Calcitonin Salmon for the Treatment of Postmenopausal Osteoporosis

Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee

March 5, 2013

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Director
Division of Reproductive and Urologic Products
U.S. Food and Drug Administration

Overview

- Welcome to our newest committee member
- Why bring calcitonin to advisory committee?
- Questions for the committee

New Committee Member

- **Amy K. Whitaker, M.D., M.S.**
  - Assistant Professor
  - Department of Obstetrics and Gynecology
  - University of Chicago

Why Discuss Calcitonin Salmon?

- No definitive evidence of fracture efficacy
- Possible signal for malignancy
- Appropriate to re-assess risk-benefit for treatment of postmenopausal osteoporosis

Question 1 for the Committee

VOTE: Does the overall benefit-risk assessment support the continued marketing of calcitonin salmon for the treatment of osteoporosis in women greater than 5 years post menopause?

Please provide a rationale for your vote and, if applicable, any additional recommendations.

Question 2 for the Committee

VOTE: For calcitonin salmon products under development, should fracture efficacy data be required for approval for treatment or prevention of postmenopausal osteoporosis indications?

Please provide a rationale for your vote and, if applicable, any additional recommendations.

Calcitonin Salmon

Regulatory History

Theresa Kehoe, M.D.
Medical Officer, Team Leader
Division of Reproductive and Urologic Products
Office of New Drugs, CDER, FDA

FDA Presentation

- **Background:** Regulatory History, Drug Use Data and the Initial Safety Signal
- **Epidemiologic Review** of the Novartis meta-analysis
- **Statistical Review** the Novartis meta-analysis
- **Efficacy Review** of Calcitonin salmon
- **Summary**

Postmenopausal Osteoporosis

- Osteoporosis is defined as a systemic skeletal disorder of compromised bone strength, predisposing an individual to an increased risk of fracture
- Bone mineral density T-score less than -2.5
- Currently, an estimated 10 million people in the US have osteoporosis (8 million women, 2 million men)

Therapies Seeking an Indication for Treatment of Osteoporosis

- Must demonstrate nonclinical evidence of bone quality including biomechanical testing of bone strength
- Must demonstrate bone quality and normal mineralization on bone biopsy (bone histomorphometry)
- Must demonstrate fracture reduction efficacy in a 3-year clinical trial
- Once fracture efficacy is established, subsequent indications or new dose regimens are based on BMD non-inferiority

Products Available for Treatment of Osteoporosis

- **Bisphosphonates**
  - **Alendronate** (Fosamax, Fosamax plus D, Binosto)
  - **Risedronate** (Actonel, Actonel with calcium, Atelvia)
  - **Ibandronate** (Boniva)
  - **Zoledronic acid** (Reclast)
- **Evista**
- **Forteo**
- **Prolia**
- **Calcitonin**
  - Miacalcin
  - Fortical

Calcitonin salmon

- Calcitonin is a 32 amino acid peptide hormone that plays an important role in mineral metabolism and bone homeostasis
  - Inhibits bone resorption by the osteoclast
  - Inhibits uptake of calcium from the intestine
  - Inhibits resorption of calcium from the kidney
- Calcitonin salmon is 50% identical to human calcitonin with a longer half-life and better receptor affinity

Calcitonin salmon Regulatory History

- The first calcitonin salmon (Calcimar) approval:
  - 1975 - Paget's disease of bone
  - 1980 - treatment of hypercalcemic emergencies

Calcitonin salmon Regulatory History

- An application for Calcimar for treatment of postmenopausal osteoporosis
  - Based on total body calcium assessed by neutron activation analysis
  - Concerns regarding partial reversal of gains in the second year
  - EMDAC in September 1981
    - Data suggested calcitonin salmon's effectiveness in increasing total body calcium in some patients for a period up to 12 months

Calcitonin salmon Regulatory History

- Calcimar was approved for treatment of postmenopausal osteoporosis December, 1984
  - With a commitment to conduct a Phase IV fracture study
- A second injectable calcitonin salmon product (Miacalcin) was approved in 1986
  - With a commitment to conduct a Phase IV fracture study

Calcitonin salmon Regulatory History

- One postmarketing fracture study was conducted (for Calcimar)
  - Enrollment was poor
  - Interim analysis was unfavorable for calcitonin
- EMDAC July, 1991
  - Calcitonin salmon reduces bone loss but no conclusions regarding the fracture data can be made

Calcitonin salmon Regulatory History

- Calcitonin salmon nasal spray (Miacalcin) was submitted in 1992
  - Three double blind placebo controlled studies of bone mineral content (BMC) or bone mineral density study (BMD)
  - Miacalcin nasal spray fracture study (CT320) was ongoing
- 1994 updated Osteoporosis Guidelines
  - requiring fracture data released during review period
- EMDAC November, 1994 – BMD changes with Miacalcin sufficient to establish clinically important efficacy

Calcitonin salmon Regulatory History

- Miacalcin nasal spray approved August, 1995
  - With a commitment to complete the ongoing fracture trial CT320
- Trial CT320 (PROOF) submitted for labeling and found not approvable in 2000

Calcitonin salmon Regulatory History

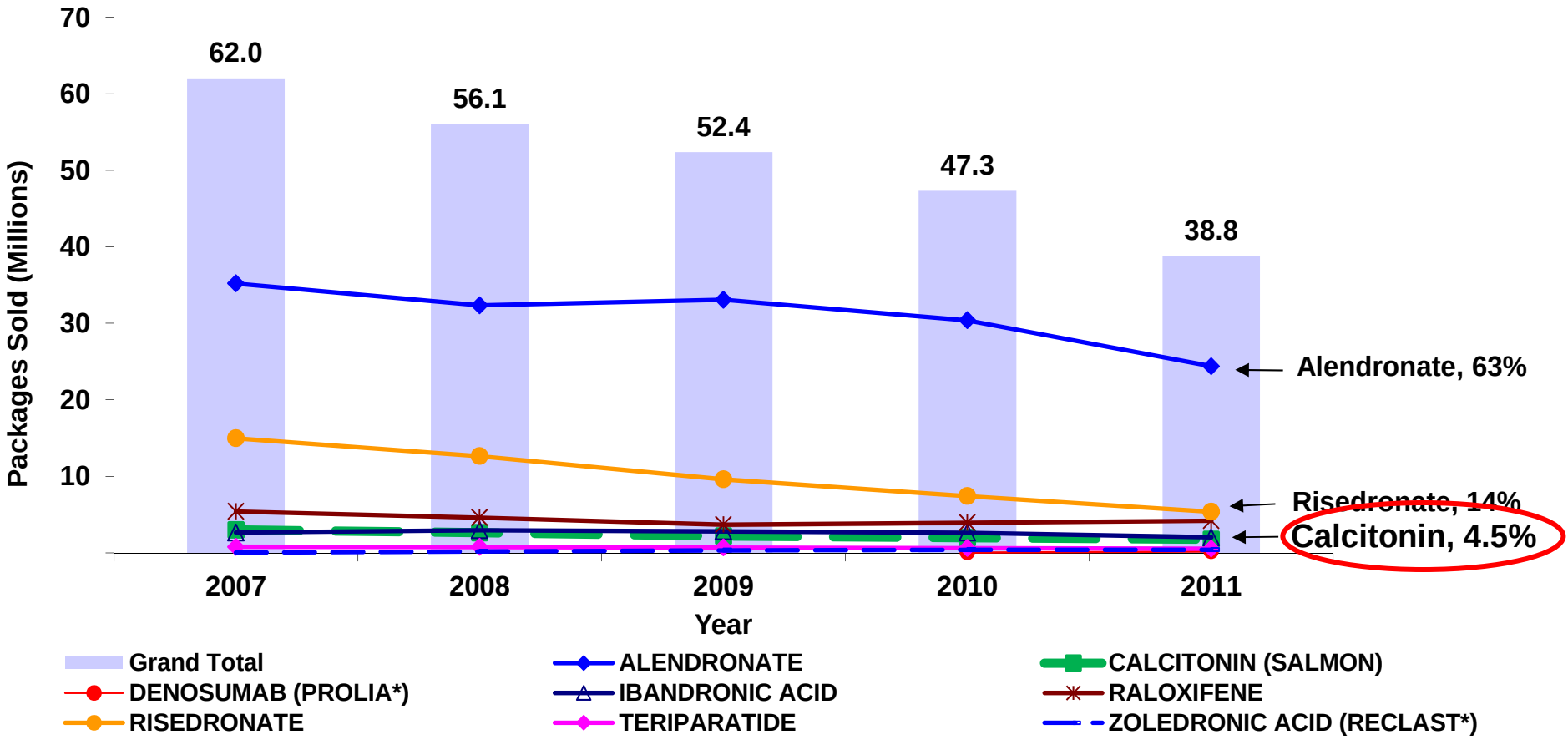
- Fortical nasal spray (recombinant calcitonin salmon) submitted in 2003, relied on FDA's prior findings of safety and effectiveness of Miacalcin nasal spray (synthetic calcitonin salmon)
- Approved in 2005

