

Calcitonin Salmon

Benefit/Risk Assessment in PMO

Presentation to the Joint Meeting of the Reproductive Health Drugs and
Drug Safety and Risk Management Advisory Committees

Novartis Pharmaceuticals Corporation

Miacalcin® Injection – NDA 17-808
Miacalcin® Nasal Spray – NDA 20-313

March 5th, 2013

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Introduction

John Orloff, MD
Chief Medical Officer
Novartis Pharmaceuticals Corporation

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Miacalcin® Product Line



- Miacalcin® Injection (50-200 IU, daily or divided dose)
 - Indicated for the treatment of symptomatic Paget's disease of bone, for the treatment of hypercalcemia, and for the treatment of postmenopausal osteoporosis.
- Miacalcin® Nasal Spray (200 IU)
 - Indicated for the treatment of postmenopausal osteoporosis.

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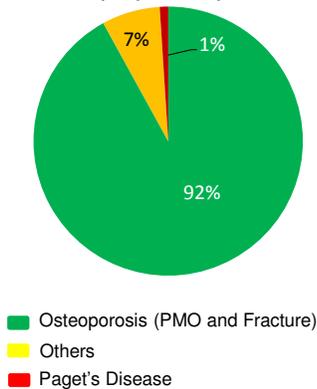
Miacalcin Regulatory History

- Miacalcin Injection approved in 1986;
Miacalcin Nasal Spray approved in 1995
 - Approvals based solely on biomarker and surrogate evidence to support efficacy
 - Requirements for efficacy endpoints (i.e. fracture and BMD endpoints) have changed
 - Subsequent approvals of other osteoporosis therapies based on fracture data with their own benefit/risk profiles
- Well tolerated, with over 10 million patient-years of experience since approval

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Current Calcitonin Use

Nasal Spray Use by Indication¹



- Small, niche use in PMO
- Unique mode of administration
- 2.4% overall segment share²
- No promotional activities
- 80 days - average duration of use for nasal spray³
- Injectable form represents less than 1% of all daily doses and is mainly used in hypercalcemia⁴

¹Pooled data from time period Oct 2009 - Sep 2012 Source: IMS MIDAS Quantum detailed medical, Q3 2012

² Source: IMS MIDAS sales market share MAT Dec 2012

³Analysis of a cohort of initiators of calcitonin in 2009-2010: Source: MarketScan Database

⁴Pooled data from time period Oct 2009 - Sep 2012 Source: IMS MIDAS Quantum, Q3 2012

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Calcitonin in Clinical Practice

- Mostly prescribed by general practitioners (75%)¹
- At least 14% of calcitonin nasal spray used for PMO with vertebral fracture¹
- Almost 50% of population prescribed calcitonin nasal spray are over 70 years²
- Calcitonin nasal spray:
 - Used for ≤ 30 days in 38% of patients
 - Used for ≤ 180 days by 76% of patients
 - Only 13% use for more than 270 days²

¹Analysis of a cohort of initiators of calcitonin in 2009-2010: Source: MarketScan Database

² Pooled data from time period Oct 2009 - Sep 2012 Source: IMS MIDAS Quantum detailed medical, Q3 2012

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Overview of Postmenopausal Osteoporosis

- Most common metabolic bone disorder
 - Over 10 million people in the U.S. have OP, another 34 million at risk (have osteopenia)
- Both under-treated and under-diagnosed; typically silent until a symptomatic fracture occurs
 - Associated with significant morbidity and mortality
- Pharmacological intervention is important to minimize fracture risk
- All of the available treatment options are associated with some risk
- Patients benefit from an array of safe and effective options

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Context for the Current Benefit/Risk Reevaluation

- Investigational oral calcitonin program (interim results 2010)
 - Phase III studies in osteoarthritis detected a possible association with prostate cancer
 - Communicated to all health authorities worldwide
- Article 31 Referral (EU) - regulatory procedure assessing benefit/risk for calcitonin containing products related to malignancy signal
- Novartis performed meta-analysis which found a signal for an increased risk of malignancies
- Proposal for updated labeling submitted to FDA in July 2012
- CHMP recommendation (November 2012) to remove PMO indication

