Briefing Book

NOVARTIS

Drug Regulatory Affairs

Miacalcin® (calcitonin-salmon)

FDA Joint Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee Meeting on the Benefit/Risk of Salmon Calcitonin for the Treatment of Postmenopausal Osteoporosis

Briefing Book

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2 List of Abbreviations

ACRHD	Advisory Committee for Reproductive Health Drugs
ACP	American College of Physicians
AE(s)	Adverse event(s)
AP	Alkaline phosphatase
ASBMR	American Society for Bone and Mineral Research
bALP	Bone alkaline phosphatase
BB	Briefing Book
BCC	Basal cell carcinoma
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BONE (study)	Chesnut et al 2004
CGRP	α-calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CMC	Chemistry / Manufacturing / Controls
CP	Centralized Procedure
CSR	Clinical study report
CT	Calcitonin
CTR	Calcitonin receptor
CTX	C-telopeptide
DSaRM	Drug Safety and Risk Management Advisory Committee
DXA	Dual-energy x-ray absorptiometry
EMA	European Medicines Agency
ET	Estrogen therapy
EPT	Estrogen progestin therapy
EU PhVWP	European Pharmacovigilance Working Party
FIT	Fracture Intervention Trial
FIT-1 (study)	Black et al 1996
FIT-2 (study)	Cummings et al 1998
FDA	(United States) Food and Drug Administration
GI	Gastrointestinal
GLP	Good Laboratory Practices
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HORIZON-PFT (study)	Black et al 2007
HORIZON-RFT (study)	Lyles et al 2007
IL	interleukin
i.m.	Intramuscular(ly)
i.v./IV	Intravenous(ly)
IND	Investigational New Drug

MA	Meta-analysis
iSCT	Injectable salmon calcitonin
ITT	Intent to treat
LOCF	Last observation carried forward
LS-BMD	Lumbar spine bone mineral density
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MORE (study)	Ettinger et al 1999
nSCT/nsSCT	Nasal salmon calcitonin
NAA	Neutron activation analysis
NCI	National Cancer Institute
NNH	Number needed to harm
NOF	National Osteoporosis Foundation
NS	Nasal spray
NTX	N-telopeptide
ONJ	Osteonecrosis of the jaw
OP	Osteoporosis
ORACAL (study)	Binkley et al 2012a
oSCT	Oral salmon calcitonin
PBO	Placebo
PD	pharmacodynamic
PI	Prescribing information
PMO	Postmenopausal osteoporosis
PROOF (study)	Study CT 320, Chesnut et al 2000
PSA	Prostate-specific antigen
PSUR	Periodic safety update report
PTH	Parathyroid hormone
PY	Patient treatment years
QUEST (study)	Chesnut et al 2005
RCT	Randomized clinical trial
RR	Relative risk
RRR	Relative risk reduction
SAE(s)	Serious adverse event(s)
rSCT	recombinant salmon calcitonin
sALP	Serum alkaline phosphatase
s.c.	Subcutaneous(ly)
SCT	Salmon calcitonin
sSCT	Synthetic salmon calcitonin
SD	Standard deviation
SDI	Spinal deformity index
SERM	Selective estrogen receptor modulator
SIR	Standardized incidence ratio
SMQ	Standardized MedDRA query
sNDA	Supplemental New Drug Application

SOF (study)	Study of Osteoporotic Fractures
TBC	Total body calcium
TNF	Tumor necrosis factor
UK PEAG	United Kingdom Patient Environment Action Group
USPI	United States Prescribing Information
VERT-MN (study)	Reginster et al 2000
VERT-NA (study)	Harris et al 1999
WHI	Women's Health Initiative
WHO	World Health Organization
WMD	Weighted mean difference

3 Executive Summary

Miacalcin® (salmon calcitonin, SCT) is available in the United States (US) as injectable and nasal spray formulations. The injectable and the nasal spray (NS) formulations were approved for the treatment of postmenopausal osteoporosis (PMO) in 1986 and 1995 respectively. The injectable form is also approved for the treatment of Paget's disease and hypercalcemia. Recent investigations have suggested a potential increased risk of malignancy following prolonged use of salmon calcitonin. In July 2012, Novartis proposed to modify the prescribing information of Miacalcin to highlight this finding and provide associated changes in treatment guidance for the treatment of PMO. On January 14, 2013, FDA announced the upcoming Advisory Committee to evaluate the benefit risk profile of salmon calcitonin in the treatment of PMO.

The observed potential increased risk in malignancies was identified through a meta-analysis comprising a total of 21 clinical studies: 18 nasal salmon calcitonin (nsSCT) and 3 investigational oral salmon calcitonin (oSCT) trials. The meta-analysis showed an increase in risk across the controlled Miacalcin® Nasal Spray studies alone (Odds-ratio = 1.54, 95% CI: 1.06, 2.23); this corresponds to a number needed to harm (NNH) of 46. When the oral calcitonin studies are included in the meta-analysis the increase in risk remains (Odds-ratio = 1.33, 95% CI: 1.07, 1.64), this corresponds to a NNH of 82. If exposure is limited to 12 months, one would need to treat approximately 91 subjects before the harm of a potential malignancy is observed. Malignancy event rates and malignancy types were within the expected range for the patient populations evaluated in these clinical trials. The malignancy risk in individual studies was generally not statistically significant; however in CT 320 (PROOF study, Chesnut et al 2000), a large vertebral fracture prevention trial in post-menopausal women, a statistically significant increase in risk of malignancy was observed (Odds-ratio = 1.62, 95% CI: 1.00, 2.61). There was no excess of malignancies with Miacalcin for treatment up to 6 months, while at longer treatment durations more malignancies were reported with Miacalcin treatment than with placebo.

Non-clinical long-term animal studies did not show evidence for tumor promotion or tumor progression and there is no clinically or mechanistically clear explanation to substantiate the imbalance in malignancy findings in the meta-analysis.

Post-marketing observations do not suggest any increased risk of malignancy for patients using SCT. Nonetheless, while the relationship of the observed risk to the drug is unclear, Novartis believes that additional information in the prescribing information will assist clinicians in weighing the benefit against the potential risk for use in specific patient groups.

Novartis proposes to change the prescribing information (PI) to recommend the use of Miacalcin® for all approved indications for the shortest possible duration and for indications other than PMO at the lowest effective dose. To appropriately inform the prescribers, a revision of the prescribing information (See Appendix 1 and Appendix 2 USPIs proposed July 2012) will highlight the possible malignancy risk identified from the meta-analysis as indicated below:

"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."*

*these risk differences were derived from an earlier version of the meta-analysis than presented in this briefing book.

There is substantial evidence for the efficacy of SCT as an anti-resorptive agent based on registration studies and post-marketing experience. Clinical studies have demonstrated rapid effects on bone turnover which can be beneficial to certain patients with PMO. Several evidence-based guidelines and reviews include calcitonin as treatment in selected patients, for whom first-line options are either contraindicated or refused (NOF, 2010; ACOG, 2012, Kanis et al., 2013, Christenson et al., 2012])

The registration of salmon calcitonin products predates current standards for establishing anti-fracture benefit. Thus, while randomized, controlled anti-fracture efficacy studies under today's standards have not been conducted for injectable SCT, the level of evidence for anti-fracture efficacy of calcitonin based on surrogate endpoints is supportive of effectiveness and comparable to that of estrogens.

Novartis believes the meta-analysis results that indicate a potential risk of malignancy beyond 6 months needs to be balanced against the real benefit to these patients. The benefit-risk ratio is acceptable for (the short-term) use of calcitonin salmon for patients who are, for a certain time period, unable to use or to tolerate other treatment options for PMO, Paget's disease, and hypercalcemia of malignancy. Because the incidence of PMO is expected to rise in an aging national population, a wide range of treatment options are needed to treat the diverse PMO patients in the U.S.

4 Introduction

The Food and Drug Administration (FDA) has convened a joint meeting of the Advisory Committee for Reproductive Health Drugs (ACRHD) and the Drug Safety and Risk Management Advisory Committee (DSaRM) to discuss whether the benefit of SCT for the treatment of PMO (thinning and weakening of bones that increases the chance of having a broken bone) outweighs a potential risk of cancer. Novartis Pharmaceuticals Corporation appreciates the opportunity to participate in this public meeting and provides information based on its experience in the development and marketing of Miacalcin® Injection and Nasal Spray formulations.

Miacalcin® (calcitonin salmon) was approved by the FDA on July 3, 1986 as an injectable preparation (Miacalcin® Injection) for the treatment of osteoporosis, Paget's disease and hypercalcemia. On August 17, 1995 the FDA approved the intranasal formulation of Miacalcin® (nasal spray) for the treatment of PMO based on studies that proved efficacy in increasing BMD over 1 to 2 years. These products have been used for many years and have been important contributors to bone health – with their use being recommended by many

professional guidelines over the last decade (NOF 2010; NAMS 2008; Hodgson et al. 2003). To date, SCT has been used for more than 2 decades and, based on available data, more than 10 million patients have been treated with SCT from 1998 onward with an estimate of 80% of these patients being PMO patients. The safety profile of SCT in marketed use is well characterized.

Over the last decade, there have been several efforts to develop an orally administered formulation of calcitonin. Novartis is the Investigational New Drug (IND) application holder for a completed Phase III program of an investigational formulation of oSCT (known as SMC021, presently unlicensed) that included one trial in women with PMO (CSMC021A2303) and two trials in men and women with knee osteoarthritis (CSMC021C2301 and CSMC021C2302). In 2010, the sponsor of the oSCT Phase III program reported that preliminary findings from the two osteoarthritis studies (CSMC021C2301 and CSMC021C2302) indicated a possible association with prostate cancer. All health authorities of countries in which Miacalcin® is marketed were informed about these preliminary safety findings.