Calcitonin salmon Regulatory History

- Calcimar injection was withdrawn from the US market by the NDA holder in 1999 (lyophilized powder formulation) and 2007 (solution formulation)
- Currently, available calcitonin salmon (sCT) products include:
  - Miacalcin (synthetic sCT) Injection
  - Miacalcin (synthetic sCT) Nasal Spray
  - Fortical (recombinant sCT) Nasal Spray
  - Generic Products (synthetic sCT)

U.S. Sales of Osteoporosis Products

Sales of Osteoporosis Products in Packages Sold† (bottles or vials) to all U.S. Channels of Distribution

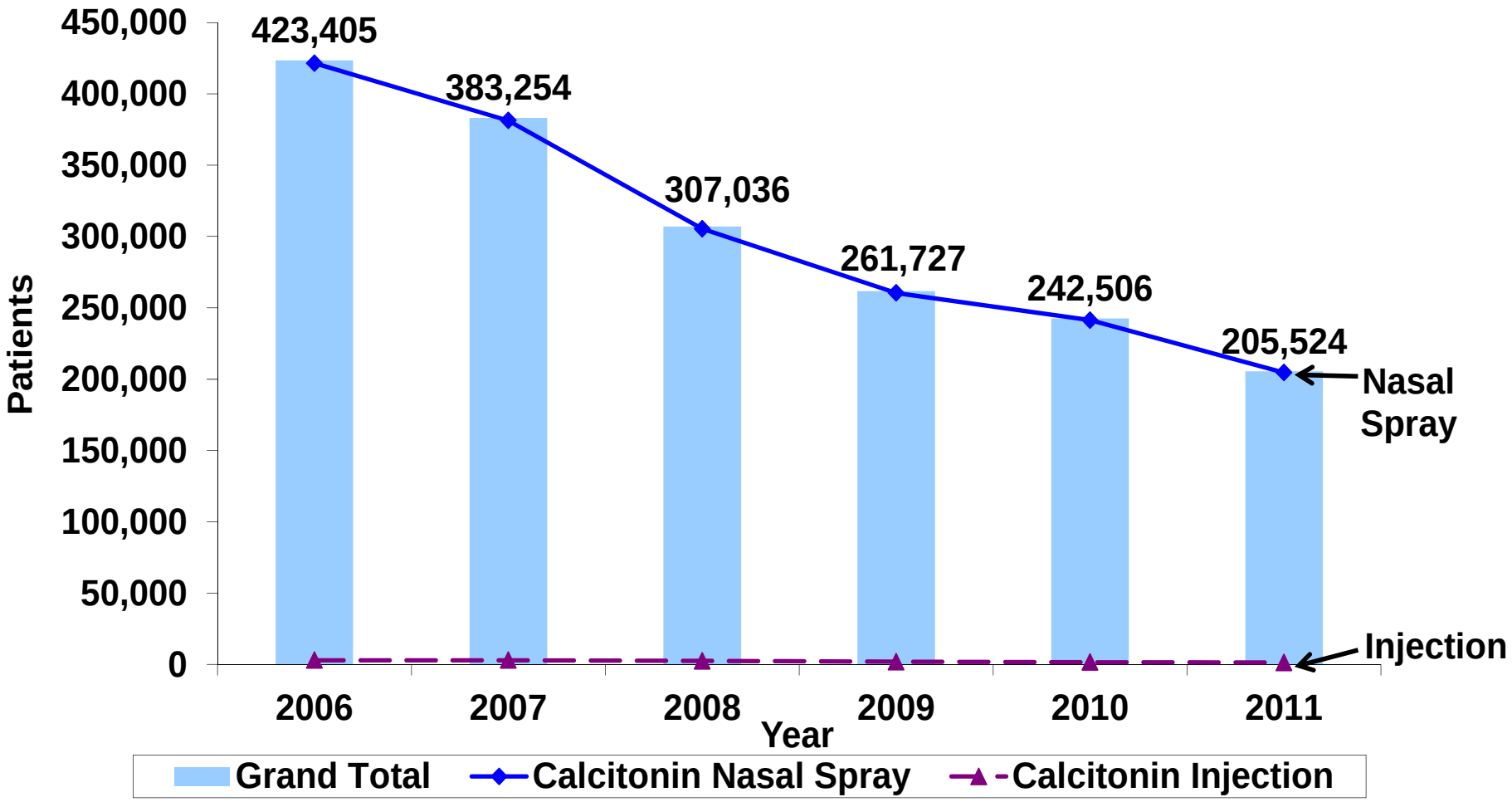


Source: IMS Health, IMS National Sales Perspectives™, Years 2007-2011, Data Extracted January 2013

† Packages = (bottles, IV bags, pre-filled syringe kits, vials)

*Only products with approved labeling for the treatment of osteoporosis were included (e.g. Xgeva and Zometa were excluded)

Patient Utilization of Calcitonin-Containing Products by Dosage Form in U.S. Outpatient Retail Pharmacies



Source: IMS Total Patient Tracker. Year 2006-2011 Data Extracted February 2013

Calcitonin salmon Postmarketing Safety

- Allergic Reactions
  - Skin testing recommended
- Nasal inflammation / ulceration
  - Periodic nasal examination recommended

Calcitonin salmon: Safety Signal

- Multiple calcitonin salmon products are currently in development for treatment of osteoporosis and other indications
- Osteoarthritis trial data from one oral calcitonin product, SMC021, showed an imbalance in prostate cancer between active drug and placebo

SMC021 Trials

- SMC021: recombinant calcitonin salmon with 5-CNAC {8-(5-Chloro-2-hydroxybenzoylamino) octanoic acid disodium salt monohydrate}
- Osteoarthritis trials C2301 and C2302
  - 2206 subjects (1430 women, 776 men) age 51-80 years
  - SMC021 0.8 mg or placebo twice daily
- Postmenopausal osteoporosis trial A2303
  - 4665 postmenopausal women age 50 – 86 years
  - SMC021 0.8 mg or placebo daily

Calcitonin salmon Safety Signal

- November, 2010 – imbalance in prostate cancer
  - 6 cases with SMC021
  - 0 cases with placebo
- All men notified and offered prostate cancer screening
  - 91% agreed to screening for prostate cancer
  - Stored serum retrospectively analyzed for PSA levels
- Total number of men with prostate cancer
  - 20 cases with SMC021
  - 16 cases with placebo