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Novartis Assessment

- Signal for incident malignancy identified in meta-analysis
- Clinical need exists for patients for whom other options are not suitable:
 - Contraindicated or intolerant or refuse other therapies
 - Treatment decisions based on individual patient benefit/risk assessment
- Actions taken:
 - Revised labeling submitted reflecting malignancy findings and limiting use and duration
 - Outline HCP communication plan
- Seek Committee's guidance on:
 - Whether Miacalcin should remain an option for treatment of PMO
 - Options to further elucidate the association of malignancy with use of calcitonin in PMO

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Consultants

- Henry Bone, MD
 - Director, Michigan Bone and Mineral Clinic
 - Section Chief, Endocrinology and Metabolism, St. John Hospital and Medical Center
 - Adjunct Professor of Medicine, University of Michigan
- Jonathan Chernoff, MD, PhD
 - Scientific Director at Fox Chase Cancer Center
 - Temple University
- Marc C. Hochberg, MD, MPH
 - Professor of Medicine and Epidemiology and Public Health
 - Head, Division of Rheumatology & Clinical Immunology
 - University of Maryland School of Medicine
- Stuart Silverman, MD
 - Medical Director, Bone Center of Excellence, Cedars-Sinai Medical Center
 - Clinical Professor of Medicine, UCLA
- L.J. Wei, PhD
 - Professor of Biostatistics, Harvard University
- Noel Weiss, MD, DrPH
 - Professor of Epidemiology
 - School of Public Health and Medicine, University of Washington

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Agenda

Introduction	John Orloff, MD Chief Medical Officer Novartis Pharmaceuticals Corporation
Efficacy and Safety of Calcitonin	Paul Atring, MD, PhD Global Program Head Novartis Pharmaceuticals Corporation
Putting Risk into Context	Noel Weiss, MD, DrPH Professor of Epidemiology University of Washington
Novartis Proposal for Risk Minimization and Further Evaluation of Calcitonin	John Orloff, MD Chief Medical Officer Novartis Pharmaceuticals Corporation

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Efficacy and Safety of Calcitonin

Paul Atring, MD, PhD
Global Program Head
Novartis Pharmaceuticals Corporation

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Salmon Calcitonin

- Miacalcin - a synthetic salmon calcitonin (SCT)
 - Polypeptide consisting of 32 amino acids in a single chain with a ring of seven amino-acid residues at the N-terminus
- SCT acts primarily by inhibiting bone resorptive activity of osteoclasts via specific receptors
 - Rapidly achieves a clinically relevant effect with significant reduction of bone resorption activity on the first day of treatment without over-suppression
- Irreversibly binds to human CT receptor

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Salmon Calcitonin

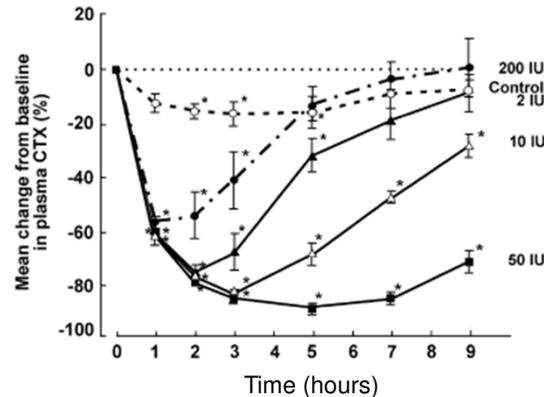
Mechanism of Action

- Receptors predominantly located in osteoclast membrane
- Sustained cAMP accumulation and inhibition of bone resorption
- Results in detachment of osteoclast from bone resorption surface

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Salmon Calcitonin Clinical Pharmacology

- Effects of SCT in young healthy women (n=6); cross-over study
- 2, 10 and 50 IU injection
- 200 IU nasal
- Rapid onset of effect



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Overview of Key PMO Studies

- Salmon Calcitonin Injection Registration Studies (Calcimar)
 - 3 controlled studies, one double-blind
 - Registration endpoint: Total Body Calcium
- Miacalcin Nasal Spray Registration Studies
 - 5 double-blind placebo-controlled studies
 - Registration endpoint: BMD, BMC
- PROOF (nasal spray)
 - Post-approval commitment fracture endpoint study

