-treated postmenopausal women. The two drugs were deemed equivalent because the 95% confidence interval for the difference between groups in the mean change from baseline to Week 12 in ß-CTx was –0.08 to 0.06 ng/ml, which is within the pre-specified equivalence margin of ± 0.20 ng/ml.

Treatment with Fortical or Miacalcin for 12 weeks resulted in statistically significant decreases in bone turnover markers. In evaluation of the primary efficacy endpoint, β-CTx, Fortical resulted in a 36% decrease compared with baseline ($p < 0.001$) and treatment with Miacalcin resulted in a 43% decrease compared with baseline ($p < 0.001$). There was not a placebo group in the study reviewed and no prior studies with Miacalcin have adequate data for comparison. The sponsor was asked to perform a meta-analysis of published literature. The results of that analysis of seven published trials in osteoporosis patients suggest that calcium supplementation with or without vitamin D results in a decrease in serum CTx of approximately 12.8 ± 4.4% at 6 months of treatment.

At 24 weeks of therapy, treatment with Fortical or Miacalcin resulted in a significant increase in bone mineral density at the AP spine. In comparison to Miacalcin, Fortical appears pharmacodynamically equivalent for the treatment of osteoporosis in women greater than 5 years post menopause.

VII. Integrated Review of Safety

VII.A. Brief Statement of Conclusions

There were no new safety signals noted with Fortical treatment. The occurrence of nasal adverse events was equally distributed between the Fortical and Miacalcin treatment groups.

VII.B. Description of Patient Exposure

A total of 195 subjects participated in these three trials evaluating the safety of Fortical nasal spray. Fifty-eight subjects received Fortical, formulation A (13 received 2000 IU on a single day and 45 received 2400 IU on a single day). There are no plans to market this formulation. Fortical, formulation B is planned for marketing and underwent further testing. A total of 126 subjects received this formulation of Fortical12 received 2000 IU on a single day, 45 received 2400 IU on a single day and 67 received 200 IU daily for 24 weeks) and 126 subjects received Miacalcin (14 received 2000 IU on a single day, 45 received 2400 IU on a single day and 67 received 200 IU daily for 24 weeks).

VII.C. Methods and Specific Findings of Safety Review

The three nasal spray studies, UGL-N9901, UGL-N9903 and UGL-N9904, were reviewed in depth for safety.

VII.C.1. Study UGL-N9904: This was a multicenter, double-blind, parallel-group, active-comparator study conducted in postmenopausal women.

Demographics: The two groups were well matched for baseline demographic characteristics. The average age of study participants was 66 years. The average BMI was 25 kg/m^2. The racial composition of the study population was 98% Caucasian.

Exposure: All subjects enrolled in the study received 200 IU salmon calcitonin (either Fortical or Miacalcin) daily for 24 weeks. A total of 134 subjects enrolled in the study (67 in each treatment group) and 118 subjects completed the study. Fourteen subjects (7 from each treatment group) withdrew due to adverse events and two (one from each treatment group) subjects withdrew for other reasons.

UGL-N9904: Drug Exposure		
	N	Total Dose received
Fortical		
Fortical – 24 weeks	59	33600 IU
Fortical – 8 weeks	5	11,200 IU
Fortical – 4 weeks	3	5,600 IU
Fortical – 0 weeks	0	< 1,400 IU
Miacalcin		
Miacalcin – 24 weeks	59	33600 IU
Miacalcin – 8 weeks	2	11,200 IU
Miacalcin – 4weeks	3	5,600 IU
Miacalcin – 0 weeks	3	< 1,400 IU

Deaths: There were no deaths during this study.

Serious Adverse Events: Three serious adverse events were reported during the study. A 70-year-old woman, receiving Miacalcin, was diagnosed with lung cancer and withdrew from the study. A 74-year-old woman, receiving Fortical, with a history of hypertension and angina controlled with multiple medications experienced an episode of hypotension requiring hospitalization. Upon discharge, she continued and completed the study. A 74-year-old woman, receiving Fortical, suffered an accidental fall during the study period, did not require hospitalization and completed the study.

Adverse Events Leading to Withdrawal: Fourteen (seven in each group) subjects withdrew from the study due to adverse events. Four subjects (two in each group) withdrew because of nasal symptoms, three of which could possibly be attributed to study medication. For a full list of adverse events leading to withdrawal, see the appendix.