In 2011, based on the sponsor communication of prostate cancer findings from 2 clinical trials of investigational oral calcitonin formulation in osteoarthritis patients, a review of the overall benefit-risk of calcitonins was initiated in the European Union (EU). As part of this European benefit-risk review procedure, Novartis was requested to conduct a meta-analysis of the occurrence of any malignancy type in calcitonin clinical trials. The results of the meta-analysis are presented and discussed in Section 7.2.3.

Based on this meta-analysis, Novartis submitted worldwide in July 2012 a proposed change of prescribing information for the treatment of PMO. The proposed changes describe the results from the meta-analysis and revised treatment guidance limiting use of Miacalcin® Injection and Miacalcin® NS to patients for whom alternative treatments are not suitable (e.g. patients for whom other therapies are contraindicated or for patients who are intolerant to or refuse to use other therapies, such as estrogens).

The purpose of this Briefing Book is to provide the Advisory Committees with detailed information on the evidence of effectiveness of SCT in the treatment of PMO and on the safety (including malignancy risk) so that an appropriate benefit-risk assessment can be made. At the request of the FDA, clinical efficacy and safety data from the investigational oral SCT program is also presented, where appropriate. To assist the Advisory Committees in putting the benefits and the risks in perspective, a review of available alternate therapeutic options is also provided in Section 7.3.1.

In addition to sharing the available data on the efficacy and safety of SCT in PMO, Novartis has outlined proposed changes to the prescribing information that will allow clinicians and patients to make informed choices regarding treatment with SCT.

Regulatory history of Miacalcin Injection and Nasal Spray

United States

The active ingredient of Miacalcin is synthetic SCT, a 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 osteoclast activity via specific receptors.

Miacalcin® Injection (200 IU per mL) has been approved in the US since 1986 and it is currently approved for PMO, Paget's disease and hypercalcemia (hypercalcemic emergencies). Miacalcin® Nasal Spray (200 IU per actuation) has been approved in the US since 1995 and is currently approved only for the treatment of PMO.

The approval and regulatory history of the first FDA-approved salmon calcitonin product (Armour Pharmaceutical Company's Calcimar® injection), Miacalcin® Injection, and Miacalcin® Nasal Spray are interlinked.

Armour received FDA approval for salmon calcitonin in the osteoporosis indication for its injectable product Calcimar (injectable) in 1984 with the commitment to carry out a post-marketing anti-fracture study in this population.

Novartis (then Sandoz Pharmaceuticals Corporation) achieved approval for the injectable form of Miacalcin in 1986 by cross-referencing and relying (with Armour's consent) on Calcimar® data.

With the Miacalcin injectable approval in 1986, Novartis also agreed to perform a post-marketing study to determine the effect of salmon calcitonin therapy on the incidence of vertebral fractures in PMO patients. In the commitment letter, Novartis noted that the data would come from either cross-reference to data from the Armour post-marketing study once completed or results from an independent study carried out by Novartis.

The post-marketing study was ultimately completed by Rhone-Poulenc Rorer (RPR), the company which acquired Armour in 1986. The study failed to demonstrate a positive effect on fracture rates because the compliance with the injectable formulation was low and the study did not meet the initially projected number of patients to be recruited. The study design was subsequently changed to use the NS formulation of SCT but the recruitment remained very poor due to limiting entry criteria (i.e., necessity of having experienced a Colles fracture). Ultimately, the recruitment was inadequate to be able to complete this study.

In 1991, the Novartis (Sandoz) PROOF (CT 320) study was initiated using Miacalcin NS formulation. The objective was to complete the pending post-marketing study commitment made under the injectable formulation NDA because an osteoporotic fracture study using the injectable form was not feasible and the Armour/RPR attempt was not successful. In addition, PROOF was intended to support a broader PMO indication for Miacalcin Nasal Spray, in the prevention of vertebral fracture and eliminating any restriction limiting its use to women who either refuse or cannot use estrogens.

In December 1992, Novartis filed an NDA for the NS formulation of SCT. The NDA was based on clinical data comprising a total of 5 double-blind placebo-controlled studies in PMO patients (study 503, study 514, study 516, study 522 and study 524).

In February 1995, Miacalcin® Nasal Spray was approved by the FDA. The approval letter for Miacalcin NS included the commitment to complete the ongoing PROOF study.

In August 2004, given the completion of the PROOF study, the FDA informed Novartis that it was released from the commitment to perform a vertebral fracture Phase IV study in osteoporosis for the injectable.

The PROOF study, which contains both biomarker evidence of benefit as well as evidence of a reduction in the risk of vertical fractures at the registered 200 IU dose, is an important

contributor to the determination of effectiveness in PMO and should be considered in supporting a positive risk-benefit assessment for the use of SCT in PMO. FDA did not consider the fracture data sufficient to include in the prescribing information and thus the current USPI reflects benefit in the treatment of PMO based on biomarker data.

Malignancy risk - regulatory status

With respect to malignancy risk, the current Miacalcin injectable and NS prescribing information include the following information regarding nonclinical carcinogenicity and mutagenicity testing:

"An increased incidence of nonfunctioning pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 I.U. per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body surface area). The findings suggest that calcitonin-salmon reduced the latency period for development of pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process."

"Calcitonin-salmon was tested for mutagenicity using Salmonella typhimurium (5 strains) and Escherichia coli (2 strains), with and without rat liver metabolic activation, and found to be non-mutagenic. The drug was also not mutagenic in a chromosome aberration test in mammalian V79 cells of the Chinese Hamster in vitro."

Europe

In Europe, several Health authority reviews of the risks and benefits of Miacalcin have been conducted since 2000:

- A review from 2000 to 2003 concentrated on the assessment of the available efficacy data for all formulations of calcitonin and the outcome resulted in a re-approval of the existing indications for PMO, acute bone loss, Paget's disease and hypercalcemia of malignancy.
- In 2004, a review of available data on a possible association between calcitonin and prostate cancer was initiated by the Medicines and Healthcare products Regulatory Agency (MHRA) based on data available from non-clinical studies and no causal relationship was identified.
- Through 2009 and 2010, the United Kingdom Patient Environment Action Group (UK PEAG) in collaboration with the European Pharmacovigilance Working Party (EU PhVWP) (2009-2010) conducted a review of publications to assess possible association of prostate cancer progression and calcitonin. Reviews concluded that evidence for an association remains limited with no regulatory action warranted.

In January 2011, the EU PhVWP in collaboration with the Committee for Medicinal Products for Human Use (CHMP) initiated a full benefit-risk review procedure. This review was initiated based on the sponsor communication of prostate cancer findings from 2 clinical trials of investigational oral calcitonin formulation in osteoarthritis patients. At the conclusion of

this full benefit-risk review, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended on November 15, 2012 that benefits of calcitonin-containing medicines did not outweigh their risks in the treatment of osteoporosis and that they should no longer be used for this condition. Given the fact that the NS formulation is solely approved for the treatment of PMO, this formulation is being suspended in the EU. For all the other approved indications (Paget's disease, acute bone loss due to sudden immobilization, and hypercalcemia caused by cancer) approved for the injectable formulation, the CHMP concluded that SCT should only be authorized for short-term use [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Calcitonin/human_referral_000319.jsp&mid=WC0b01ac0580024e99].

Genesis of the Novartis salmon calcitonin meta-analysis malignancies

In the context of this most recent benefit-risk review procedure in Europe, a review of the available clinical data of calcitonin was performed. Studies include evaluations of a variety of indications, routes of administration, populations and endpoints. From the review of studies, double-blind randomized studies that had a placebo control for which data on malignancies was available were selected for inclusion in a meta-analysis, while open-label studies (and extensions). Those studies with only an active comparator arm were excluded from consideration. The design features of these studies are summarized in Table 7-25. As is the case with all meta-analyses, the findings are highly dependent on the studies selected for inclusion, as well as those that are excluded and therefore need to be considered in that context. Importantly, one needs to consider the underlying data to determine their relevance to the questions the analysis is intended to address. Novartis acknowledges these limitations; however, the company has proceeded with prudence in informing worldwide health authorities of the potential malignancy findings as well as recommending changes in treatment guidance in order to put the findings in the proper context with respect to the treatment of PMO.

The PROOF study (Study CT 320), which contains both biomarker evidence of benefit as well as evidence of a reduction in the risk of vertical fractures at the registered 200 IU dose, is an important contributor to the determination of effectiveness in PMO and should be considered in supporting a positive risk-benefit assessment for the use of SCT in PMO. Novartis acknowledge that during the review of the data from PROOF, the FDA did not consider the fracture data sufficient to include in the prescribing information. The current USPI reflects benefit in the treatment of PMO based on biomarker data.

The clinical and non-clinical data provided support the conclusion that Miacalcin has a favorable benefit-risk profile for managing patients with PMO and are consistent with the proposal that calcitonin remain an option for patients in whom other options are either inappropriate or contraindicated.

5 Non-clinical data and clinical pharmacology

5.1 Physiology of calcitonin

CT is a 32 amino acid natural hormone secreted by the parafollicular "C" cells of the thyroid gland in mammals and by the ultimobranchial body in the non-mammalian vertebrates which

was first described as a hypocalcemic hormone in 1961 (Copp and Cameron 1961; Copp et al 1962). Porcine- and SCT were sequenced (Potts et al 1968; Niall et al 1969), and the chemical structure of human CT, consisting of a proline amide at residue 32 and an N-terminal disulphide bridge between residues 1 and 7 was established in 1986 (Neher et al 1968). In addition, CT is synthesized as a 136 amino acid precursor molecule, which is processed prior to its release by proteolytic cleavage and by amidation of the terminal proline residue. The same gene transcript encodes both, calcitonin and α-calcitonin gene-related peptide (α-CGRP), both of which are alternative splice products occurring on chromosome 11 between the catalase and parathyroid hormone (PTH) genes (Kittur et al 1985). In contrast to CT, whose function is intimately linked to mineral metabolism, α-CGRP is a 37 amino acid peptide expressed in neuronal cells of the central and peripheral nervous system which is committed to the modulation of the vascular tone (Huang et al 2006).