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Salmon Calcitonin for Injection

Summary of Registration Efficacy Studies

Investigator	Diagnosis	Treatment	N	Duration (months)	TBC-NAA, BL (SE) Month 20	% Change from Month 26
Zanzi Study No. 1	PMO	100 IU/d SCT + 1.2g Ca	17 ¹	26	+2.54 (1.67)*	+2.14 (1.63)*
		1.2g Ca	17 ¹		-2.51 (1.27)	-2.10 (0.93)
Baylink + Chesnut Study No. 2 (Gruber et al. 1984)	PMO	100 IU/d SCT + 1.2g Ca	26	26	+2.18 (0.80)**	+1.39 (1.14)
		1.2g Ca	24		-2.23 (0.89)**	-1.43 (0.93)
Wallach Study No.3	Osteoporosis in males	100 IU/d SCT + 1.2g Ca +Vit. D	12	26		+2.62
		Vit. D +1.2g Ca	13			+0.61
		Vit. D	13			+0.55

¹ 3 males were also included in each group. However, only the results on females are reported here.

* p<0.05 versus control group; ** p < 0.02 versus baseline

N = No. of patients; BL = base line; TBC = total body calcium; NAA = neutron activation analysis, PMO = postmenopausal osteoporosis

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Miacalcin Nasal Spray Studies

Bone Mineral Density

Study	Treatment groups	N	Mean % change at endpoint	P-value vs. placebo
2 yr endpoints				
SMCO 522	Placebo	51	+0.20	---
	50 IU/d	47	+1.59	0.04
	100 IU/d	49	+1.36	0.09
	200 IU/d	49	+1.56	0.05
SMCO 514*	Placebo	21	-1.85	---
	200 IU/d [†]	17	-0.77	0.28
	200 IU/d	18	+1.02	0.004

[†] administered 3 d/week, other 200 IU treatment arm is daily administration

* Patient numbers are for the established PMO population in the trial

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Fracture Evidence

PROOF Study (CT320)

- Multicenter, double-blind, randomized study
 - Investigated efficacy of Miacalcin Nasal Spray for prevention of osteoporosis vertebral fractures
- Primary endpoint to evaluate the effect of 200 IU SCT vs. placebo on incidence of new vertebral fractures
 - Secondary endpoints included: fractures at non-vertebral sites, BMD, biomarkers, and SCT antibody titers

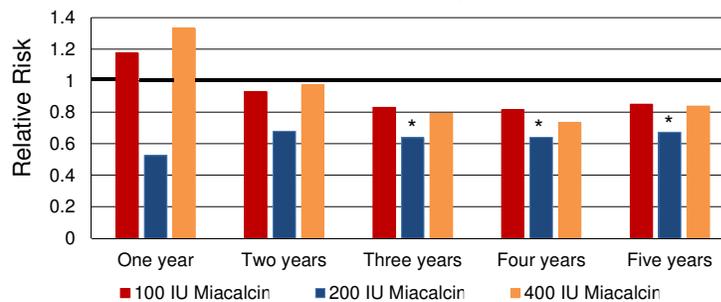
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PROOF Study Results

New Vertebral Fracture Risk Reduction

SCT showed a statistically significant, relative risk reduction (33%) of new vertebral fractures at five years (RR=0.67, 95% CI: 0.47-0.97, p=0.03)

Relative Risk of Developing a New Vertebral Fracture Versus Placebo by Year of Treatment in PROOF Study