Adverse Events: : There were a total of 271 adverse events reported by subjects treated with Fortical and 294 adverse events reported by subjects treated with Miacalcin (see table below). The most common adverse events were rhinitis, headache, epistaxis, nausea, and rash.

UGL-N9904: Adverse Events, by Body System		
	Fortical	Miacalcin
Subjects Receiving Dose	67	67
Subjects with At Least 1 AE	58 (87%)	63 (94%)
Systems:		
Gastrointestinal	19 (28%)	32 (48%)
Cardiovascular	9 (13%)	9 (13%)
Body as a whole	30 (45%)	35 (52%)
Musculoskeletal	13 (19%)	19 (28%)
Nervous	15 (22%)	14 (21%)
Respiratory	47 (70%)	53 (79%)
Skin and Appendages	22 (33%)	17 (25%)
Special Senses	3 (4%)	8 (12%)
Blood and Lymphatic	5 (7%)	3 (4%)
Endocrine/Metabolic	5 (7%)	4 (6%)
Urogenital	9 (13%)	8 (12%)

Adverse event reports were also analyzed based on age. A total of 61 subjects (31 in the Fortical group and 30 in the Miacalcin group) were less than or equal to age 65 at study enrollment. Of those enrolled, 57 subjects (87.1% of the Fortical-treated subjects and 100% of the Miacalcin-treated subjects) experienced adverse events during the study period. A total of 73 subjects (36 in the Fortical group and 37 in the Miacalcin group) were greater than age 65 at the beginning of the study. Of those enrolled, 64 subjects (86.1% of the Fortical-treated subjects and 89.2% of the Miacalcin-treated subjects) experienced adverse events during the study period. Nasal adverse events, known adverse effects of Miacalcin, have been shown to increase with patient age. In this study, nasal adverse events were equally distributed based on age.

Adverse Events of Special Interest: Nasal Events**:** One safety concern noted with Miacalcin is the effect on nasal mucosa. The table below provides comparison of nasal symptoms experienced with Fortical and Miacalcin. There were no increases in nasal events noted with Fortical use during this short 24-week study.

UGL-N9904: Adverse Events Related to the Nose		
	Fortical	Miacalcin
Rhinitis	13 (19%)	17 (25%)
Epistaxis	6 (9%)	5 (7%)
Nasal Irritation	5 (7%)	4 (6%)
Nasal Edema	1 (1%)	2 (3%)
Nasal Polyp	0 (0%)	1 (1%)
Nasal Tenderness	0 (0%)	1 (1%)
Nasal Septal Discharge	2 (3%)	2 (3%)
Nasal Septum Disorder	1 (1%)	0 (0%)
Tongue discoloration	2 (3%)	0 (0%)

Fracture: Fracture endpoints were not formally evaluated in this trial. There were no adverse event reports of fracture. Adverse event reports of back pain could possibly be attributed to vertebral fracture in some settings. Reports of back pain were equally distributed between the two groups (5 subjects (7%) in the Fortical-treated group and 4 subjects (6%) in the Miacalcin-treated group).

Laboratory: Safety laboratory assessments were performed at screening, Week 12 and Week 24 or last visit. The mean change between screening and follow-up was statistically significant in many of the laboratory parameters, though none were of clinical significance and levels remained well within the normal range. Clinically significant laboratory changes include a subject, treated with Miacalcin, who developed elevated liver function tests by Week 12. Tests remained elevated by Week 24. One subject, treated with Miacalcin, developed anemia by study end. The elevated liver function tests could possibly be due to Miacalcin use. There are two prior reports of elevated liver function tests in the AERS database, both resolved with discontinuation of Miacalcin use. There are no reports of anemia attributed to Miacalcin in the AERS database and it is unlikely that the anemia could be attributed to the drug therapy.

Calcium levels increased in both treatment groups, resulting in above normal levels in 7 subjects (2 in the Fortical-treated group and 5 in the Miacalcin-treated group). These increases are most likely related to the requisite calcium and vitamin D supplementation. One subject, receiving Fortical, developed asymptomatic mild hypocalcemia by Week 12, which normalized by Week 24.

Other Safety Tests: There were no clinically significant differences between treatment groups in temperature, respiratory rate, blood pressure or heart rate noted during the study. New abnormal findings on nasal examination were noted in 8 subjects (4 in each group) during the study. There were no findings of nasal ulceration in either group.