The CT sequence has been determined for many species, the common features being that it is a 32-amino acid peptide with a carboxyterminal proline amide and a disulfide bridge between cysteine residues at positions 1 and 7 (Sexton et al 1999; Poyner et al 2002). The CT-peptides are well conserved within the N-terminal loop region but exhibit considerable divergence in the rest of the sequence. Based on their amino-acid sequence homologies the different species are classified into three groups:

1. Teleost/avian including salmon, eel, goldfish and chicken CT differing by 4 amino acids
2. Artiodactyl including porcine, bovine and ovine CT, differing by 4 amino acids.
3. Primate/rodent including human and rat CT differing by 2 amino acids.

The common structural features are important for biological activity with the standard assay used since the discovery of CT measuring the hypocalcemic response in the young rat. Subsequently receptor-based assays have been used also, and structure-function relationships are preserved in these various assays. The order of biological potency of the CTs is teleost ≥ artiodactyl ≥ human, although absolute biological activities vary considerably among CTRs of different species and receptor isoforms within species. Although ^{125}I-human CT binds reversibly to its receptor, sCT binds irreversibly in virtually all systems tested, resulting in sustained cAMP accumulation (Fischer et al 1981a; Hilton et al 2000; Purdue et al 2002). Therefore, the affinity of ^{125}I-sCT receptor binding cannot be evaluated. The teleost class and especially sCT has the highest intrinsic activity, is less prone to degradation and lacks Met residues in its sequence, which in other CTs may become oxidized resulting in loss of biological activity. Nonetheless, CT receptors exhibit a general relative potency of sCT ≥ porcine CT ≥ hCT > amylin, CGRP, adrenomedullin. Salmon CT and hCT have similar efficacy at human CTRs, with hCT having approximately 3 to 10-fold lower affinity in competition binding studies. At the rCT receptor, hCT is roughly 10-fold weaker in stimulating cAMP accumulation and is 100- to 1000-fold weaker in competing for ^{125}I-sCT binding (Azria 1989; Sexton et al 1999; Poyner et al 2002).

CT lowers the serum calcium level, antagonizes parathyroid hormone, and reduces renal tubular reabsorption of calcium, phosphorus and sodium ions. Several articles provide an excellent overview over the molecular physiology and pharmacology of calcitonin (Huang et al 2006; Wallach et al 1999; De Paula and Rosen 2010). The inhibition of osteoclast mediated bone resorption and the decrease in calcium tubular resorption results in lower serum calcium (Chambers, et al. 1986), indirectly influencing the synthesis of 1,25-$(OH)_2$D3 (Shiniki et al

1999). Recent evidence suggests that the transcription factor C/EBPβ is strongly up-regulated in kidney cells resulting in significant enhancement of calcitonin induction of 1α(OH)ase transcription and protein expression (Zhong et al 2009). This finding is supportive of a physiological role of calcitonin during times of increased calcium requirement (Wang et al 2003) and may explain the increase in $1,25(OH)_2D_3$ which is observed. In addition, CT was able to prevent lactation induced decrease in bone mineral content in calcitonin/calcitonin gene-related peptide-α null mice, indicating that CT may have an important physiological role in the protection of the maternal skeleton against excessive resorption and attendant fragility during lactation (Woodrow et al 2006).

5.1.1 Calcitonin receptors

There is only one gene encoding a specific CTR. Several receptor subtypes have been cloned and sequenced (Poyner et al 2002). Nevertheless, all CTRs show high binding affinity for CT and weaker binding affinity for other ligands such as CGRP, amylin and adrenomedullin (Goldring, et al. 1993). Analysis of the predicted structure of the CTRs reveals that they are members of the seven-trans-membrane domain spanning, GTP-binding protein-coupled receptor superfamily, and share homology with the PTH and PTH-related peptide (PTH/PTHrP) receptors (Juppner et al 1991), and the receptors for the secretin/glucagon peptides (Ishihara et al 1991). There is roughly 80% homology between different calcitonin receptor species with the primary structure exhibiting a well conserved pattern of multiple hydrophobic domains that are flanked by charged residues and six cys residues in the extracellular loops. CTRs are expressed predominantly in the osteoclast (Quinn et al 1999), the medullary and cortical thick ascending limb of the loop of Henle and in the distal convoluted tubule of the kidney (Sexton et al 1987) and the rat and human brain (Fischer et al 1981a,b). In kidney, CT modulates calcium and magnesium excretion, while in the brain, central actions include analgesia, appetite suppression and modulation of hormone release (Sexton 1991).

5.1.2 Mode of action in bone

5.1.2.1 In vitro effects

The inhibition of bone resorption by CT is mediated by its binding to high affinity (dissociation constant, K_d, 1 to $6x10^{-10}$) osteoclast membrane receptors (Nicholson et al 1986; Quinn et al 1999). It has been estimated that one individual osteoclast expresses approximately 1 million CTRs. Several studies have demonstrated that binding of CT to its receptor activates the cAMP-Protein kinase A and the Ca^{2+}-Protein kinase C signaling pathways (Nicholson et al 1986; Hilton et al 2000; Purdue et al 2002; Sexton et al 1999). These post-receptor events are likely conveying the *in vivo* effects of calcitonin at pharmacological doses.

Binding of low concentrations of calcitonin to the CTR on osteoclasts *in vitro,* induces a rapid change in the cytoskeletal structure including the disruption of the sealing zone (Chambers and Moore 1983; Shyu et al 2007; Suzuki et al 1996). Chambers et al were the first to demonstrate a direct effect of calcitonin on lamellipodial activity within minutes following osteoclast exposure at extremely low, femtomolar concentrations, followed by gradual fragmentation and retraction of lamellipodia, thereby directly demonstrating a cellular basis

for this action (Chambers and Magnus 1982). Thus, exposure of osteoclasts to sCT causes the ruffled border to disappear resulting in its detachment from the bone resorption surface (Kallio et al 1972; Chambers and Magnus 1982). Osteoclast detachment and podosome disassembling occurs via the modulation of Pyk2 and Src phosphorylation state (Shyu et al 2007). It radically alters the internal structure of isolated osteoclasts, inhibiting cytoplasmic mobility, which is essential for bone resorption (Chambers and Dunn 1983). Its long-term systemic administration has also been reported to produce a more prolonged reduction in osteoclast numbers in bone. More detailed cellular studies have demonstrated that when applied at near-physiological femtomolar concentrations to isolated osteoclasts *in vitro,* calcitonin also inhibits cytoplasmic motility (Chambers and Magnus 1982).

In addition to its effect on the cytoskeleton, CT was also shown to reduce the secretion of acid into the resorption lacunae underneath the osteoclast (Kajiya et al 2006). There is a reduced synthesis and release of tartrate resistant acid phosphatase (TRAP) (Yumita et al 1991), alterations in Na^+-K^+-ATPase activity and in the cellular localization of carbonic anhydrase. A direct inhibitory effect upon H^+-ATPase activity in turn results in a reduction of osteoclast acid secretion (Akisaka and Gay 1986; Chambers et al 1987).

Calcitonin was also tested in more complex organ culture systems, which confirmed the effects which are seen on isolated osteoclasts. The peptide was demonstrated to exert inhibitory effects on both the basal and stimulated rate of resorption of organ cultured intact bone (Holtrop et al 1974). In their studies, CT decreased the proportion of ruffled border area significantly by 1 h, and this was followed by a decrease in ^{45}Ca release from previously ^{45}Ca-labelled fetal rat bones. Furthermore, in a neonatal mouse calvaria organ culture model, human CT inhibited PTH-stimulated osteoclast formation *in vitro* at a concentration of 100 ng/mL (Feldman et al 1980). In the same study, CT transiently inhibited PTH-stimulated calcium release for up to 24-48h after its addition. The results were interpreted to indicate that CT exerted an early inhibitory effect on osteoclast precursor cell fusions. In contrast, sCT appears to promote the survival of rat osteoclasts *in vitro*, cultured either on glass or bone, by delaying the onset of apoptosis (Selander et al 1996).

By inhibiting osteoclast activity via its specific receptors and reducing osteoclast formation from precursor cells, sCT markedly reduces bone turnover in conditions with an increased rate of bone resorption, such as osteoporosis.

5.1.2.2 In vivo effects

In vivo there are several studies confirming that calcitonin treatment leads to loss of ruffled border formation (Ikegame et al 2004). Data from the QUEST study indicated that the bone protective effect appears to be dependent on the skeletal compartment with a more pronounced effect on osteoclasts in trabecular/high turnover bone (Chesnut et al 2005).

Calcitonin deficient mice develop a condition of high bone turnover with aging, suggesting that calcitonin may be a physiological inhibitor of bone turnover (Huebner et al 2006). Mechanical studies (Wallach et al 1999) have shown that bone strength is increased by sCT. In addition, experimentally induced fractures show either accelerated healing (Li et al 2007; Bulbul et al 2008) or normal healing when the animals are treated with sCT (Wallach et al 1999).