* p<0.05

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PROOF Secondary Analysis

Relative Risk Reduction in Elderly at 5 Years – 200 IU

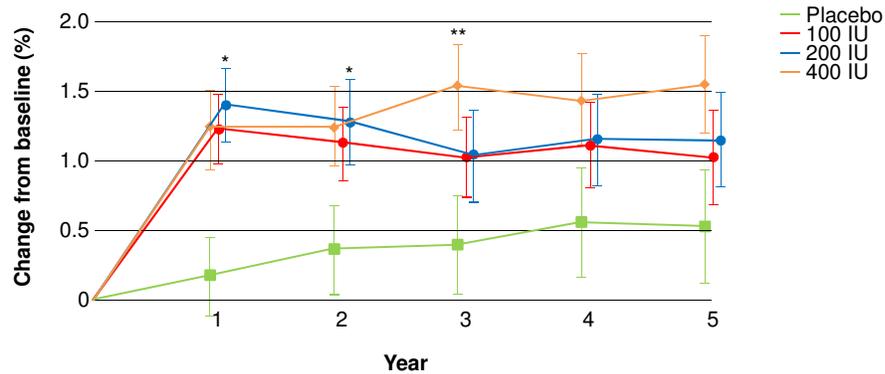
Secondary Analysis	Nasal SCT n(%)	Placebo n(%)
Patients ≥ 70 yrs	134	104
≥1 new vertebral fracture	26 (19)	35 (34)
RR to placebo (95% CI) survival analysis	44%; 0.56 (0.34-0.93) p=0.03	

NOF 2005

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PROOF Study Results

Lumbar Spine BMD Increase



*p<0.05, **p<0.01 vs placebo
Chesnut et al, Am J Med 2000;109:267-76

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PROOF Study Conclusions

- Met primary endpoint as agreed with FDA, and consistent with the 1994 guidelines
- BMD data consistent with fracture reduction; no suggestion of adverse effect on skeleton
- PROOF fulfilled post-approval commitment for Miacalcin
 - Fracture reduction not approved for the label
 - FDA questions: lack of dose response, drop-out rate over 5 years, and lack of statistically significant secondary endpoints

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Other Published Studies with Miacalcin Nasal Spray

- Meta-analysis (Cranney, 2002)
 - Identified 30 randomized studies (including PROOF) that examined the effects of calcitonin on bone density or fracture incidence for at least one year in postmenopausal women
 - Authors concluded that calcitonin increases BMD and likely reduces the risk of vertebral fracture

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Oral Calcitonin Trial A2303

Effects on BMD

Percentage change in lumbar spine BMD from baseline by treatment and visit
(ITT analysis set) in A2303

Visit	Treatment	n	LSM (SE)	Treatment difference (95% CI)	p-value
Month 12	oSCT	1839	1.24 (0.10)	1.19 (0.96, 1.42)	<.0001
	Placebo	1981	0.05 (0.10)		
Month 24	oSCT	1690	1.17 (0.11)	1.11 (0.84, 1.37)	<.0001
	Placebo	1824	0.07 (0.11)		
Month 36	oSCT	1860	1.02 (0.12)	0.83 (0.54, 1.13)	<.0001
	Placebo	1941	0.18 (0.16)		

n = the number of patients with evaluable measurements.
LSM = least squares mean, SE = standard error of LSM, CI = confidence interval.
Treatment difference = LSM difference of oSCT minus placebo.

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Vertebral Fracture Outcomes

PROOF (CT320) vs. A2303

Study	SCT n (%)	Placebo n (%)
Oral (A2303)	94 / 2064 (4.6)	99 / 2125 (4.7)
PROOF (CT320) – 200 IU	37 / 280 (12.9)	55 / 269 (20.4)

- 3 year outcomes shown for the PROOF study

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Fracture Risk

PROOF (CT320) vs. A2303

Marked differences in baseline patient characteristics

	Prevalent Vertebral Fractures at Baseline		
	0	1-5	>5
Oral (A2303) N = 4,665	3169 (67.9%)	1020 (21.9%)	0
PROOF (CT320) N = 1,225	65 (5.2%)	910 (72.5%)	269 (21.4%)

- Prevalent fracture unknown in 10.2% of study participants in A2303

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Summary of Effectiveness

- Anti-resorptive pharmacologic effects with rapid onset of action
- Clinical effectiveness in PMO
 - BMD increases
 - PROOF (nasal spray): 200 IU marketed dose met fracture efficacy endpoint; other doses did not
 - A2303 (oral): did not meet fracture efficacy endpoint
- Evidence of effectiveness supported by meta-analysis (30 studies)

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Miacalcin Safety and Malignancy Evaluation

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Non-Clinical Data Carcinogenicity Studies