Calcitonin salmon Safety Signal

- Prostate cancer incidence in these two trials was high
  - perhaps due to some differences in routine background screening for prostate cancer at study locations
- Most cases had an elevated PSA at baseline
- PSA levels increased in both treatment groups
- Prognostic factors similar between treatment groups
- While *in-vitro* evidence suggests a role for calcitonin in the tumorigenicity of prostate cancer, there is no evidence that:
  - Calcitonin induces prostate cancer in benign epithelium
  - Calcitonin causes a latent cancer to become more aggressive

Nonclinical Data

- No neoplastic findings in a two year mouse carcinogenicity study
- Early increased incidence of pituitary adenomas observed at one year in carcinogenicity studies conducted in two strains of rats
  - No mechanistic explanation for this finding
  - Pituitary adenomas are common in aged rats
  - No other treatment-related neoplastic findings in rats

Further Evaluations: AERS

- An AERS database search for postmarketing events of malignancy following calcitonin exposure was conducted
  - No potential signal for prostate cancer or any other malignancy was identified

Further Evaluations

- The Applicant (Novartis) conducted a trial-level meta-analysis to evaluate the risk of malignancy in patients treated with calcitonin salmon

Calcitonin salmon RCTs – Safety Signal

Joint Meeting of the Advisory Committee Reproductive Health Drugs and the Drug Safety Risk Management Advisory Committee
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CDR David Moeny, MPH, R.Ph.
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Overview of Presentation

- Safety Concern and Meta-analysis
- Calcitonin Randomized Controlled Trials
- Malignancy Assessment
- Need for Meta-analysis
- Safety trends- dose and duration
- Issues with meta-analysis
- Conclusions

Safety Concern - Malignancies

- Safety signal from an oral calcitonin clinical trial indicated a potential increased cancer risk, particularly prostate cancer
- Cancer cases seen in previous trials but calcitonin not suspected
- Individual studies were inadequately powered to measure the risk of cancer
- Was the malignancy finding a chance event?
- Meta-analysis may help to clarify the risk.

Calcitonin Studies (Product Development)

- Novartis identified studies through an internal search and from PubMed
- No published epidemiologic studies identified
- Three calcitonin dosage forms: injection, nasal, and oral (in development)
  - only nasal and oral considered here
- 19 Randomized controlled trials, 1 open label
  - 17 nasal dosage form (CT211-CT320, SMCO005-SMCO524, MIA16, 2402)
  - 3 oral dosage form (A2303, C2302, C2303)

17 Studies for Nasal Formulation *

- Initiated between 1985 and 2002
- Range of doses – 50, 100, 200, and 400 IU daily, 3 times weekly
- Primarily single country/single center
- Small number of patients: < 100 calcitonin subjects per arm
- Recruited mostly women (2 studies included men)

**18 in Novartis's background package*

17 Studies for Nasal Formulation *

- Evaluation of
  - Peri/post-menopausal osteoporosis treatment or prevention
  - Strength and pain post forearm fracture
  - Corticosteroid induced osteoporosis
- Most studies enrolled women ages ~45-65 years
- Duration varied but most were 2-year trials

Duration	6 Months	1 Year	2 Years	3 Years	5 Years
Number of Trials	1	1	9	4	1

**18 in Novartis's background package*

Examples of Nasal Formulation Studies

Study	Date	n (calcitonin/ placebo)	Population	Dose	Duration
320	1991	944/311	Female only, low bone mineral density, prior vertebral or thoracic fractures	3 arms: 100, 200 400 IU daily	5 years
311, 312	1992	201/102	Male or female*, daily oral corticosteroid, RA or pulmonary disease	2 arms: 200, 400 IU daily	3 years
2402		149/148	Female, age >60 years with a forearm fracture	200 IU daily	6 months
005	1988	32/10	Females age 45-75 years, recent history of Colles fracture	3 arms: 50, 100, 200 IU daily	1 year

**All females were postmenopausal*

3 Studies for Oral Formulation

- Initiated in 2007 and 2008
- 2 enrolled both men and women
- Multi-center, multi-national
- Relatively large studies enrolling 588, 521, and 2,334 calcitonin subjects
- Evaluated
  - Post-menopausal osteoporosis
  - Knee osteoarthritis (2 studies)

Summary of Oral Formulation Studies

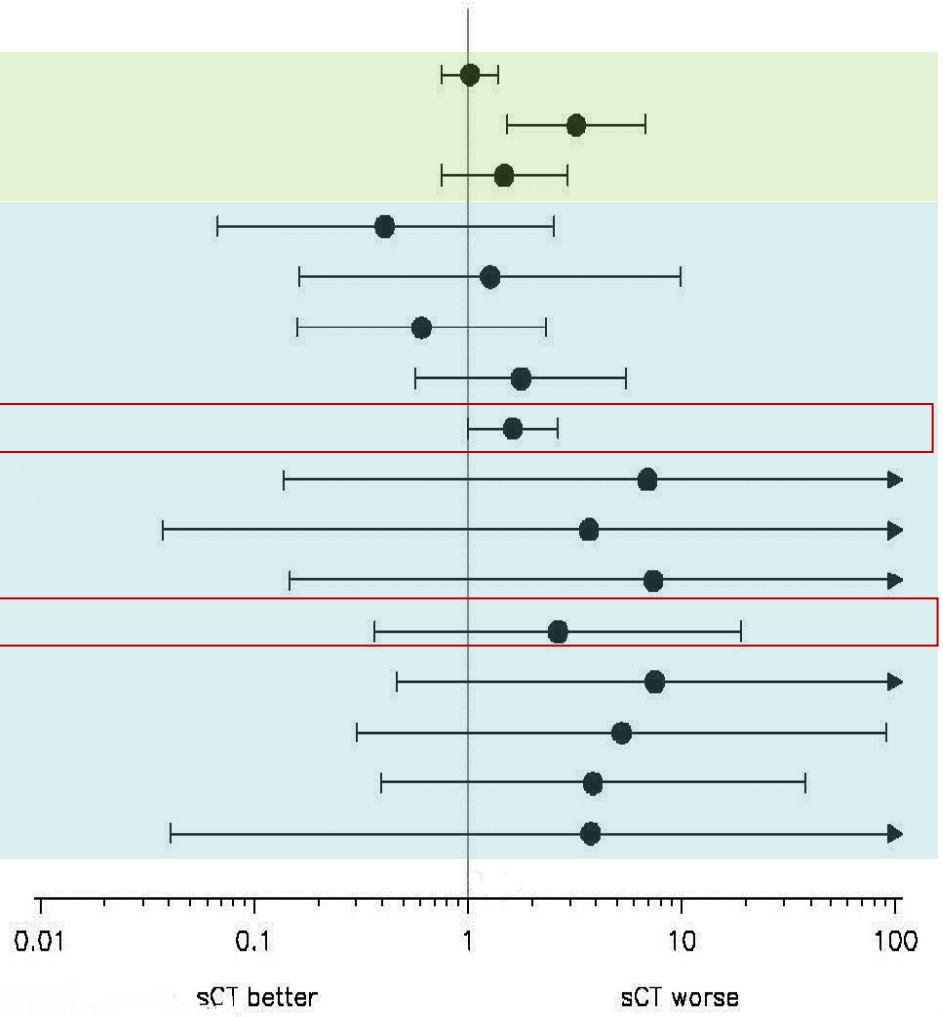
Study	Date	n (calcitonin /placebo)	Population	Dose	Duration
2301	2007	585/584	Men, women 51-80 years old, 2 years post-menopause, knee osteoarthritis	0.8 mg twice daily	2 years
2302	2008	521/509	Men, women 2 years post-menopause, 51-80 years old, knee osteoarthritis	0.8 mg twice daily	2 years
2303	2007	2334/2331	Women 55-85 years old, post-menopause, osteoporosis	0.8 mg once daily	3 years