5.1.3 Clinical pharmacology

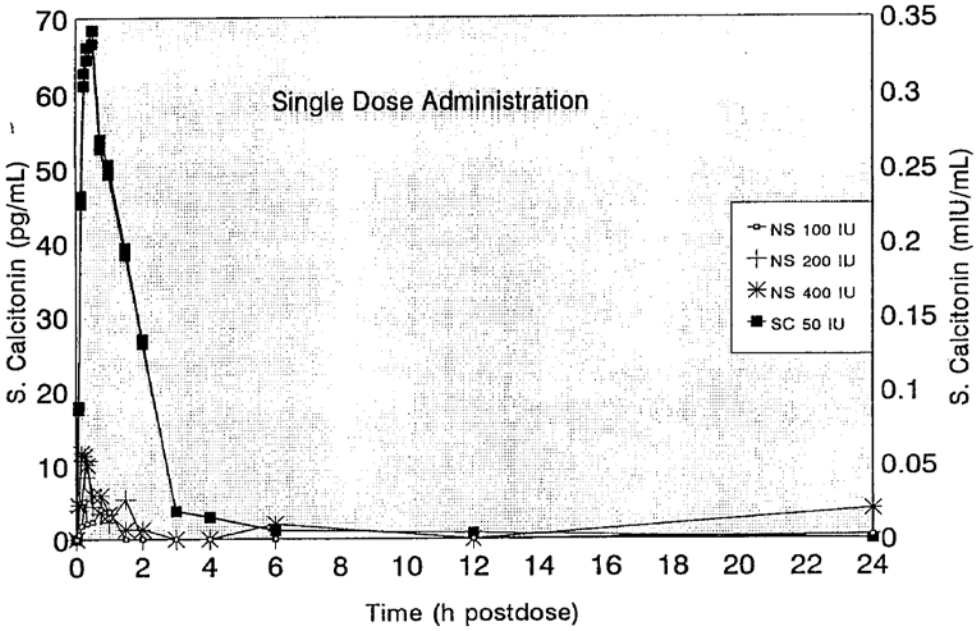
Clinical pharmacology studies have been conducted and, consistent with the preclinical findings, application of the 200IU dose nSCT and injectable salmon calcitonin (iSCT) is associated with suppression of osteoclast activity.

The clinically administered doses of injectable Miacalcin are 50 IU single dose or 200 IU in divided doses for the subcutaneous (s.c.) injection; while the dose of nasal spray is 200-400 IU.

The pharmacokinetics and pharmacodynamics (PD) of nsSCT and subcutaneous sCT were compared in a clinical study in 18 subjects (Study B106). The plasma concentration-time profile of SCT (Figure 5-1) was well defined after subcutaneous injection, however the nasal administration resulted in low plasma concentrations, often close to the lower limit of sensitivity of the analytical method.

After subcutaneous administration at 50 IU dose, peak plasma concentration (Cmax) 0.411 IU/mL was achieved within 1 h (range 0.16 – 1 h) post dose; while the Cmax after nasal administration at 400 IU dose was 0.085 IU/mL within 24 h (range 0-24 h) post dose. There was huge variability in the pharmacokinetics of sCT after nasal administration due to concentrations below the lower limit of assay sensitivity. The overall mean exposure increased corresponding to the dose (AUC for 100, 200 and 400 IU intranasal dose was 0.035 ± 0.076, 0.061±0.102 and 0.213±0.491 mIU.h/mL). The Cmax values were 0.072±0.104 mIU/mL (range 0-0.347 mIU/mL), 0.099±0.100 mIU/mL (range 0-0.299 mIU/mL) and 0.085±0.100 mIU/mL (range 0-0.238 mIU/mL) for the 100, 200 and 400 IU doses respectively.

Figure 5-1 Plasma concentration time profile of SCT following s.c. injection at 50 IU dose and intranasal administration at 100, 200 and 400 IU dose



In the absence of sensitive analytical methods, the pharmacodynamic markers (serum ionized and total calcium, and phosphate levels) provided a valuable alternative. The PD markers showed a dose dependent decrease following administration of nSCT at 100 to 400 IU dose. A dose response relationship at higher doses (up to 1600 IU) could not be established for serum calcium, however a significant relationship for phosphate was observed. The lack of proportional or considerable increase in the exposure of SCT after nasal administration at higher doses (800 and 1600 IU) suggests that nasal administration of higher doses may not be therapeutically beneficial.

In a single-dose study , the bone resorption marker serum C-telopeptide of type 1 collagen (serum-CTX-1) showed a maximum suppression of 55% within 1 hour of parenteral sSCT administration (2 to 50 IU) as well as for nasal SCT 200 IU (Zikan and Stepan 2002). For suppression of osteoclast activity (in the setting of osteoporosis) nSCT 200 IU/d was shown to be sufficient. Continued use of nSCT (for 6 months) led to a gradual decrease over time in overnight fasting serum-CTX-1 levels (Srivastava et al 2004). After 6-months, nSCT (200 IU/d) showed a statistically significant reduction of 34% in serum-CTX-1 vs. baseline and vs. placebo in elderly, postmenopausal women with high bone turnover.

In conclusion, treatment with nSCT was shown to rapidly achieve a clinically relevant effect with significant reduction of bone resorption activity already on the first day of treatment.

6 Background on PMO

6.1 Epidemiology of PMO

Osteoporosis (OP) is a disorder of the skeletal system that predisposes people to increased risk of fractures (Lewiecki 2011). Often under-recognized and thus undertreated, osteoporosis is a clinically silent disease until it presents, usually as a fracture (Lin and Lane 2004). About 50% of women and 20% of men in the US will have an osteoporosis-related fracture at some point in their lives (Liewiecki 2011). Improved screening technology and the recognition of the importance of dietary Vitamin D and calcium intake can mitigate but not eliminate fractures due to osteoporosis.

Osteoporosis is most likely to occur in people over 50, as it is caused by decreased gonadal hormone production (estrogen and testosterone), which in turn leads to decreased bone mineralization and increased bone resorption. The population most at risk is postmenopausal women (Lewiecki 2011). Across both sexes, this age range is the same one in which cancers are most likely to occur (source: http://seer.cancer.gov).

In the United States, approximately 10 million Americans have OP and another 34 million have low bone mass (osteopenia) and are at risk of developing OP; 80% of these are women. Women with low bone mass have an increased fracture risk (compared with those with normal bone density) unless bone loss is prevented (NOF 2010).

Over 2 million osteoporotic fractures are reported each year, which is greater than the annual incidence of heart attack, stroke, and breast cancer, combined (NOF 2008, AHA 2008, ACS 2008). Fractures related to OP will affect approximately 1 of every 2 women and 1 of every 5 men over the age of 50 in the United States. The most common fractures are those of the spine, hip and wrist. Hip fractures result in 10 to 20 percent excess mortality within one year.

Over half of women who sustain a hip fracture do not return to their previous functional state and become dependent on others for their daily activities (Bentler 2009; Cauley 2000).

Additionally, hip fractures are associated with a 2.5 fold increased risk of future fractures. Mortality is also increased following spine fractures, which can cause significant complications including back pain, height loss and kyphosis. Multiple thoracic fractures may result in restrictive lung disease, and lumbar fractures may alter abdominal anatomy, leading to abdominal pain, distention and constipation (NOF 2010).

The societal impact of OP is significant; with meaningful direct and indirect costs and is expected to increase by as much as 50% over the next decade, reflecting an increase in the US population of persons aged 50 years and over (NOF 2010).

6.2 Treatment of PMO

6.2.1 Guidelines for the treatment of PMO

Over the last 20 years the guidelines for the diagnosis of osteoporosis and the methods to assess fracture risk have evolved since the release of the draft guidelines by the FDA: *Preclinical and Clinical Evaluation of Agents Used in the Treatment or Prevention of Postmenopausal Osteoporosis* in 1994. The patient populations studied to obtain new regulatory approval for the treatment of PMO have also evolved due to the many approved therapies. The most recent guidance for the treatment and prevention of osteoporosis from the National Osteoporosis Foundation (NOF 2010, http://www.nof.org/live/treating), calls for treatment of patients who have prevalent fractures and/or who have risk factors that indicate that their probability of experiencing a fracture over the next 10 years is above a specific probability threshold.

The following recommendations to clinicians by NOF are provided for men and women 50 years and older:

Prevention and screening:

- Counsel on the risk of osteoporosis and related fractures.
- Check for secondary causes.
- Advise on adequate amounts of calcium (at least 1,200 mg per day) and vitamin D (800-1,000 IU per day) including supplements if necessary for individuals age 50 and older.
- Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.
- Advise avoidance of tobacco smoking and excessive alcohol intake.
- In women age 65 and older and men age 70 and older, recommend bone mineral density (BMD) testing.
- In postmenopausal women and men age 50-69, recommend BMD testing when you have concern based on their risk factor profile.
- Recommend BMD testing to those who have had a fracture, to determine degree of disease severity.

Treatment initiation:

- Initiate treatment in those with hip or vertebral (clinical or morphometric) fractures.

- Initiate therapy in those with BMD T-scores ≤ -2.5 at the femoral neck or spine by dual-energy x-ray absorptiometry (DXA), after appropriate evaluation.
- Initiate treatment in postmenopausal women and men age 50 and older with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck or spine and a 10-year hip fracture probability ≥ 3% or a 10-year major osteoporosis-related fracture probability ≥ 20% based on the US-adapted WHO absolute fracture risk model (FRAX®; www.NOF.org and www.shef.ac.uk/FRAX).

Patient management under treatment:

- BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss. For patients on pharmacotherapy, it is typically performed two years after initiating therapy and every two years thereafter; however, more frequent testing may be warranted in certain clinical situations.

6.2.2 Pharmacologic treatment options

Current FDA-approved pharmacologic options for the prevention and/or treatment of PMO include, in alphabetical order: bisphosphonates (alendronate, alendronate plus D, ibandronate, risedronate, risedronate with 500 mg of calcium carbonate and zoledronic acid), calcitonin, denosumab, estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene) and parathyroid hormone (PTH(1-34), teriparatide). All of these therapies, except for teriparatide, act as anti-resorptive agents with their primary effect on the osteoclasts. Current NOF guidance for treatment of osteoporosis acknowledges that the potential risks and benefits of all osteoporosis interventions should be reviewed with patients and the unique concerns and expectations of individual patients be considered in any final therapeutic decision. A discussion of the limitations of alternative treatment options is included in the benefit-risk assessment (Sections 7 and 8).

7 Miacalcin benefit/risk evaluation

7.1 Benefits – efficacy assessment

7.1.1 Miacalcin injectable for PMO

Injectable formulations of Miacalcin® have been approved for use in the treatment of osteoporosis for a number of years, the first registration occurring in 1974. The first regulatory approvals for this indication were based on clinical studies whose primary efficacy parameter was measurement of total body calcium (TBC) using neutron activation analysis (NAA). At this time and for many years subsequently, fracture data were not specifically required for regulatory approval in the treatment of PMO.