- No genotoxic potential
- Carcinogenicity evaluated in two 104-week studies in rats and mice:
 - No evidence of treatment-related prostate cell neoplasia or hyperplasia in all studies conducted
 - An increased incidence of benign pituitary adenoma was noted in male rats but considered a rat-specific observation and not relevant to human safety
- No evidence of tumor progression
 - No increase in common spontaneous tumors
 - No shift toward tumors that are more malignant
 - No evidence for more invasive growth

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Other *in vitro* Data

Literature Reports

- *In vitro* studies of prostate cancer cell lines:
 - Increased growth in genetically engineered cells
 - Phenotypic changes consistent with invasiveness
- Inconsistent results from other investigators
- Calcitonin signaling pathways are not consistent with cell proliferation effects

Shah GV, Rayford W, Noble MJ et al. Endocrinology 1994;134(2):596-602.

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Overview of Miacalcin Post-marketing Experience

- More than 10 million patient-years of experience over 2 decades
- Collective marketing experience reflects the AE profile in the label based on spontaneous post-marketing reports

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Adverse Event Profile

USPI

Adverse Reaction	Miacalcin Nasal Spray % of Patients (N=341)	Placebo % of Patients (N=131)
Rhinitis	12.0	6.9
Symptom of Nose	10.6	16.0
Back Pain	5.0	2.3
Arthralgia	3.8	5.3
Epistaxis	3.5	4.6
Headache	3.2	4.6
Miacalcin Injection % of Patients		
Nausea with or without vomiting		10.0
Local inflammatory reactions at site of injection		10.0
Flushing of face or hands		2-5

Miacalcin® (*calcitonin-salmon*) Injection, Synthetic. USPI. 4/8/2012
Miacalcin® (*calcitonin-salmon*) Nasal Spray. USPI. 4/8/2012

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Calcitonin and Malignancy Prior FDA Reviews

- Initial registration review showed no malignancy signal
- PROOF – numerical imbalance in malignancies but high proportion of basal cell carcinoma
 - Reviewed and discussed with FDA (1998-1999)
 - Recommended no further action

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Overview of Malignancy Findings from Investigational Oral Calcitonin Program