Malignancy not a Primary Objective

- For all studies, malignancy was
  - Not a pre-defined outcome
  - Captured as an adverse event
  - Adverse event identification methods and documentation varied among studies
- Malignancy occurrences were identified through review of study reports

Incidences and Odds Ratio for Any Malignancy: Nasal and Oral* (Novartis)

	Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
Oral	A2303	89/2334 (3.81)	87/2331 (3.73)	1.02(0.76– 1.38)
	C2301	22/ 585 (3.76)	6/ 584 (1.03)	3.22(1.52– 6.81)
	C2302	21/ 520 (4.04)	14/ 508 (2.76)	1.48(0.75– 2.90)
Nasal	CT 211	3/ 31 (9.68)	3/ 15 (20.0)	0.41(0.07– 2.51)
	CT 310	4/ 211 (1.90)	1/ 68 (1.47)	1.27(0.16– 9.95)
	CT 311	8/ 244 (3.28)	4/ 79 (5.06)	0.61(0.16– 2.32)
	CT 312	11/ 201 (5.47)	3/ 102 (2.94)	1.77(0.57– 5.51)
	CT 320	81/ 944 (8.58)	16/ 311 (5.14)	1.62(1.00– 2.61)
	MIA 16	1/ 32 (3.13)	0/ 30 (0.00)	6.94(0.14– 350.5)
	SMCO 005	1/ 32 (3.13)	0/ 10 (0.00)	3.72(0.04– 370.3)
	SMCO 504	1/ 29 (3.45)	0/ 29 (0.00)	7.39(0.15– 372.4)
	SMCO 506	3/ 147 (2.04)	1/ 141 (0.71)	2.63(0.37– 18.91)
	SMCO 511	2/ 60 (3.33)	0/ 60 (0.00)	7.52(0.46– 121.6)
	SMCO 514	2/ 71 (2.82)	0/ 46 (0.00)	5.27(0.31– 91.09)
	SMCO 522	4/ 156 (2.56)	0/ 52 (0.00)	3.87(0.40– 37.81)
	SMCO 524	1/ 100 (1.00)	0/ 33 (0.00)	3.78(0.04– 353.5)



**4 Studies without malignancies reported are not included*

Calcitonin Trial Arms with Fewer Events than Placebo*

	100	200	400	Placebo
	Events/n (%)	Events/n (%)	Events/n (%)	Events/n (%)
CT-211		3/16 (18.8)	0/15 (0.0)	3/15 (20.0)
CT-310	0/71 (0.0)	3/72 (4.2)	1/68 (1.5)	1/65 (1.5)
CT-311	4/83 (4.8)	1/82 (1.2)	3/79 (3.8)	4/79 (5.1)
CT-312		7/102 (6.7)	4/99 (4.0)	3/102 (2.9)
CT-320	26/316 (8.2)	24/316 (7.6)	31/312 (9.9)	16/311 (5.1)
SMCO-005	0/10 (0)	1/11 (9.1)		0/10 (0.0)
SMCO-504	1/29 (3.4)			0/29 (0.0)
SMCO-511	2/60 (3.3)			0/60 (0.0)
SMCO-514		2/36 (5.6)		0/46 (0.0)
SMCO-522	0/43 (0.0)	2/52 (3.8)		0/52 (0.0)
SMCO-524	0/33(0.0)	1/34 (2.9)	0/34 (0)	0/33 (0.0)
MIA-16			1/32 (3.1)	0/30 (0.0)
2402		0/149 (0.0)		0/147 (0.0)
SMCO-503	0/26 (0.0)			0/26 (0.0)
SMCO-517		0/84 (0.0)		0/83 (0.0)
SMCO-520	0/33 (0.0)	0/32 (0.0)		0/32 (0.0)

*25, 50 IU and non-daily dosing arms omitted

Calcitonin Trial Arms with More Events than Placebo*

	100	200	400	Placebo
	Events/n (%)	Events/n (%)	Events/n (%)	Events/n (%)
CT-211		3/16 (18.8)	0/15 (0.0)	3/15 (20.0)
CT-310	0/71 (0.0)	3/72 (4.2)	1/68 (1.5)	1/65 (1.5)
CT-311	4/83 (4.8)	1/82 (1.2)	3/79 (3.8)	4/79 (5.1)
CT-312		7/102 (6.7)	4/99 (4.0)	3/102 (2.9)
CT-320	26/316 (8.2)	24/316 (7.6)	31/312 (9.9)	16/311 (5.1)
SMCO-005	0/10 (0)	1/11 (9.1)		0/10 (0.0)
SMCO-504	1/29 (3.4)			0/29 (0.0)
SMCO-511	2/60 (3.3)			0/60 (0.0)
SMCO-514		2/36 (5.6)		0/46 (0.0)
SMCO-522	0/43 (0.0)	2/52 (3.8)		0/52 (0.0)
SMCO-524	0/33 (0.0)	1/34 (2.9)	0/34 (0)	0/33 (0.0)
MIA-16			1/32 (3.1)	0/30 (0.0)
2402		0/149 (0.0)		0/147 (0.0)
SMCO-503	0/26 (0.0)			0/26 (0.0)
SMCO-517		0/84 (0.0)		0/83 (0.0)
SMCO-520	0/33 (0.0)	0/32 (0.0)		0/32 (0.0)

*50IU and non-daily dosing arms omitted

Trials with no Malignancies*

	100	200	400	Placebo
	Events/n (%)	Events/n (%)	Events/n (%)	Events/n (%)
CT-211		3/16 (18.8)	0/15 (0.0)	3/15 (20.0)
CT-310	0/71 (0.0)	3/72 (4.2)	1/68 (1.5)	1/65 (1.5)
CT-311	4/83 (4.8)	1/82 (1.2)	3/79 (3.8)	4/79 (5.1)
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SMCO-522	0/43 (0.0)	2/52 (3.8)		0/52 (0.0)
SMCO-524	0/33(0.0)	1/34 (2.9)	0/34 (0)	0/33 (0.0)
MIA-16			1/32 (3.1)	0/30 (0.0)
2402		0/149 (0.0)		0/147 (0.0)
SMCO-503	0/26 (0.0)			0/26 (0.0)
SMCO-517		0/84 (0.0)		0/83 (0.0)
SMCO-520	0/33 (0.0)	0/32 (0.0)		0/32 (0.0)

*50 IU and non-daily dosing arms omitted

Malignancy Signal

- 13 of the 17 nasal formulation studies and all of the 3 oral formulation studies reported at least 1 malignancy in calcitonin treated groups
- Malignancy reports were identified by case and study reviews
- Malignancies occurred only in the treatment arm(s) or more frequently in the treatment arm(s) than in the placebo arm

Imbalance in Occurrence of Malignancy (Novartis)

	Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
Oral	A2303	89/2334 (3.81)	87/2331 (3.73)	1.02(0.76– 1.38)
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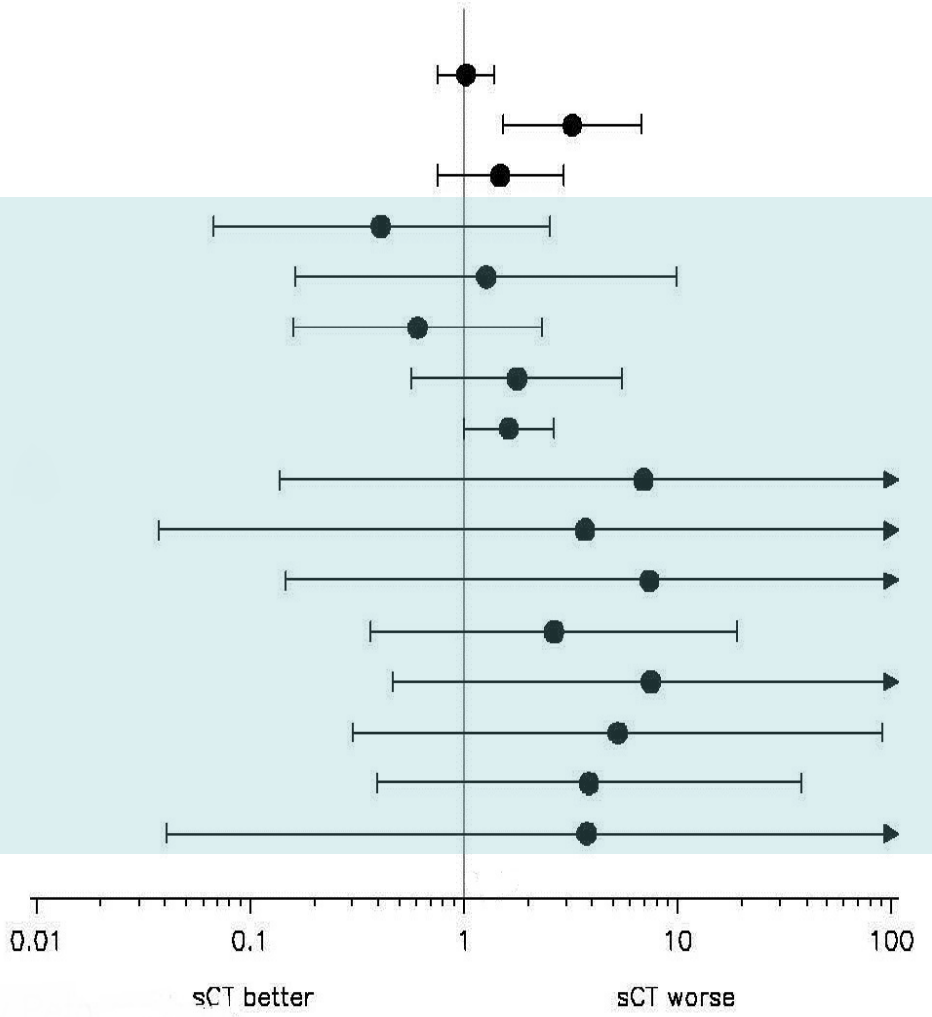


*Studies without malignancies reported are not included

Reasons to Consider a Meta-analysis

- Individual trials underpowered to evaluate the risk
- Multiple randomized clinical trials available for inclusion
  - No published observational studies identified by Novartis or by the Office of Surveillance and Epidemiology
- Full study reports available to assess malignancy occurrence

Overall Risk Estimate Consistent with Dose Level Estimates

- Summary of Norvartis's meta-analytic estimates of malignancy risk for calcitonin compared to placebo

Dose Form		Estimate	95% confidence interval
Nasal	Odds Ratio	1.6	1.1-2.3
100 IU		1.5	0.9-2.7
200 IU		1.6	1.0-2.7
400 IU		1.5	0.9-2.5
Oral	Risk Ratio	1.3	1.0-1.7

Unanswered Questions

- Higher risk in calcitonin groups but studies evaluated different doses
  - Dose response not apparent
- Are there consistent trends over time?

Novartis's Malignancy Trends Over Time

	Months							
	0	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Nasal calcitonin	2634	2377 0.9%	2077 1.2%	1885 0.7%	1770 0.6%	742 3.2%	495 1.4%	383 3.9%
Nasal Placebo	1234	1105 0.8%	902 0.2%	826 0.2%	784 0.3%	334 1.2%	154 0.6%	128 3.9%
Oral Calcitonin	3439	2876 0.7%	2664 0.8%	2507 1.2%	2094 1.0%	427 8.9%		
Oral Placebo	3423	3092 0.5%	2887 0.8%	2757 0.7%	2290 0.8%	404 7.4%		

Novartis Pooled dose analysis through month 36
Stratification by dose not performed

Issues with Analysis Submitted to FDA

- Poor documentation of methods utilized
  - No methods presented in a unified manner
  - Analytic protocol provided for oral studies, but not nasal studies
- Failure to assess quality of included studies
  - Two studies were noted to have been conducted in poor compliance with good clinical practice with missing case report documentation
- High attrition and differential dropout
  - Study 320 had 59% dropout overall
  - Study 311 had a 41% dropout among calcitonin and 32% dropout in placebo, and a lower risk estimate than the similar study 312 which did not have differential dropout to the same extent

Issues with Analysis- Clinical Heterogeneity

- Failure to assess and interpret the impact of clinical heterogeneity
  - Appropriateness of including studies with differing indications of interest such as osteoporosis, steroid induced osteoporosis, osteoarthritis
  - Differences in exclusion for malignancy at baseline

Strengths

- Meta-analysis summarizes individual studies not adequately powered to assess the malignancy risk
- Publication bias less likely
- Malignancy was not a primary objective
  - Flushing and nausea from calcitonin may reveal treatment assignment to investigators
  - Malignancy was not suspected and biased reporting or identification is less likely

Limitations

- Methodological issues limit interpretation
- Many of the included studies were small with short duration
- Some studies had differential and/or high dropout
- Malignancy assessment not a primary objective
- Ability to identify malignancies early may have changed over time
- Unable to examine time to event
- Study populations differed

Conclusions

- Interpretation difficult
  - Inadequate documentation, different study populations, study quality and heterogeneity not assessed
- Causality cannot be determined
- Occurrence of cancer numerically higher in treatment groups
  - 11 of 17 nasal (4 with no cancer in either arm)
  - 2 of 3 oral
- Increased estimate may be due to failure of randomization
- Despite limitations and issues the overall picture shows a trend towards increased cancer occurrence with calcitonin use

Calcitonin Salmon and Malignancy Risk: Statistical Review of Meta-Analyses

Janelle K. Charles, PhD
Mathematical Statistician
Division of Biometrics VII
Office of Biostatistics, OTS,CDER, FDA

Joint Meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee

March 5, 2013

Outline

1. Introduction
2. Statistical Analyses
3. Results
4. Limitations and Conclusions

Introduction

Points to Consider

- No protocol, SAP, or outcome adjudication
- Outcome: all malignancies regardless of biological similarities
- Trial heterogeneity
  - Primary objectives
  - Randomization ratios
  - Sample size
  - Daily doses
  - Duration
  - Eligibility criteria

Data Source

- Novartis's randomized controlled trials (RCTs)
- 20 RCTs total: 17 nasal spray (NS) trials (16 DB*+1OL*), 3 oral trials
- No RCTs for injectable formulation included
- Trial-level data obtained from Novartis review of CSRs; electronic patient-level data not available for all trials

*DB=double blind, OL=open label

Statistical Analyses

FDA's and Novartis's Statistical Analyses

Trials Analyzed	FDA's Analysis	Novartis's Analysis*
NS Trials Only	All 17 trials MH fixed-effect RD overall and by dose-level	13 trials with events Peto fixed-effect OR overall and by dose-level
Combined NS and Oral Trials	All 20 trials MH fixed-effect RD overall	16 trials with events Peto fixed-effect OR overall

MH=Mantel-Haenszel, RD=risk difference, OR=odds ratio
*Peto method OR excludes trials with no events in both treatment groups

FDA's Sensitivity Analyses

- Analyses of all malignancies in NS trials only
  - Using double-blind (DB) only trials
  - Excluding CT320 (PROOF) trial from all trials
  - Excluding CT320 trial from DB trials

- Analyses of malignancies excluding basal cell carcinoma in the NS trials and the combined NS and oral trials