7.1.1.1 Registration Studies

The approval for injectable SCT (iSCT) in osteoporosis was based on three controlled studies one of which was double-blind. These studies were conducted with Calcimar the product which Novartis relied on for its NDA. Efficacy was investigated in these three studies, which were controlled, randomized and performed over a 2-year period, involving a total of 128 patients (Table 7-1). Both postmenopausal women and male patients with senile

osteoporosis were studied. Dosage in all three studies was 100 IU/day, with additional administration of 1200 mg calcium and in one of the studies additionally 500-800 international units (IU) of Vitamin D daily.

Table 7-1 Summary of registration efficacy studies with injectable calcitonin

Investigator	Diagnosis	Treatment	N	Duration	TBC-NAA , % Change from BL (SE)	
				(months)	Month 20	Month 26
Zanzi Study no. 1	PMO	100 IU/d SCT + 1.2 g Ca	17[1]	26	+2.54 (1.67)*	+ 2.14 (1.63)*
		1.2 g 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+1.2 g Ca	26	26	+ 2.18 (0.80)**	+ 1.39 (1.14)
		1.2 g Ca	24		- 2.23 (0.89)**	- 1.43 (0.93)
Wallach Study no. 3	Osteoporosis in males	100 IU/d SCT + 1.2 g Ca + Vit.D	12	26		+ 2.62
		Vit.D + 1.2 g 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

When evaluating the results of the above studies, the method of evaluating TBC as well as the small number of patients in the trials has to be taken into account (treatment group sizes of 12-26 patients).

In Study 1, there was a statistically significantly greater increase relative to the control group of +5.1% and +4.2% at 20 and 26 months, respectively. In Study 2, the increases relative to the control group at the two time points were +4.4% and +2.8% respectively, but neither increase was statistically significant. At 20 months, the changes observed were statistically significantly different from baseline for the treatment groups studied, with an increase in TBC in the active group and a decrease in the control group. The difference versus baseline was not statistically significant at 26 months in either treatment group. A comparable trend was observed in the third study which was not statistically significant, but this was a study in males only.

There were no statistically significant changes in secondary efficacy parameters in the studies: bone density at the mid radial shaft, incidence of fractures, height, bone pain and mobility.

In conclusion, the PMO studies showed a statistically significant increase in TBC compared to baseline and in study 1 compared to the control group. In the studies in PMO, the increases in the calcitonin groups relative to the control groups were approximately 4-5 % at 20 months and 3-4 % at 26 months.

7.1.1.2 Published studies with Miacalcin injectable

A number of studies with the injectable formulation have been conducted in patients with osteoporosis have been published since the introduction of photon absorptiometry to assess bone mineral content (BMC) (Table 7-2).

In a 1-year study comparing the effects of 100 IU SCT daily and 100 IU every second day with the effects of calcium alone (Gennari et al 1985), BMC decreased in the control group but increased in the SCT groups. The differences in BMC vs. placebo were 12.9% and 8.4%, respectively, when SCT was given 100 IU every day or every other day. There was a 13% decrease in total alkaline phosphatase relative to baseline at 9 months ($p<0.05$) and a 7% decrease relative to baseline at 12 months (non-significant) in the 100 IU group. Urinary hydroxyproline decreased significantly in the 100 IU/day group at all timepoints ($p<0.01$) relative to baseline (21% at 12 months). There was no difference from baseline in the control group. In a further 2-year controlled study by the same investigator (Gennari and Agnusdei 1988) in patients with PMO, lumbar bone density decreased by 7% in controls, and increased by 5% in patients given 100 IU SCT every other day ($p<0.02$). There were no statistically significant changes in urinary hydroxyproline, but the sample size was only 7 patients in each group.

Table 7-2 Publications of clinical trials using SCT and its effect on bone mineral content (BMC)

Author	Diagnosis	Treatment	N	Duration (months)	BMC, % change from baseline	
					Lumbar vertebrae	Femoral shaft
Gennari et al1985	PMO	1 g/d Ca+100 IU i.m./s.c. SCT /d 1 g/d Ca+100 IU i.m./s.c. SCT 2nd d 1 g Ca	15 15 15	12	+8.5* +4.0* -4.4**	+2.5** +1.2** -2.5**
Gennari and Agnusdei 1988	PMO	1 g/d Ca+100 IU iv SCT /2nd d 1 g/d Ca	7 7	24	+5† -7	
Mazzuoli et al 1986	PMO	1 g/d Ca+100 IU i.m. SCT /2nd d 1 g Ca	16 16	12	Extreme distal radius +12‡ -5	
Civitelli et al 1988	PMO High turnover Low turnover	50 IU/2 d SCT s.c.	17 36	12	+22 0	0 -5
Ringe 1990	Primary osteoporosis	1 g/d Ca+100 IU SCT/d 1 g/d Ca+100 IU SCT/2 d	20 19 20	12	Distal radius +7.1 +5.5 -4.3	Proximal radius +3.3 +2.8 -1.6

		1 g/d Ca				
Aloia et al 1991	PMO	50 IU s.c./3 d per week	46	24	3.08* (±0.79)	Radius -1.01 (±0.81)
Rico et al 1995	PMO	100 IU SCT i.m../d + 500 mg Ca/d for 10 days/months 500 mg Ca/d for 10 days/months	36 36	24	Axial BMC +17 data NA, but neg.	Pelvic BMC +30.7 data NA, but neg.

N = number of patients, *p<0.05 vs. baseline value, **p<0.01 vs. baseline value, †p<0.02, ‡p<0.05 vs. control group, NA = not available, neg. = negative.

The study of Mazzuoli et al (1986) examined BMC in the distal radius using dual photon absorptiometry. BMC increased in the SCT group and decreased in the calcium-treated controls (12% vs. –5%, p<0.05) There was also a 30% statistically significant difference (p<0.05) in urinary hydroxyproline/creatinine at 12 months between the Miacalcin® treated group and the control group. Another study (Civitelli et al 1988) also showed decreases in distal and proximal radius BMC in control patients, and increases in BMC in those treated with 100 IU every day or every other day.

These studies confirm earlier findings of the positive effect of 100 IU/day injectable Miacalcin® on TBC. The percentage changes in BMC in the lumbar spine were found to be greater than those in TBC. This was to be expected, since TBC also includes those parts of the skeleton that are less active and thus less affected by calcitonin. This is supported by the study by Ringe (Ringe 1990). The distal radius, a region of pronounced bone turnover activity, showed a 2-fold greater change in BMC than the diaphysis, an area of low turnover.

Therapeutic effects were observed at lower doses in patients with high-turnover osteoporosis. Women with PMO were treated with 50 IU SCT every other day (Civitelli et al 1988). There was a 22% increase in lumbar BMC in patients with high bone turnover, while in the normal turnover group the level remained constant. Aloia et al (1991) reported a 24 months uncontrolled study in 46 postmenopausal women treated with 50 IU three times per week. There was a statistically significant mean annual increase for spine BMC [3.08%, 95% CI = 1.43%, 4.08%)] and a non-significant decrease at the radius (1.0%).

Another study (Rico et al 1995) also assessed the effects of Miacalcin® 100 IU/day on fracture incidence. At 24 months there was a statistically significant reduction (p<0.001) in the incidence of vertebral fractures per year between the Miacalcin® group (0.07 per patient year) and the control group (0.45 per patient year). Trunk densitometry showed a 16% increase in the axial skeleton in the SCT group and a loss in the control group. There was a 30.7% increase in pelvic BMC and a 3.5% increase in total body BMC (p<0.001 vs. baseline) in the Miacalcin® group, while controls showed bone loss in all areas.

A meta-analysis (Kanis and McCloskey 1999), identifying 14 trials of injectable and nasal spray SCT which included 1309 men and women, showed a 57% relative reduction of any fracture for individuals taking calcitonin versus not taking calcitonin (57%; 95% CI 50-62%). The significant relative risk reduction was observed for both vertebral fractures (RRR = 55%; 95% CI 47-61%) and for non-vertebral fractures (RRR = 66%; 95%CI 32-82%).

In a retrospective study (Kanis et al 1992) of 2086 women treated with drugs affecting bone metabolism and 3532 controls, injectable calcitonin has been shown to reduce the risk of hip

fracture. After adjustment for differences in risk factors, the relative risk of having a hip fracture was 0.69 (95% CI: 0.51 to 0.92, p=0.0015) after treatment with calcitonin. The median duration of treatment was 2 years.

Overall, these studies showed that injectable SCT given to osteoporotic patients at a dose of 50-100 IU/d increases BMC at the lumbar spine by 8-22%, compared to calcium treated control groups. Furthermore, bone turnover is decreased by 21-30% as judged by urinary hydroxyproline. Cyclic SCT therapy can increase BMC by 3.5-30% at various sites and significantly reduce the risk of fracture.

7.1.1.3 Conclusion – Miacalcin injectable for PMO

The results from the originally submitted data are positive with regard to Total Body Calcium (TBC). After the approval of Miacalcin® given as either intramuscular or subcutaneous injection, many studies have been published. They show a positive effect on lumbar spine BMC, with increases from 8-22%, and decreases in bone turnover of 21-30% in different studies. A meta-analysis showed that calcitonin treatment resulted in a 57% reduction in the risk of any fracture (Kanis and McCloskey 1999). Furthermore, a 31% reduction in the risk of hip fracture has been shown in a retrospective study (Kanis et al 1992).

This data needs to be held in the proper context given the different regulatory requirements at the time of study conduct where the demonstration of anti-fracture benefit was not required. However, the consistencies of the results of the surrogate markers for anti-fracture efficacy were comparable to estrogens justifying approval at the time of the original regulatory decision.