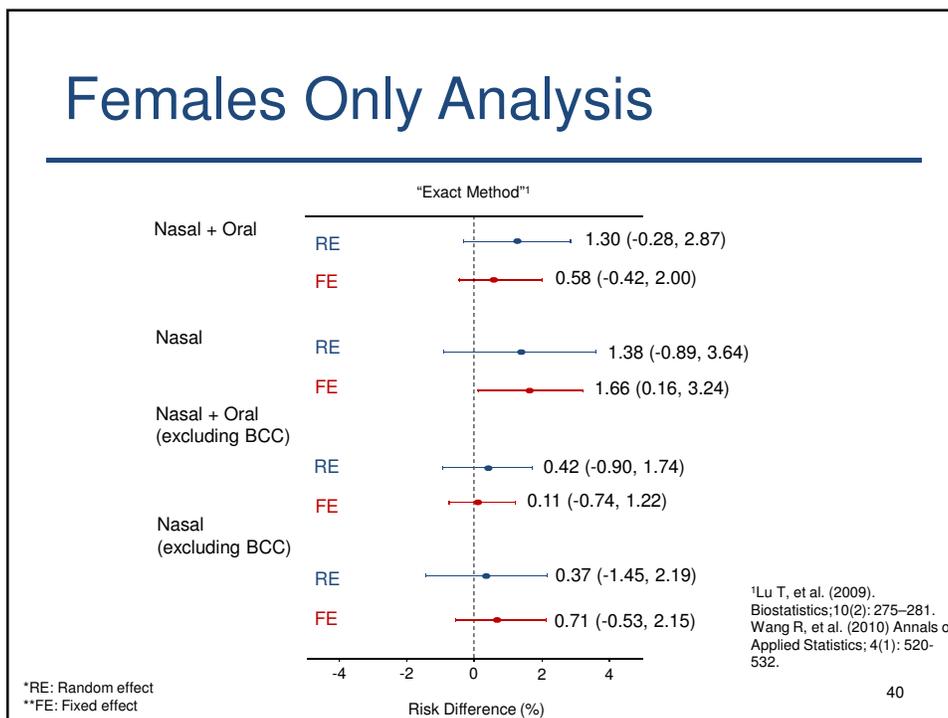
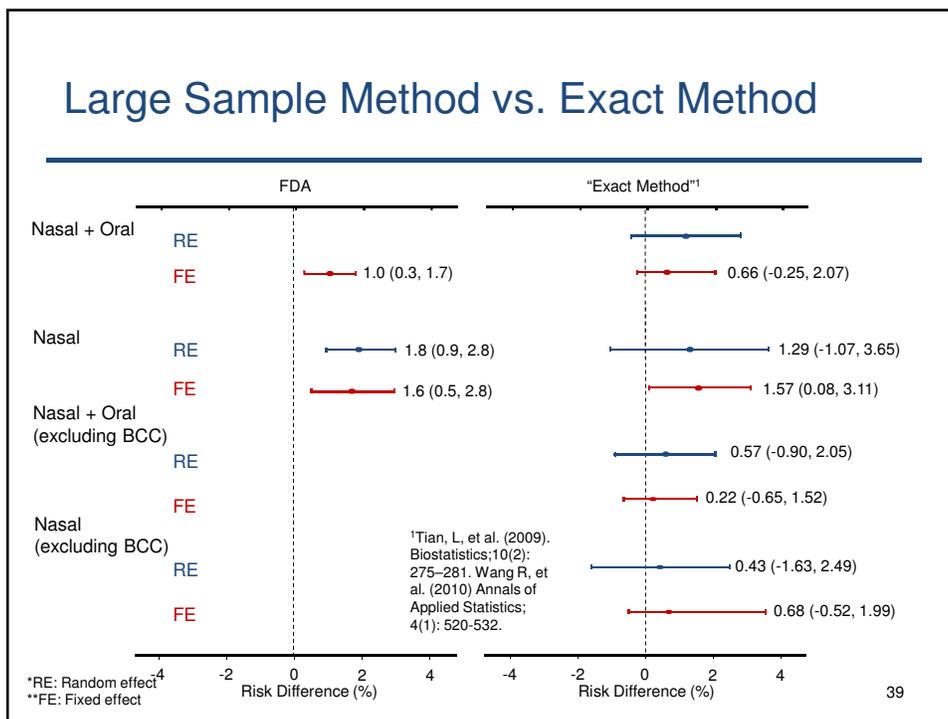
- Nordic/Novartis Phase III oral calcitonin programs
 - 2 trials in men and women with osteoarthritis of the knee
 - 1 trial in women with PMO
- Imbalance in prostate cancer reports observed in interim analysis of OA studies
 - Not confirmed in final analysis
 - Reported to Health Authorities worldwide (November 2010)

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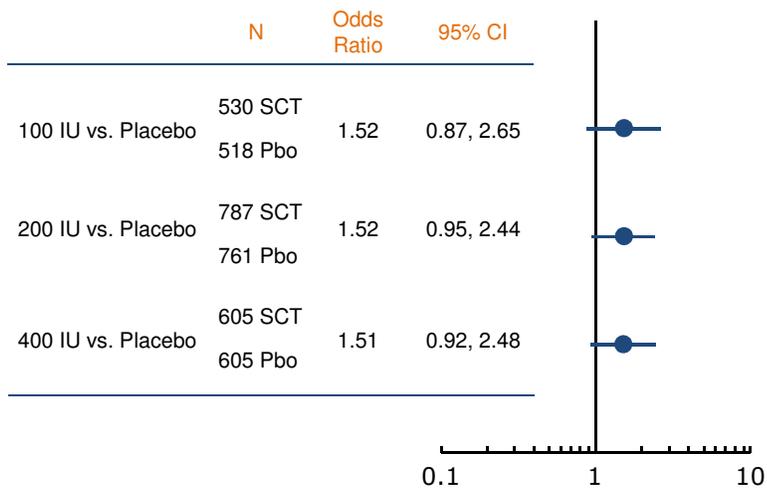
Overview of Malignancy Meta-Analyses