Medical Officer Conclusions: There are no new safety signals noted with Fortical treatment. The occurrences of nasal adverse events were equally distributed between the Fortical and Miacalcin treatment groups. There was no evidence of increased nasal adverse events in the population over age 65 years. Events noted in the high-dose pharmacokinetic trials (nausea, dizziness, postural hypotension) were not seen in the pharmacodynamic trial. There were no clinically significant laboratory changes noted. No fractures were noted in this short trial, although fracture outcomes were not formally evaluated (i.e., morphometric assessments).

VII.C.2. Study UGL-N9903: This is a single-center, single-blind, crossover bioequivalence study comparing Fortical nasal spray and Miacalcin nasal spray in normal volunteers.

Demographics: A total of 108 subjects were screened for enrollment into this trial. Enrollment criteria included healthy women, age 18-45 years with a BMI of 19-30 kg/m^2 with normal vital signs, ECG and laboratories, who demonstrated measurable levels of synthetic calcitonin following nasal administration of 800IU Miacalcin nasal spray (two 400 IU doses given 20 minutes apart). A total of 47 subjects were enrolled and received at least one dose of study medication. The average age of study participants was 29.4 years. The average BMI was 23.1

kg/m^2. The racial composition of the study population was mixed (63.8% Caucasian, 29.8% Hispanic, 4.3% African American and 2.1% Asian).

Exposure: A total of 47 subjects received study medication, 45 subjects completed the study and received all three treatments. Each participated in three treatment phases, one week apart. During each treatment phase, subjects were exposed to six doses of 400 IU test drug every 20 minutes for a total of 2400 IU over a period of 100 minutes. One test drug per treatment phase was administered and included Forcaltonin A, Forcaltonin B and Miacalcin. The two subjects who withdrew from the trial withdrew after the first treatment period. One received Forcaltonin B, the other received Miacalcin.

Deaths: There were no deaths during this study.

Serious Adverse Events: There were no serious adverse events during this study.

Adverse Events Leading to Withdrawal: There were no withdrawals due to adverse events.

Adverse Events: There were a total of 60 adverse events for Forcaltonin A, 44 adverse events for Forcaltonin B and 47 adverse events for Miacalcin (see table below). The most common adverse events were nausea, rhinitis, vomiting, postural hypotension and vasodilation. Rhinitis was equally distributed among the groups [13 (29%) in the Forcaltonin A-treated group, 9 (20%) in the Forcaltonin B-treated group and 8 (17%) in the Miacalcin-treated group]. Nausea was also equally distributed among the groups [13 (29%) in the Forcaltonin A-treated group, 14 (30%) in the Forcaltonin B-treated group and 13 (28%) in the Miacalcin-treated group]. There were no severe adverse events reported.

UGL-N9903: Adverse Events, by Body System			
	Forcaltonin A	Forcaltonin B	Miacalcin
Subjects Receiving Dose	45	46	46
Subjects Reporting AEs	30 (67%)	28 (61%)	25 (54%)
Events:	60	44	47
Digestive	22	20	19
Nervous	0	0	1
Respiratory	14	10	12
Body as a whole	8	5	7
Cardiovascular	9	6	5
Blood and Lymphatic	2	1	1
Skin	2	1	0
Special Senses	1	0	0
Urogenital	2	1	2

Laboratory: Safety laboratory assessments were performed at screening and follow-up. The mean change between screening and follow-up was statistically significant in many of the laboratory parameters, though none were of clinical significance and levels remained well within the normal range. Four subjects had a clinically significant decrease in hematocrit, hemoglobin or red blood cell count. These decreases were attributed to the required frequent blood sampling. No subjects were discontinued from the study due to abnormal laboratory tests.

Other Safety Tests: There were no statistically significant abnormalities noted in blood pressure or heart rate during the study. Four subjects were noted to have nasal septum deviations on screening, no other nasal abnormalities were noted.

Nine subjects had abnormal ECG findings at screening, none were considered clinically significant. Changes in ECG parameters between the screening and follow-up (after all three dosing periods) visits are listed in the table below. These changes are not clinically significant.

UGL-N9903: Changes in ECG Parameters				
ECG parameter	Screening mean value	Follow-up mean value	Change	p-value
QT (mmsec)	390.28	383.43	-6.85	0.00965
PR (mmsec)	149.13	154.51	+5.38	0.00332
QRS (mmsec)	80.38	79.43	-0.96	0.04838

Medical Officer Conclusions: In this bioequivalence trial, healthy young volunteers received 2 different formulations of recombinant salmon calcitonin (Fortical) and one formulation of synthetic salmon calcitonin (Miacalcin) nasal spray, each at doses 12 times that of the daily recommended dose. Nasal symptoms (i.e., rhinitis) and nausea were equally distributed among the three groups. No clinically significant laboratory or ECG changes were noted. No new safety signals were detected in this short, high-dose trial.