7.1.1.4 Miacalcin NS for PMO

Miacalcin® NS in the treatment of osteoporosis was submitted to the US FDA with a clinical data package comprising a total of 5 double-blind placebo-controlled studies in PMO patients (studies SMC 503, SMC 514, SMC 516, SMC 522 and SMC 524). Studies SMC 503 and SMC 524 were conducted in women in early menopause (less than 5 years post-menopause) with the aim toward prevention of bone loss in women at risk of postmenopausal osteoporosis. Studies SMC 516 and SMC 522 were conducted in women who were more than 5 years post menopause with significant osteoporosis. Study 514 was conducted in women within 6 to 120 months of menopause with mild to moderate osteoporosis.

The Miacalcin® NS prescribing information summarizes the data from two placebo-controlled studies that were 2 years in duration (SMC 514 and SMC 522). Efficacy was determined based on the percentage change in LS-BMD at 24 months relative to baseline. The main characteristics of these studies are presented in Table 7-3.

Table 7-3 Overview of studies contributing efficacy data on Miacalcin® NS as described in the USPI for the indication treatment of PMO

Study code	(Age)† [post-menopause]	Dura-tion	Dosage	Efficacy ITT_E (n)	Efficacy parameters
Treatment of PMO : pivotal studies					
SMCO 522 (Overgaard et al 1992)	(68-72) [not specified]	2 yr	Placebo Mia 50 IU / d Mia 100 IU / d Mia 200 IU / d	51 47 49 49	BMD (DXA) BMC (SPA) new vertebral deformities
SMCO 514 (Ellerington et al 1996)	(35-65) [menopause 6 mo - 10 yr]	2 yr	Placebo /d or 3d /wk Mia 200 IU/ 3d /wk Mia 200 IU / d	43 34 35	BMD (DPA) new vertebral deformities

† age range given is actual age range, not that specified in protocol
ITT_E = intention to treat for the efficacy patient group; BMC = bone mineral content; BMD = bone mineral density, bone density; DPA = dual photon absorptiometry; DXA = dual energy X-ray absorptiometry; SPA = single photon absorptiometry; Mia = Miacalcin® Nasal Spray;
d = day; wk = week; mo = month; yr = year

The first evidence of efficacy for the 200 IU dose came from a small European pilot randomized double-bind study of 1 year duration at three dose levels (SMCO 005). Both 50 IU/d and 100 IU/d were less effective. Subsequently, the same dosage range was tested in trial SMCO 522, which confirmed the results of the first pilot study.

7.1.2 PROOF study (CT 320)

In particular, PROOF, initiated in 1991, was intended to support a broader PMO indication for Miacalcin Nasal Spray reflecting the product's safe and effective use in the prevention of vertebral fracture.

7.1.2.1.1 Fracture prevention (efficacy in the PROOF study)

Study overview

The PROOF study was a multicenter, double-blind, randomized study to investigate the efficacy of Miacalcin® Nasal Spray in the prevention of osteoporotic vertebral fractures. 1,255 postmenopausal women patients were randomized in 47 centers (42 in the US, 5 in the UK) between February 1991 and July 1993; the last patient was completed in April 1998.

Patients were randomized to receive either SCT nasal spray (Miacalcin® Nasal Spray 100 IU, 200 IU or 400 IU/day), or placebo nasal spray for 5 years. All patients had a total daily intake of at least 1500 mg calcium and 400 IU of Vitamin D during the study.

Key patient selection criteria

Non-black (i.e. White, Asian, or Hispanic) women were eligible to participate if:

- They were postmenopausal for at least 1 year,
- Had 1 to 5 prevalent thoracic or lumbar vertebral compression fractures (as evaluated "onsite" at the study center) and

- Had a lumbar spine bone mineral density (LS-BMD) at least 2 standard deviations (SD) below normal for young normal pre-menopausal females (age 30 years)

Women with a history of hip fractures or with a history of diseases, conditions, or chronic usage of medications (e.g., corticosteroids) that could affect bone metabolism or bone mass measurements were excluded. Women who had been treated with calcitonin, estrogens, or fluorides within 3 months of study entry, continuous bisphosphonates for at least 3 months within 24 months or cyclical bisphosphonates within 18 months were also excluded.

With regard to malignancies, patients with a history of malignant disease within 5 years, or evidence of recurrence were excluded, except for basal cell and squamous cell carcinoma of the skin.

Objectives

The primary efficacy objective was to evaluate the effect of 200 IU SCT versus placebo on the incidence of new vertebral fractures. (The effect of the 100 IU and 400 IU SCT dose levels and the effect on the incidence of new and/or worsening vertebral fractures were also analyzed, separately). Secondary objectives included the effect of SCT versus placebo on:

- fractures at non-vertebral sites,
- bone mineral density (BMD) at lumbar spine and hip,
- biomarkers of bone turnover,
- SCT antibody titers.

Safety variables assessed included adverse events, concomitant medications, physical examinations, nasal examinations, electrocardiograms and laboratory evaluations.

Study assessments and visit schedule

All baseline evaluations, including inclusion/exclusion criteria, background information and pretreatment efficacy and safety evaluations were conducted at Month 0, within 2 weeks prior to initial dose of study drug. The baseline evaluations were used for determination of the patient's study eligibility, as well as baseline measurement for changes that occurred during the study. Eligible patients were provided with study drug at the baseline visit and started therapy on the morning following the baseline visit. Evaluations were performed at months 1, 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 to assess whether any changes occurred while on treatment. Spinal radiographs, LS-BMD and hip BMD, serum type-I collagen cross-linked C-telopeptide (serum CTX-1), bone-specific alkaline phosphatase (AP), osteocalcin levels, urinary type-1 collagen cross-linked N-telopeptide levels (urine-NTX), and calcitonin binding antibodies were assessed every year.

Vertebral fracture assessment

Lateral thoracic and lumbar radiographs were evaluated qualitatively at each study center before enrollment, and the 1,255 women were enrolled based on the initial radiograph report at the study site. Subsequently, all baseline and follow-up lateral thoracic and lumbar radiographs were analyzed centrally at the University of California San Francisco, using a combined quantitative and semi-quantitative method. Prevalent fractures were defined as a 3 or greater SD reduction in any height ratio (versus normative data) by quantitative

morphometry and a fracture grade 1 or greater (grade 0 = "no fracture" and grade 3 = "severe fracture") using a semi-quantitative evaluation. Two independent radiologists made the evaluation, with adjudication by a third radiologist for resolution of discrepant quantitative and semi-quantitative results. Incident fractures were defined as a 20% or greater and greater than 4-mm decrease in any vertebral height (versus previous radiograph) by quantitative morphometry, as well as a change in the fracture grade from 0 to 1 or greater by semi-quantitative evaluation (Chesnut et al 2000).

Based on this review, 269 (21.4%) out of the 1,255 women who were initially determined by the study site principal investigator to meet the criteria of 1 to 5 vertebral fractures were found to have only a mild compression fracture that did not meet the enrollment criteria. Additional 65 (5.2%) women were found to have more than 5 vertebral fractures. Spinal radiographs could not be evaluated in 11 women. Overall, 910 (72.5%) participants had 1 to 5 prevalent vertebral fractures at baseline.

Statistical methods

Vertebral fractures

The primary analysis for the incident vertebral fracture endpoint was an intent-to-treat (ITT) analysis among all participants with at least one follow-up radiograph. Secondary analyses were performed among participants with 1 to 5 prevalent vertebral fractures at enrollment (i.e. the originally foreseen population as per protocol), and among those who received the study drug for at least 3 years or who had a fracture during the first 3 years of treatment (3-year valid completer analysis). The primary statistical assessment was the pairwise comparison of SCT 200 IU versus placebo using a Cox Proportional Hazard (COX-PH) model with treatment as an explanatory variable. Additional sensitivity analyses were performed based on 1) a COX-PH model with treatment and pooled center as explanatory variables, 2) a log-rank test, and a stratified log-rank test by pooled center. The study had a power of 80% to show a 50% reduction in the risk of new vertebral fractures, on the assumption that 20% of participants would have a fracture in the placebo group compared with 10% in the SCT 200 IU group (Chesnut et al 2000). The study was not designed to have power to discriminate between doses. All reported p-values are two-sided, and treatment contrasts are presented with their 95% confidence intervals (CI). Relative risks (RR) were estimated as hazard ratios. Kaplan-Meier estimates and plots provided descriptive measures of fracture rates.

Patient characteristics

1,255 patients were randomized. Of these patients, 944 (75.2%) received SCT and 311 (24.8%) received placebo. 511 (40.7%) patients completed the 5-year study (383 on SCT and 128 placebo). 783 (62.3%) of patients completed at least 3 years. At study completion, there was a comparable distribution of patients among treatment groups (see Table 7-4). There were no significant differences between treatment groups at baseline with respect to age, weight, height, lumbar spine BMD, BMI, SDI, vertebral fractures or history of smoking/alcohol use. The majority of patients was Caucasian (97.2%), was more than 5 years postmenopausal and had prior dietary calcium supplementation. Patient age ranged from 44 to 94 years (see Table 7-5).