- Request from EMA:
 - Collect all malignancy-related data from calcitonin clinical trials
 - Subsequent request for meta-analysis of all malignancies
- Novartis meta-analysis design
 - Included all data available from placebo-controlled clinical trials (oral and nasal)
 - 21 studies/ 10,883 patients (6,151 on SCT)
 - Open label extensions excluded
- Limitations
 - No adjustment for covariates/baseline history of malignancy, no adjudication, heterogeneous patient population across studies, differential dropout rates

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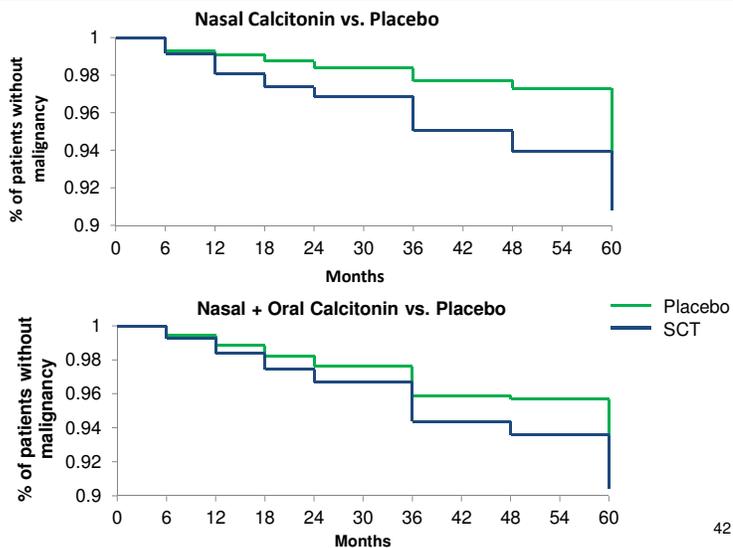
Malignancy Meta-Analysis Nasal Calcitonin Dose Evaluation



Peto Method

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Malignancy Life-table Analysis Time to First Malignancy



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Malignancy Meta-Analysis

Malignancy Types

Malignancy Events	Nasal		Oral		Cont'd	Nasal		Oral	
	Active (n=2712)	Placebo (n=1309)	Active (n=3439)	Placebo (n=3423)		Active	Pbo	Active	Pbo
BCC	38	5	27	11	Ovarian	5	2	4	1
SCC	10	2	3	1	Breast	25	5	29	22
Skin	3	1	13	8	Uterine	2	-	8	3
Melanoma	4	-	3	3	Prostate	2	1	12	6
Lip/Oral	2	-	-	-	Lung	9	2	11	11
Colon	10	1	2	1	Brain	1	1	-	-
Rectal	-	-	4	3	Bladder	1	-	2	2
Gastric	1	2	2	8	Renal	-	-	1	2
Pancreatic	6	1	-	3	Thyroid	-	-	16	18
Leukemia	1	1	4	4	Others	5	3	11	10
Multiple Myeloma	-	2	4	-					
Lymphoma	4	1	3	2					
					Total	129	30	159	119

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Malignancy Evaluation Conclusions

- Meta-analysis results consistent with an increase in the incidence of malignancies with salmon calcitonin
 - Similar results across statistical methods
 - Basal cell carcinoma is the most frequent malignancy
- Magnitude of the risk estimate is uncertain
- Imbalance becomes apparent at 12 months
- Biological plausibility of malignancy findings uncertain
 - Diverse malignancy types
 - No apparent dose relationship
 - Sporadic medullary thyroid carcinoma – no increase in other malignancies

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Putting Risk into Context

Noel Weiss, MD, DrPH
Professor of Epidemiology
University of Washington

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Question

Does the use of calcitonin nasal spray increase the risk of one or more forms of cancer in women during the first several years of use?

Maybe, but the nature of the available data provide no more than a hint that an increase in risk might be present.