VII.C.3. Study UGL-N9901: This was a phase I, single-center, non-blinded, clinical study evaluating the safety, tolerability and pharmacokinetics of repeated intranasal dose of Forcaltonin, a recombinant salmon calcitonin, compared with Miacalcin, a synthetic salmon calcitonin.

Demographics: A total of 14 subjects were screened for enrollment into this trial. Enrollment criteria included healthy women, age 18-45 years with a BMI of 19-30 kg/m^2 with normal vital signs, ECG and laboratories. All 14 subjects screened were enrolled and received at least one dose of study medication. The average age of study participants was 22.5 years. The average BMI was 23.2 kg/m^2. All study subjects were Caucasian.

Exposure: A total of 14 subjects received study medication, twelve subjects completed the study and received all three treatments. Each participated in three treatment phases, one week apart. During each treatment phase, subjects were exposed to five doses of 400 IU test drug every 20 minutes for a total of 2000 IU over a period of 80 minutes. One test drug per treatment phase was administered and included Forcaltonin A, Forcaltonin B and Miacalcin. A total of thirteen subjects received Forcaltonin A, twelve subjects received Forcaltonin B and fourteen subjects received Miacalcin.

Deaths: There were no deaths during this study.

Serious Adverse Events: There were no serious adverse events during this study.

Adverse Events Leading to Withdrawal: Two subjects withdrew from the study due to adverse events. One withdrew after receiving Miacalcin in treatment period one. The second subject withdrew after completing treatment periods one and two (Miacalcin and Forcaltonin A).

Adverse Events: There were a total of 41 adverse events for Forcaltonin A, 50 adverse events for Forcaltonin B and 27 adverse events for Miacalcin (see table below). The most common adverse events were rhinitis, nausea, vomiting, dizziness and vasodilation. Of note, rhinitis occurred more frequently with Forcaltonin use (A formulation: 9 events, B formulation: 7 events) compared to Miacalcin (2 events). Dizziness also occurred more frequently with Forcaltonin (A formulation: 6 events, B formulation: 9 events) compared to Miacalcin (1 event). Nausea was equally distributed among the groups (9 in the Forcaltonin A-treated group, 10 in the Forcaltonin B-treated group and 9 in the Miacalcin-treated group.

UGL-N9901: Adverse Events, by Body System			
	Forcaltonin A	Forcaltonin B	Miacalcin
Subjects Receiving Dose	14	14	14
Subjects Reporting AEs	9 (64%)	9 (64%)	6 (43%)
Events:	41	50	27
Digestive	16	10	12
Nervous	8	15	7
Respiratory	10	9	2
Body as a whole	6	12	2
Endocrine/Metabolic	-	-	2
Musculoskeletal	-	-	2
Cardiovascular	1	-	-
Blood and Lymphatic	-	3	-

Adverse events classified as severe included an episode of syncope in a subject receiving Forcaltonin A; one episode of severe nausea and two episodes of somnolence in one subject receiving Forcaltonin B; and two episodes of nausea and one episode of abdominal pain in one subject receiving Miacalcin.

Laboratory: Safety laboratory assessments were performed at screening and follow-up. All fourteen subjects enrolled in the trial had at least one abnormal laboratory value at some point during the trial, most were not clinically significant, however. The most common abnormality was a decrease in hematocrit, occurring in 11 subjects and attributed to the frequent blood sampling required for pharmacokinetic testing.

Other Safety Tests: There were no abnormalities noted in blood pressure or heart rate during the study. There were no clinically significant changes in ECG parameters during the study. One subject had developed a hand tremor, noted on the follow-up physical examination.

Medical Officer Conclusions: In this phase 1 trial, healthy young volunteers received 2 different formulations of recombinant salmon calcitonin (Fortical) and one formulation of synthetic salmon calcitonin (Miacalcin) nasal spray, each at doses 10 times that of the daily recommended dose. No new safety signals were noted. Nasal symptoms and dizziness were more

commonly experienced with the recombinant (Fortical) formulations than with Miacalcin. The significance of this difference is not clear. Occurrences of nausea were equally distributed among the groups. No new safety signals were detected in this short, high-dose trial.