Table 7-4 Patient disposition by treatment group in PROOF study

	Treatment groups				
	Miacalcin®				
Number of patients	**100 IU**	**200 IU**	**400 IU**	**Pooled**	**Placebo**
Randomized	316	316	312	944	311
Discontinued prematurely	192	184	185	561	183
Completed study	124	132	127	383	128
Completed at least 3 years	189	204	200	593	190

Note: Pt. No. 45017 is not treated as discontinued prematurely in this table

Table 7-5 Summary of background data (all randomized patients) in PROOF study

Category	100 IU Miacalcin®	200 IU Miacalcin®	400 IU Miacalcin®	Placebo	p-value[2]
Age					0.3503
N	316	316	312	311	
Mean	68.19	68.96	67.92	68.19	
Minimum	47.00	44.00	47.00	48.00	
Median	69.00	69.00	68.00	67.00	
Maximum	87.00	94.00	88.00	91.00	
Race					0.0380[3]
Caucasian	304 (96%)	312 (99%)	307 (98%)	297 (95%)	
Oriental	4 (1%)	0 (0%)	3 (1%)	2 (1%)	
Other	8 (3%)	4 (1%)	2 (1%)	12 (4%)	
BMI (kg/m^2)					0.8129
N[1]	315	315	312	309	
Mean	24.72	24.97	24.86	24.71	
Median	24.26	24.64	24.37	24.53	
LS BMD (g/cm^2) at Baseline					0.5078
N[1]	279	287	277	273	
Mean	0.84	0.85	0.84	0.85	
Median	0.84	0.86	0.85	0.86	
SDI (adjudicated data)					0.4054
N[1]	311	309	307	305	
Mean	0.14	0.16	0.16	0.15	
Mean # vertebral fractures at Baseline per patient[4] (from SDI adjudicated data)					no p-value was calculated
N[1]	311	309	307	305	
Mean	1.82	2.08	2.08	1.95	
Smoker					0.5970
Yes	49 (16%)	44 (14%)	38 (12%)	48 (15%)	
No	267 (84%)	272 (86%)	274 (88%)	263 (85%)	
Drinker					0.8340
Yes	150 (47%)	141 (45%)	150 (48%)	146 (47%)	
No	166 (53%)	175 (55%)	162 (52%)	165 (53%)	

[1]Indicates the number of patients for whom data were available.
[2]Comparisons between treatment groups.
[3]Warning: P-value for the Chi-square test should be viewed with caution if any individual cell size is less than 5.
[4]Statistics performed on SDI adjudicated data

Primary efficacy results

New vertebral fractures in the overall population (overall analysis)

Of the 1,255 patients randomized, 1,244 (99.1%) had a baseline X-ray and 1,108 (88.3%) had a follow-up X-ray and were at risk of new and/or worsening vertebral fractures (n=270 on placebo, n= 273, 287 and 278 on SCT 100 IU/d, 200 IU/d and 400 IU/d, respectively). New vertebral fractures occurred in 51 (17.8%) of 287 patients at risk in the 200 IU group and in 70 (25.9%) of 270 patients at risk in the placebo group. This relative risk reduction of 33% for new vertebral fractures in favor of SCT was statistically significant (RR=0.67, 95% CI: 0.47-0.97, p=0.03). The relative risk of new vertebral fractures was numerically lower by 15% and 16% versus placebo, in the SCT 100 IU and SCT 400 IU dose groups. These differences were not statistically significant (see Table 7-6); however, the results shown for all doses trend toward a favorable effect of calcitonin treatment.

The analysis of new vertebral fractures per 1000 patient X-ray years showed a 40% decrease in the SCT 200 IU group compared to placebo (p=0.02). In these supportive analyses, the differences between placebo and the SCT 100 IU and the SCT 400 IU dose groups also did not achieve statistical significance (see Table 7-6).

Table 7-6 Summary of vertebral fracture efficacy results in PROOF study

Statistics	Placebo	Miacalcin®		
		100 IU/d	200 IU/d	400 IU/d
All patients				
No. of patients at risk	270	273	287	278
Pat. with ≥1 new vertebral fracture (%)	70 (25.9%)	59 (21.6 %)	51 (17.8%)	61 (21.9%)
Risk relative to placebo (95% CI)	NA	0.85 (0.60, 1.21)	0.67 (0.47, 0.97)	0.84 (0.60, 1.18)
P-value vs. placebo[1]	NA	0.370	0.032	0.316
New vertebral fractures per 1000 patient X-ray years	131	129	78	111
P-value vs. placebo	NA	0.327	0.017	0.292

NA = not applicable;
[1] Wald p-value from SAS PROC PHREG without composite centre in Model

The analysis of the data by year of treatment (Figure 7-1 and Table 7-7) shows a trend already at Year 1 (p = 0.10) towards a 47% reduction in the risk of developing new vertebral fractures for the SCT 200 IU group versus placebo. At Year 3, the relative risk reduction (36%) became statistically significant (p=0.03). In Years 4 and 5, the relative risk reduction was 36% and 33% respectively (p= 0.02; p=0.03, respectively).

Figure 7-1 Cumulative percentage of patients with at least 1 new fracture per year in PROOF study

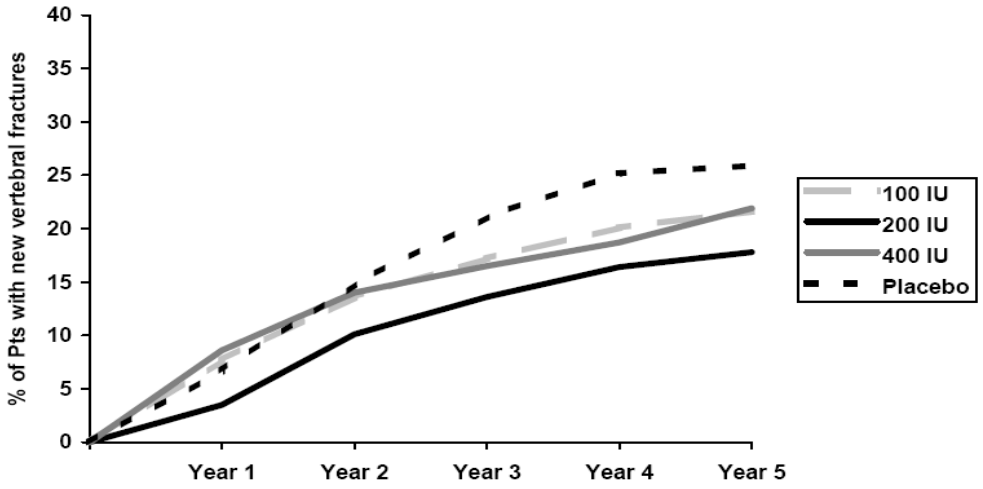


Table 7-7 Relative risk of developing a new vertebral fracture versus placebo by year of treatment in PROOF study

Category	100 IU Miacalcin®	200 IU Miacalcin®	400 IU Miacalcin®
one year	1.175	0.526[1]	1.333
two years	0.931	0.681[1]	0.974
three years	0.831	0.639[2]	0.793
four years	0.815	0.641[2]	0.737[1]
five years	0.853	0.674[2]	0.839

[1] 0.05 <p<0.20; [2] p<0.05

New and/or worsening fracture analysis

The number of patients with at least one new/and or worsening fracture was 59/287 (20.6%) in the SCT 200 IU group and 74/270 (27.4%) in the placebo group (RR 0.75; 95% CI 0.53-1.05, p=0.09).

The RR versus placebo was 0.90 (95% CI 0.65-1.25; p=0.53) for the SCT 400 IU dose group and was 0.83 (95% CI: 0.59-1.17; p= 0.29) for the SCT 100 IU dose group.

New vertebral fractures in the population with 1 to 5 prevalent vertebral fractures and in 3-year valid completers

The patient selection criteria in PROOF required patients to have 1 to 5 prevalent vertebral fractures at baseline. Patient eligibility was originally based on the evaluation of spine radiographs at the enrolling study sites. However, after central adjudication of baseline spine radiographs, only 910 (72.5%) out of 1,255 women had one to five prevalent vertebral fractures as specified by the protocol, 269 (21.4%) had no vertebral fractures, and 65 (5.2%) had more than 5 fractures. Spinal radiographs could not be evaluated in 11 (0.9%) women, who were excluded from all analyses.

Of the 910 patients with 1 to 5 prevalent vertebral fractures at baseline 817 had a follow-up X-ray and were at risk of new and/or worsening vertebral fractures (n=203 on placebo, n= 201, n=207 and n=206 on SCT 100 IU/d, 200 IU/d and 400 IU/d, respectively).

The analysis in patients with 1 to 5 prevalent vertebral fractures at baseline and the analysis in 3-year valid completers were consistent with the results in the overall study population. Comparison of the SCT 200 IU group versus placebo in patients with 1-5 prevalent vertebral fractures at baseline showed a statistically significant relative risk reduction by 36% in favor of SCT (RR 0.64; 95% CI 0.43-0.96; p=0.03). The SCT 400 IU group showed a trend towards reducing the risk of new vertebral fractures (RR 0.78; 95% CI 0.53-1.14; p=0.2). The RR in the SCT 100 IU dose group was 0.94 (95% CI 0.65-1.36; p=0.7) (see Table 7-8).

An additional analysis in 3-year valid completers (patients who stayed on study drug for at least 3 years or experienced vertebral fractures within the first 3 years) was also consistent with the result in the main analysis. Comparison of the SCT 200 IU group versus placebo showed a statistically significant relative risk reduction by 34% in favor of SCT (RR 0.66, 95% CI 0.44-0.99, p=0.04) (see Table 7-8).

Table 7-8 Vertebral fracture sensitivity analyses for PROOF study

Statistics	Placebo	Miacalcin®		
		100 IU/d	200 IU/d	400 IU/d
Patients with 1 - 5 prevalent fractures				
No. of patients at risk	203	201	207	206
Pat. with ≥1 new vertebral fracture (%)	60 (29.6%)	52 (25.9%)	40 (19.3%)	48 (23.3%)
Risk relative to placebo	1.0	0.94	0.64	0.78
P-value vs. placebo[1]	NA	0.73	0.03	0.20
Three year valid Completers				
No. of patients at risk	162	152	157	155
Pat. with ≥ 1 new vertebral fracture (%)	59 (36.4)	49 (32.2)	40 (25.5)	42 (27.1)
Relative risk	1	0.91	0.66	0.71
P-value vs. placebo[1]	NA	0.64	0.04	0.09

NA = not applicable; [1] Wald p-value from SAS PROC PHREG without composite centre in Model

Secondary efficacy results

Non-vertebral fractures

Non-vertebral fractures were collected by standard adverse event reporting and were classified according to the anatomical region (upper limb, including humerus, radius, ulna, and wrist), or hip and femur. Non-vertebral fracture information was collected through the case report forms, with the hip data being checked against serious adverse event forms. Analyses were performed for each region and overall. The PROOF study was not powered to demonstrate a reduction in the risk of non-vertebral fractures and the results are limited by the relatively small number of events. In all analyses the SCT 100 IU group had the lowest non-vertebral fracture rate, the SCT 200 and SCT 400 IU groups having an intermediate result and the placebo group the highest fracture rate. However, the number of events was too low to draw any firm conclusions on between-group differences of the different doses.