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FDA Meta-analysis of Randomized Trials of the Nasal Spray Formulation

- 17 trials
- Mostly 2-year duration (range of 0.5-5 years)
- 50 IU – 400 IU daily
- Outcome ascertainment by means of non-adjudicated patient reporting at periodic study visits

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Reports of Cancer Occurrence

Calcitonin			Placebo			Relative risk*
# of cases	# of participants	%	# of cases	# of participants	%	(95% CI)
122	2666	4.6	28	1264	2.2	1.6 (1.1 – 2.3)

*As estimated from the adjusted odds ratio

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Dose and Duration of Treatment

Size of risk ratio did not vary appreciably according to a calcitonin dose or duration of treatment

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Relative Risk by Type of Malignancy

	RR	95% CI
Basal cell carcinoma	1.95	0.99 - 3.88
Other cancers	1.34	0.88 - 2.04

- From all 21 nasal and oral studies

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Cancer Mortality

	Calcitonin	Placebo
# of cancer deaths	12	2
% of patients	0.19	0.043

- From all 21 nasal and oral studies

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Interpretation

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The Strength of the Data Included in the Meta-analysis Lies in the Randomization of Trial Participants:

- Assuming that the randomization was performed properly and that blinding was largely achieved, there will be no bias as a result of the preferential selection of high-risk (for cancer) patients for calcitonin treatment.

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But These Data have Important Limitations:

- Ascertainment of malignancies in the study participants is, at least to some extent, both incomplete and inaccurate
- Duration of followup does not extend to the time period of greatest a priori concern
- Relatively small number of trial participants, even considered in aggregate, limits the ability to examine data for specific forms of cancer. (If there truly is an increased risk associated with the use of calcitonin salmon, it will almost certainly not be present for all cancers.)

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Conclusion

- Because of these limitations, I believe it would be premature to draw any conclusions concerning an altered risk of cancer in postmenopausal users of calcitonin salmon

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Novartis Proposal for Risk Minimization and Further Evaluation of Calcitonin

John Orloff, MD
Chief Medical Officer
Novartis Pharmaceuticals Corporation

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Calcitonin Benefit/Risk Assessment

- Demonstrated effectiveness as an anti-resorptive agent
- Signal for malignancy of uncertain biological plausibility
- For consideration: calcitonin as an alternative for patients where other treatment options are contraindicated or not tolerated

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Proposal for Risk Minimization

- Labeling changes –limited use settings, short duration of use and warnings
- Inclusion of a Medication Guide
- “Dear Health Care Provider Letter” to advise of labeling changes
- Risk education program

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Proposed Labeling Changes

Indications and Dosage & Administration

PMO Indication

- Miacalcin® should be reserved for patients for whom alternative treatments are not suitable (e.g. patients for whom other therapies are contraindicated or for patients who are intolerant or refuse to use other therapies).

All Indications

- Due to the association between occurrence of malignancies and long term calcitonin use, the treatment duration in all indications should be limited to the shortest period of time possible and using the lowest effective dose.

Submitted to FDA July 2012

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Proposed Labeling Changes

Warning - Meta-Analysis Results

“Meta-analyses of randomized controlled trials conducted in patients with osteoarthritis and osteoporosis have shown that long term calcitonin use is associated with a small but statistically significant increase in the incidence of malignancies compared to placebo. These meta-analyses demonstrated an increase in the absolute rate of occurrence of malignancies for patients treated with calcitonin compared to placebo which varied between 0.7% and 2.36%. Numerical imbalances between calcitonin and placebo were observed after 6 to 12 months of therapy. A mechanism for this observation has not been identified. Patients in these trials were treated with oral or intra-nasal formulations. The benefits for the individual patient should be carefully evaluated against possible risks.”

Submitted to FDA July 2012

Options for Further Evaluation

- *Retrospective cohort study in PMO patients comparing calcitonin-treated to non calcitonin-treated*
- Uncontrolled study (registry of users) uninterpretable
- Prospective study impractical

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Summary and Conclusion

- Benefit in PMO
- Generally well tolerated
- Signal for malignancy; association with calcitonin is uncertain, but warrants action:
 - Label changes/communication plan proposed to reflect results of the meta-analysis, limit use and duration
 - Further elucidate the association of malignancy with use of calcitonin in PMO (retrospective cohort study)
- Seek Committee's guidance on:
 - Whether salmon calcitonin should remain an option for treatment of PMO

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