VII.D. Adequacy of Safety Testing

The safety testing conducted in these three trials was adequate to evaluate known safety concerns and to detect new safety signals should they exist. However, given the small sample sizes of these trials, an adverse event would have to be greatly skewed in one group more than another before any conclusions could be made regarding safety differences between Fortical and Miacalcin.

VII.E. Summary of Critical Safety Findings and Limitations of Data

There were no new safety signals noted with Fortical treatment. In the studies utilizing high dose salmon calcitonin, nasal symptoms and dizziness were more commonly experienced with the recombinant (Fortical) formulations in the small phase 1 study; however, in the larger bioequivalence study, nasal symptoms were equally distributed among the treatment groups. The occurrence of nasal adverse events was equally distributed between the Fortical and Miacalcin treatment groups in the large pharmacodynamic study. Events noted in the high dose pharmacokinetic trials (nausea, dizziness, postural hypotension) were not seen in this trial. There were no clinically significant laboratory or ECG changes noted in any of the trials. No fractures were noted in the trials, although fracture outcomes were not systematically evaluated.

Human immunogenicity data has not been provided. Although the recombinant salmon calcitonin peptide molecule is authentic when compared to synthetic salmon calcitonin, studies have shown that changes in manufacturing techniques can result in different immunogenicity profiles for peptides. Synthetic salmon calcitonin is known to induce antibody formation in 40 – 70% of patients treated for more than 4 months, with some antibodies having a neutralizing effect[2].

VIII. Dosing, Regimen, and Administration Issues

Unigene Laboratories is requesting approval of a single dose of recombinant salmon calcitonin (Fortical) nasal spray: 200 IU daily. The currently marketed synthetic salmon calcitonin nasal spray dose is also 200 IU daily.

IX. Use in Special Populations

[2] Grauer A, Ziegler R, Raue F. Clinical significance of antibodies against calcitonin. Exp Clin Endocrinol Diabetes. 1995; 103(6):345-351.

IX.A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation
Fortical is indicated for the treatment of postmenopausal women with osteoporosis. All of the subjects enrolled in these trials were women.

IX.B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy
Nearly all subjects in these pharmacokinetic and pharmacodynamic trials were Caucasian. Therefore, the effects of race/ethnicity on the safety and efficacy of recombinant salmon calcitonin (Fortical) cannot be assessed.

IX.C. Evaluation of Pediatric Program
The proposed indication for Fortical is restricted to postmenopausal women. The efficacy and safety of recombinant salmon calcitonin nasal spray has not been evaluated in the pediatric population.

X. Conclusions and Recommendations

X.A. Conclusions
Unigene Laboratories has provided sufficient evidence that recombinant nasal calcitonin (Fortical) is comparable to synthetic salmon calcitonin (Miacalcin) when evaluated in pharmacokinetic and short term pharmacodynamic studies. To date, there are no adequately-conducted fracture prevention trials with salmon calcitonin that show calcitonin's efficacy in preventing osteoporotic fractures in postmenopausal women.

No significant safety issues were raised by the submitted data. Human immunogenicity data has not been provided and this data will be needed.

X.B. Recommendations
This reviewer recommends that Fortical 200 IU for the treatment of osteoporosis in women greater than 5 years post menopause be deemed approvable. Approval is contingent upon completion of adequate human immunogenicity studies.

The human immunogenicity studies should address the following concerns:
1) Is there formation of antibodies against recombinant and/or synthetic salmon calcitonin by study end (6 months, from study UGL-N9904)?
2) If antibody formation is detected, what percentage demonstrate a neutralizing effect? and
3) Is there any cross-reactivity between the recombinant salmon calcitonin antibody and human calcitonin?

XI. Appendix

XI.A. Other Relevant Materials

Study UGL-N9904: Withdrawals due to Adverse Events		
	Age (yr)	Last Visit
Fortical		
Vomiting / acid reflux	72	8 week
Upper and lower motor neuron disease	74	4 week
Hypertension	66	8 week
Angioedema	61	8 week
Exacerbation of nasal rhinitis	56	4 week
Nose bleed	60	4 week
Labyrinthitis	73	8 week
Miacalcin		
Purpuric macular rash over ankles	67	8 week
Blocked nasal passages	71	0 week
Headache	61	0 week
Fatigue	51	0 week
Lung Cancer	70	8 week
Nasal pharyngeal irritation	53	4 week
Worsening of asthma	45	4 week

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