Results

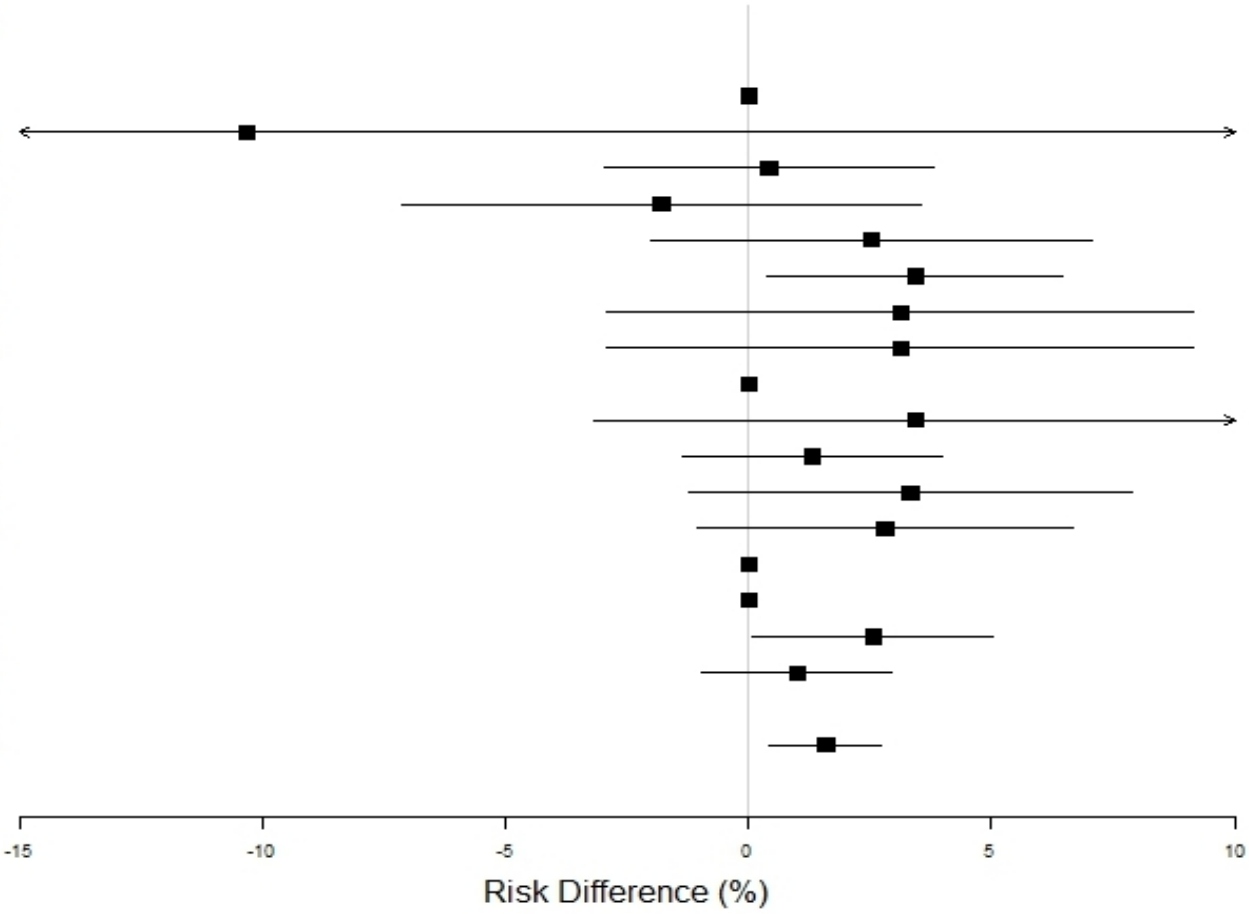
Meta-Analyses Results: All Malignancies

Trials Analyzed	Calcitonin n/N (%)	Placebo n/N (%)	MH RD% (95% CI)	Peto OR (95% CI)
NS Only Trials				
All trials	122/2666(4.6)	28/1264 (2.2)	1.6 (0.4, 2.7)	1.6 (1.1, 2.3)
DB trials	119/2519(4.7)	27/1123(2.4)	1.6 (0.4, 2.9)	1.6 (1.1, 2.3)
All w/o CT320	41/1722(2.4)	12/953 (1.3)	0.9 (-0.2, 1.9)	1.6 (0.9, 2.9)
DB w/o CT320	38/1575 (2.4)	11/812 (1.4)	0.8 (-0.3, 1.9)	1.5 (0.8, 2.8)
NS + Oral Trials	254/6105(4.2)	135/4687(2.9)	1.0 (0.3, 1.7)	1.4 (1.1, 1.7)

FDA's sensitivity analyses noted in shaded cells
n=number of patients with malignancies, N=total number of patients, MH=Mantel-Haenszel
OR=odds ratio (null value=1) , RD=risk difference (null value=0)
DB=double blind trials excluding OL trial SMCO 506, w/o=without

Meta-Analyses RD Results: All Malignancies (NS Trials Only)

Trial	RD (%)	95% CI
2402	0.0	.
CT 211	-10.3	(-33.1, 12.4)
CT 310	0.4	(-3.0, 3.8)
CT 311	-1.8	(-7.1, 3.5)
CT 312	2.5	(-2.0, 7.1)
CT 320	3.4	(0.4, 6.5)
MIA 16	3.1	(-2.9, 9.2)
SMCO 005	3.1	(-2.9, 9.2)
SMCO 503	0.0	.
SMCO 504	3.4	(-3.2, 10.1)
SMCO 506	1.3	(-1.3, 4.0)
SMCO 511	3.3	(-1.2, 7.9)
SMCO 514	2.8	(-1.0, 6.7)
SMCO 517	0.0	.
SMCO 520	0.0	.
SMCO 522	2.6	(0.1, 5.0)
SMCO 524	1.0	(-1.0, 3.0)
Overall	1.6	(0.4, 2.7)



Meta-analyses Dose-Level Results: All Malignancies (NS Trials Only)

	100IU	200IU	400IU
MH RD (%)	1.6 (-0.5, 3.6)	1.7 (0.1, 3.3)	2.0 (-0.4, 4.5)
Peto OR	1.6 (0.9, 2.7)[1]	1.6 (1.0, 2.7)	1.5 (0.9, 4.5)

[1]FDA's results using Peto OR due to omission of trial SMCO504 from Novartis's 100IU analysis

MH=Mantel Haenszel, RD=risk difference (null value=0)
OR=odds ratio (null value=1)

Meta-Analyses Results: Non-BCC Malignancies

	Calcitonin n/N (%)	Placebo n/N (%)	MH RD% (95% CI)
NS trials	84/2666 (3.2)	28/1264 (2.2)	0.9 (-0.2, 1.9)
NS + Oral trials	195/6105(3.2)	120/4687(2.6)	0.5 (-0.1, 1.2)

n=number of patients with malignancies, N=total number of patients
BCC=basal cell carcinoma
MH=Mantel-Haenszel, RD=risk difference (null value=0)

Limitations and Conclusions

Limitations of Meta-analyses (1)

- No protocol, SAP, or safety outcome adjudication
- Retrospective meta-analyses
- Trial design differences: primary objectives, randomization ratios, daily doses, sample size, duration

Limitations of Meta-analyses (2)

- Study outcome
  - Variable trial inclusion/exclusion criteria with respect to malignancies
- Trial-level data only
  - No rigorous time to event analyses
  - No subgroup analyses

Conclusions

- Higher overall risks of malignancies in calcitonin salmon over placebo
  - NS Only: All malignancies RD=1.6%, CI (0.4, 2.7), non-BCC malignancies RD=0.9%, CI (-0.2, 1.9)
  - NS + Oral: All malignancies RD= 1.0%, CI (0.3, 1.7), non-BCC malignancies RD=0.5%, CI (-0.1, 1.2)
- Analyses of all malignancies heavily influenced by single large trial of 5-year duration
- Difficult to adequately assess strength of potential cancer signal with this data

Efficacy of Calcitonin salmon in the Treatment of Postmenopausal Osteoporosis

Joint Meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee

March 5, 2013

Stephen Voss M.D.
Medical Officer
Division of Reproductive and Urologic Products
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Calcitonin salmon: Efficacy

Calcimar injection

- Studies for approval
- Fracture study RHCG-CT-401

Miacalcin nasal spray

- Studies for approval
- Fracture study CT320 (PROOF)

SMC021 oral tablet

- Fracture study

Calcitonin salmon injection (Calcimar)

- Two 2-year open-label studies (late 1970s)
- Primary endpoint: total body calcium
- Postmenopausal women age 50-74 y/o
  - Vertebral osteopenia by xray and at least one baseline compression fracture
  - Total body calcium <85% of expected normal
- Calcimar 100 IU daily (SC or IM), or no treatment
  - Calcium 1200 mg, vitamin D 400 IU
- 84 enrolled, 69 with 2-year data

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Calcitonin salmon injection: Total body calcium, Percent Change from Baseline

	6 months	12 months	18-20 months	24-26 months
Study 1				
Calcimar	+1.2	+2.1	+2.2	+1.4
Control	-0.5	-1.3	-2.2	-1.4
Difference	+1.7	+3.3	+4.4	+2.8
Study 2				
Calcimar	+2.1	+5.2	+2.5	+2.1
Control	-0.5	-1.0	-2.5	-2.1
Difference	+2.6	+6.2	+5.1	+4.2

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Calcitonin salmon injection

- Concerns about total body calcium:
  - Small decline during 2nd year of treatment
  - Unknown validity as a surrogate for fracture risk
- Approval (1984)
  - With a commitment to conduct a postmarketing fracture study

Study RHCG-CT-401

- 3-year open-label study, initiated in 1985
- Primary endpoint: new vertebral fractures
- Postmenopausal women >45 y/o
  - Vertebral osteopenia and 1-3 baseline compression fractures
  - Exclusion: conditions (except for osteoporosis) or medications potentially affecting bone
- Calcimar 100 IU daily (SC or IM) or no treatment
  - Calcium 1000 mg, vitamin D 400 IU
- Planned enrollment: 300 subjects (150/group)

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Study RHCG-CT-401

- Interim report after 4 years:
  - 151 enrolled (50% of planned)
  - 77/151 (51%) withdrew, mostly in 1st year
    - 65 completed 3-year study
    - 95 had post-baseline X-ray for efficacy evaluation
- Demographics
  - Mean age: 67 years
  - Mean # of baseline fractures (efficacy analysis subjects): 1.9 Calcimar, 1.7 control

Study RHCG-CT-401: New vertebral fractures

	Calcimar	Control
N	52	43
Subjects with new fractures	12 (23%)	5 (12%)
New fractures	22	14
Fracture rate (per 1000 subject-yr)	181	133
Adjusted rate (for baseline fracture status)	162	165

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Study RHCG-CT-401

Vertebral BMD, Percent Change

by dual photon absorptiometry (DPA)

	Calcimar	Control
Year 1, n	18	15
% change from BL	+3.15	-0.37
Year 2, n	16	14
% change from BL	+3.30	-0.50
Year 3, n	12	10
% change from BL	+0.68	-0.89

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EMDAC Advisory Committee, July 1991

RHCG-CT-401 study flaws:

- slow enrollment
- high dropout rate
- imbalance in randomization (?due to open-label)
- decision to stop enrollment, end study

Conclusions:

- fracture data were unreliable and inconclusive
- increasing trend in lumbar spine BMD

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Calcitonin salmon nasal spray (Miacalcin)

- Three randomized, double-blind trials in women with PMO who were >5 years post-menopause
- Inclusion criteria based on bone mass (T-score < -1), not prevalent fractures

Trial	Duration	Baseline T-score	Primary endpoint	Total N rand	Dosage regimens	Calcium supp.
522	2 yr	-2.5	LS-BMD DXA	196	50, 100, 200, Plac	Yes
514	2 yr	-2.2	LS-BMD DPA	112	200 QD, 200 3x/wk, Plac	No
516	1 yr	-2.0	LS-BMD DPA	40	100 BID, Plac	Yes

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Miacalcin nasal spray 200 IU
Lumbar spine BMD, Percent Change

	Month 12/ Endpoint	Month 24/ Endpoint
Study 522 (with Ca++ supplements)		
Miacalcin	+2.44	+2.05
Placebo	+0.45	0.00
Difference	+1.99	+2.05
Study 514 (no Ca++ supplements)		
Miacalcin	+1.03	+1.38
Placebo	-1.21	-1.73
Difference	+2.24	+3.11
Study 516 (with Ca++ supplements)		
Miacalcin	+3.2	-
Placebo	-0.4	-
Difference	+3.6	-

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Miacalcin nasal spray

- EMDAC meeting November 1994
- Concerns:
  - Available fracture data limited and inconclusive
  - The fracture trial (CT320, PROOF) was ongoing
- Recommendation: the BMD changes were sufficient to establish clinically important efficacy of nasal calcitonin
- Approval
  - With commitment to complete the fracture study

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Trial CT320 (PROOF)

- 5-year study
- Primary endpoint: vertebral fractures
- Postmenopausal women
  - Lumbar spine BMD T-score < -2.0
  - X-ray: vertebral osteopenia, 1-5 compression fractures
  - No bone disorders except osteoporosis
  - No confounding medications e.g. glucocorticoids, estrogens, bisphosphonates
- Calcitonin 100 IU, 200 IU, 400 IU, vs. placebo
  - Calcium 1000 mg, vitamin D 400 IU
- Double-blind to treatment, but not to BMD results

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Trial CT320 (PROOF): Disposition

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N randomized	311	316	316	312
Completed ≥ 3 yr	190 (61%)	189 (60%)	204 (65%)	200 (64%)
Completed study (5 yr)	128 (41%)	124 (39%)	132 (42%)	127 (41%)
Discontinued (<5 yr)	183 (59%)	192 (61%)	184 (58%)	185 (59%)
D/C due to adverse event	77 (25%)	69 (22%)	70 (22%)	88 (28%)

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Trial CT320: Demographics

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
Mean age (range)	68 (48-91)	68 (47-87)	69 (44-94)	68 (47-88)
Years post-menopause	22	22	23	22
% Caucasian	95%	96%	99%	98%
% w/ prevalent fractures	80%	75%	79%	81%
Mean # of prevalent fractures	1.95	1.82	2.08	2.08

Trial CT320: New and/or worsening vertebral fractures ITT_E

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N	270	273	287	278
n (%) with ≥ 1 new and/or worsening fractures	74 (27.4%)	61 (22.3%)	59 (20.6%)	68 (24.5%)
Relative risk vs. placebo (95% CI)	-	0.83 (0.59-1.17)	0.75 (0.53-1.05)	0.90 (0.65-1.25)
p-value vs. placebo	-	0.29	0.09	0.53

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Trial CT320
New vertebral fractures - ITT_E

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N	270	273	287	278
n (%) with ≥ 1 new fracture	70 (26%)	59 (22%)	51 (18%)	61 (22%)
Relative risk vs. placebo (95% CI)	-	0.85 (0.60-1.21)	0.67 (0.47-0.97)	0.84 (0.59-1.18)
p-value vs. placebo	-	0.37	0.03	0.32
Relative risk reduction	-	15%	33%	16%
Absolute risk reduction	-	4%	8%	4%

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Trial CT320
Non-vertebral fractures - ITT_E

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N	305	313	315	312
Any nonvertebral fracture (%)	48 (15.7%)	32 (10.2%)	46 (14.6%)	41 (13.1%)
Upper limb (humerus, radius, ulna, wrist)	16	6	13	14
Hip and femur	9	1	5	7

Trial CT320
Lumbar Spine BMD: Mean Percent Change

	Placebo NS (n=273)	Calcitonin 100 IU (n=279)	Calcitonin 200 IU (n=287)	Calcitonin 400 IU (n=277)
Month 12	0.17	1.22	1.39	1.23
Month 24	0.36	1.13	1.27	1.24
Month 36	0.40	1.03	1.04	1.54
Month 48	0.57	1.12	1.16	1.44
Month 60	0.54	1.03	1.16	1.54

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Trial CT320 Summary

- 1255 women with PMO, mean age 68, 79% with baseline vertebral fractures
- Calcitonin 200 IU (relative to placebo):
  - Non-significant 25% reduction in subjects w/ new and/or worsening fractures
  - 33% relative reduction in subjects w/ new vertebral fractures (8% absolute risk reduction: 18% vs. 26%)
  - Trend of increased lumbar spine BMD (~1-1.5%), but no change after 1 year
  - No effect on non-vertebral fractures

Trial CT320: Limitations

- Lack of dose-response: 200 IU dose reduced vertebral fractures, 100 IU and 400 IU did not
- 400 IU group: increases in lumbar spine BMD were numerically greater than with 200 IU
  - Narrow therapeutic window?
  - Type 1 error with 200 IU fracture results?
  - BMD not a valid surrogate for fracture risk?
- 100 IU group: most favorable trend in non-vertebral fractures (esp. hip/femur)
- Potential effects of high dropout rate
  - Loss of data
  - Potential bias?

Oral Calcitonin salmon: SMC021

- SMC021 = recombinant calcitonin salmon 0.8 mg (4800 IU) with 5-CNAC (absorption enhancer)
- Systemic exposure higher than Miacalcin nasal spray, but lower than injectable calcitonin

Oral calcitonin fracture trial – A2303

- 3-year randomized, double-blind, placebo-controlled trial, 4500 subjects
- Primary endpoint: new vertebral fractures
- Postmenopausal women with osteoporosis
  - BMD T-score ≤ -2.5 with no more than 2 baseline mild or moderate vertebral fractures or:
  - BMD T-score ≤ -1.5 with 1 or 2 baseline vertebral fractures (Genant, any grade)
- SMC021 or placebo tablet daily (pre-dinner)
  - Calcium 800-1000 mg, vitamin D 400-800 IU (AM)

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Trial A2303: Disposition

	SMC021 (calcitonin)	Placebo
N randomized	2334	2331
Completed study drug	1578 (68%)	1732 (74%)
Subjects with off-drug month-36 assessments	269 (12%)	204 (9%)
Discontinued (<3 yr)	756 (32%)	599 (26%)
Discontinued due to adverse event	367 (16%)	215 (9%)

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Trial A2303: Demographics

	SMC021 (calcitonin)	Placebo
Age – mean (range)	66.5 (55-86)	67.0 (50-85)
Years post-menopause	19	19
% White	67	66
% Asian	13	13
% Hispanic	19	19
% with prevalent vertebral fractures	21	23

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Trial A2303
New vertebral fractures

	SMC021 (calcitonin)	Placebo
N with post-baseline X-ray	2064	2125
n (%) with ≥ 1 new fracture	94 (4.55%)	99 (4.66%)
Relative risk (95% CI)	0.98 (0.74-1.29)	-
p-value	0.94	-

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Oral calcitonin fracture trial – A2303 Summary – fracture incidences

	SMC021 (calcitonin)	Placebo
Vertebral fractures	4.55%	4.66%
Non-vertebral fractures	3.21%	3.52%
Clinical fractures	4.76%	5.11%
Hip and femur fractures	0.21%	0.73%

Trial A2303: Lumbar spine BMD Percent Change from Baseline

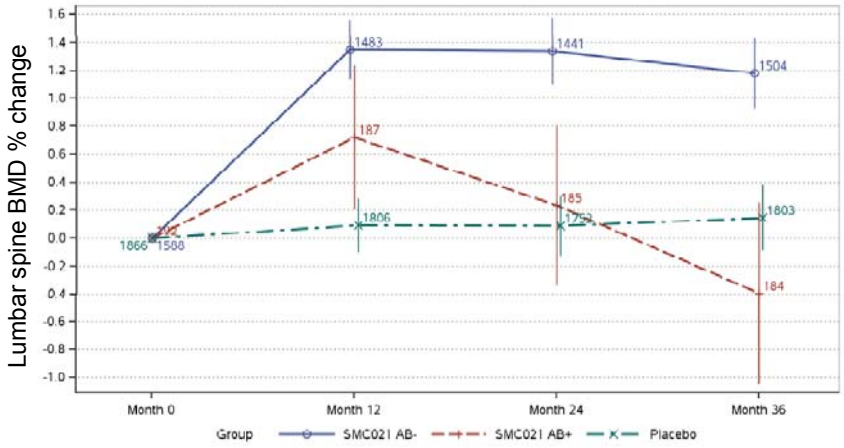
	SMC021 (calcitonin)	Placebo	Difference (95% CI)	P-value
Month 12	+1.24	+0.05	+1.19 (0.96-1.42)	<.0001
Month 24	+1.17	+0.07	+1.10 (0.84-1.37)	<.0001
Month 36	+1.02	+0.18	+0.83 (0.54-1.13)	<.0001

Oral calcitonin fracture trial A2303
Summary: Bone density
Percent change from baseline (36 months)

	SMC021 (calcitonin)	Placebo	Difference
Lumbar spine	+1.02	+0.18	+0.83
Total hip	-0.79	-1.11	+0.31
Femoral neck	-0.94	-1.38	+0.44

Trial A2303

Lumbar spine BMD percent change from baseline by calcitonin antibody status



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Trial A2303: Summary

- 4665 women with PMO, mean age 67, 22% with baseline vertebral fractures
  - > 80% completed assessments at 3 years
- SMC021 0.8 mg daily
  - No vertebral or nonvertebral fracture reduction
  - Trend of increased lumbar spine BMD (1.2%), but no change after 1 year
  - Striking loss of BMD effect after 1 year in subjects with positive antibody titers

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Calcitonin Salmon

Summary

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Calcitonin salmon Risks and Benefits

- Calcitonin salmon products have been marketed in the U.S. since 1975
- Declining use of calcitonin over the last 5 years
- Few postmarketing safety concerns have been raised over the years

Calcitonin salmon Risks and Benefits

- Recent clinical study findings raised concern regarding calcitonin use and malignancy
- A meta-analysis of available clinical trial data was conducted by Novartis and by FDA

Calcitonin salmon Risks and Benefits

- Multiple limitations exist with both Novartis's and FDA's meta-analysis
- Causality cannot be determined
- Higher numbers of malignancy in calcitonin groups compared to placebo raise a concern for a potential overall increased risk
- The findings were consistent across dose groups

Calcitonin salmon Risks and Benefits

- We cannot assess the strength of the potential cancer signal with the data at hand but it appears plausible
- With this potential risk, assessment of benefit becomes necessary
- At this time, calcitonin salmon is the only product approved for treatment of osteoporosis that has not demonstrated definitive evidence of fracture efficacy

Calcitonin salmon Risks and Benefits

- Three fracture trials have been conducted with calcitonin salmon products
  - A randomized, open-label study where results were unfavorable toward calcitonin, but the study was flawed and results were unreliable
  - A five year randomized, double-blind, placebo-controlled trial demonstrated a risk reduction in only one treatment group, with no dose response despite dose dependent increases in BMD
  - A three year, randomized, double-blind, placebo-controlled trial demonstrated BMD increases, but not fracture reduction efficacy

Calcitonin salmon Risks and Benefits

- Intervention to reduce the risk of fracture is the standard for osteoporosis treatment
- There remain significant questions regarding calcitonin salmon's effectiveness in reducing fractures in postmenopausal women
- This lack of effectiveness when combined with the potential for a cancer risk associated with calcitonin therapy raises concerns about the overall risk and benefit assessment of calcitonin for treatment of postmenopausal osteoporosis

Questions