For the SCT 200 IU group, there was a non-significant 25% (upper limb), 48% (hip/femur) 37% (upper limb and hip/femur) reduction in the risk of developing a non-vertebral fracture compared to placebo (p=0.136).

A summary of non-vertebral fracture results is presented in Table 7-9.

Table 7-9 Non-vertebral fractures (overall analysis) in PROOF study

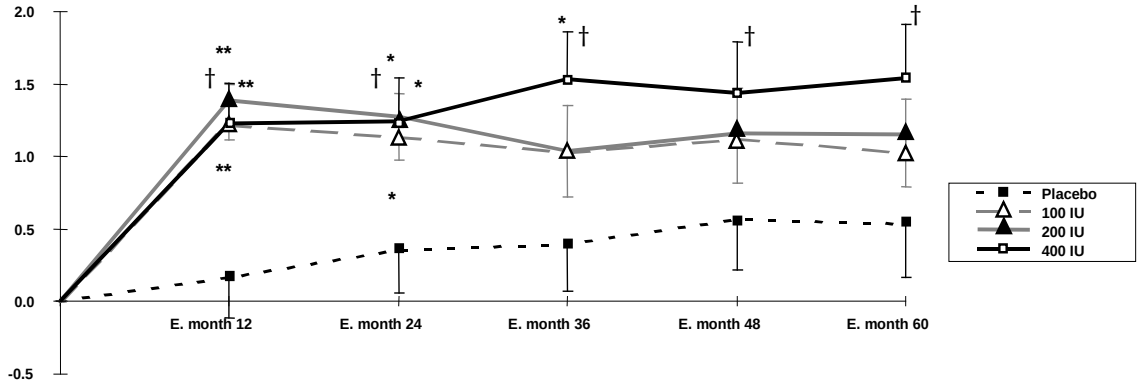
Non- Vertebral fractures	Placebo	Miacalcin®		
		100 IU/d	200 IU/d	400 IU
No. of patients at risk	305	313	315	312
≥ 1 fracture of the hip/femur (%)	9 (3.0%)	1 (0.3%)	5 (1.6%)	7 (2.2%)
Risk relative to placebo	1.0	0.110	0.520	0.747
P-value vs placebo[1]	NA	0.036	0.241	0.563
≥ 1 fracture of the upper limb (%)	16 (5.2%)	6 (1.9%)	13 (4.1%)	14 (4.5%)
Risk relative to placebo	1.0	0.362	0.750	0.840
P-value vs placebo[1]	NA	0.034	0.442	0.633
≥ 1 fracture of the hip/femur and/or upper limb (%)	25 (8.2%)	7 (2.2%)	17 (5.4%)	21 (6.7%)
Risk relative to placebo	1.0	0.268	0.626	0.803
P-value vs placebo[1]	NA	0.002	0.136	0.458

NA = Not applicable [1] Wald p-value from SAS PROC PHREG without composite centre in Model

BMD

There was a statistically significant increase from baseline in LS-BMD 1.0% to 1.5% in all the SCT treatment groups (see Figure 7-2) which was consistently maintained over the 5-year study period. There was also a non-significant increase of 0.5% versus baseline in the placebo group. The SCT 100 IU, SCT 200 IU and SCT 400 IU dose groups had a statistically significantly greater increase in LS-BMD relative to placebo at Year 1 and Year 2. The SCT 400 IU group maintained this statistically significant greater increase relative to placebo up to Year 3.

Figure 7-2 LS-BMD mean percent change (SEM) from baseline in PROOF study



* * p<0.01 vs placebo; * p<0.05 vs placebo; † p≤0.003 vs baseline for all dosage groups
LS-BMD = bone mineral density of the lumbar spine

The percentage change in hip BMD relative to baseline in the SCT 200 IU group was consistently above the placebo group by 0.7% to 2.1% in all regions but the differences versus placebo were not statistically significant (with the exception of Ward's triangle at 1 year).

Table 7-10 Percent change from baseline in BMD at 1 year and at 5 years in PROOF study

Area	Time point	Mean % change from baseline			
		Placebo	SCT 100 IU	SCT 200 IU	SCT 400 IU
Lumbar spine	Year 1	0.17%	1.22%*	1.39%*	1.23%*
	Year 5	0.54%	1.03%	1.16%	1.55%
Femoral Neck	Year 1	-0.25%	-0.28%	0.38%	0.35%
	Year 5	-1.95%	-1.67%	-1.13%	-1.38%
Wards Triangle	Year 1	0.96%	2.23%	3.08%*	1.72%
	Year 5	-1.69%	0.14%*	0.23%	-0.99%
Trochanter	Year 1	0.15%	0.58%	1.22%	0.89%
	Year 5	-1.50%	-0.65%	-0.84%	-0.64%

Mean baseline LS BMD (g/ cm^2) was 0.85 for placebo and SCT 200 IU; and 0.84 for SCT 100 IU and SCT 400 IU

Mean baseline FN BMD (g/ cm^2) was 0.69 for placebo and SCT 400 IU; 0.695 for SCT 200 IU and 0.70 for SCT 100 IU

Mean baseline WT BMD (g/ cm^2) was 0.50 for placebo and SCT 400 IU; 0.49 for SCT 200 IU and 0.51 for SCT 100 IU

Mean baseline TR BMD (g/ cm^2) was 0.60 for placebo and SCT 200 IU and SCT 400 IU; and 0.61 for SCT 100 IU

* $p<0.05$ versus placebo

Biochemical markers

Urinary NTX

Inhibition of bone resorption was shown by a statistically significant reduction in urinary-NTX after 1 year for the SCT 200 IU and SCT 400 IU dose groups versus placebo. After 5 years the differences in urinary NTX were less pronounced and not statistically significant (see Table 7-11). Urinary NTX data did not appear to be normally distributed and therefore between-group comparisons were analyzed using Wilcoxon statistics. Urine samples were analyzed in multiple batches, and a decrease in the recovery of urinary creatinine was seen over time, probably due to the fact that the urine was stored at –20°C only. For biochemical markers end-points were analyzed using last observations carried forward.

Table 7-11 Percent change from baseline in urinary NTX at 1 year and at 5 years in PROOF study

Urinary NTX	Time point	% change from baseline (mean)			
		Placebo	SCT 100 IU	SCT 200 IU	SCT 400 IU
	Year 1	-2.46%	-8.71%	-15.29%*	-17.06%*
	Year 2	-5.08%	-8.51%	-9.60%	-14.39%*
	Year 3	-5.16%	-5.44%	-6.34%	-13.40%
	Year 4	1.72%	0.65%	1.76%	-1.35%
	Year 5	9.34%	-5.67%	7.16%	0.91%

Mean baseline urinary NTX (nmolBCE/mmolCRT) was 70.9 (placebo), 67.5 (SCT 100); 73.5 (SCT 200); 70.0 (SCT 400).

*p < 0.05 versus placebo (Wilcoxon)

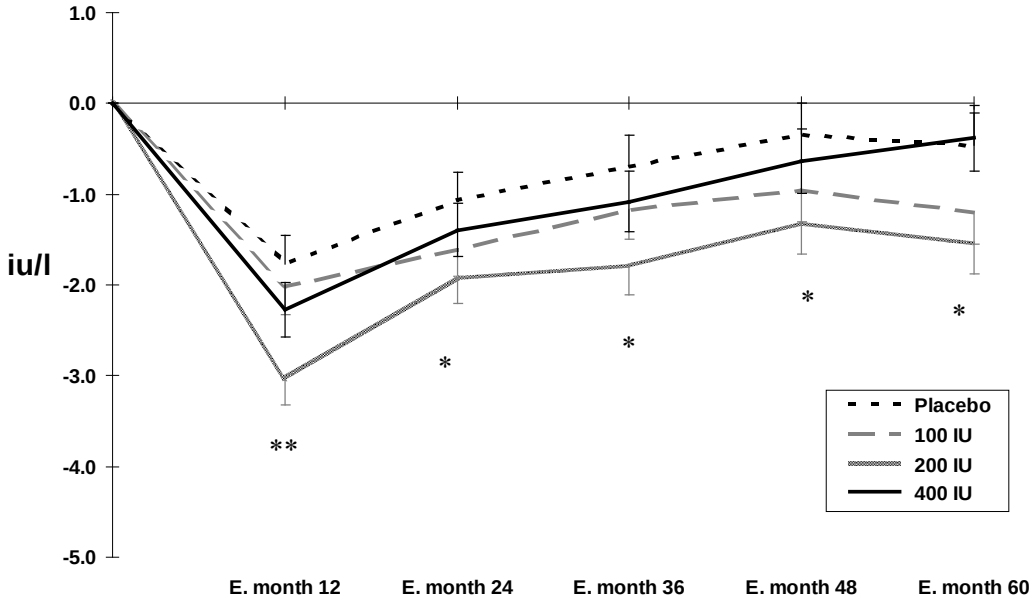
Bone alkaline phosphatase (bALP)

A mean absolute change was considered more appropriate for bALP due to the relevant percentage of baseline values which were equal to zero which would impact any analysis that would use the percentage change from baseline as an efficacy outcome variable. Mean Baseline values (IU/L) were 12.010 in the 100 IU group, 12.847 in the 200 IU group, 11.843 in the 400 IU group and 11.954 in the placebo group. For endpoint analyses, the mean absolute change (SE) from Baseline at Month 60 was -1.197 (0.355) for the 100 IU Miacalcin® NS group, -1.533 (0.349) for the 200 IU Miacalcin® NS group, -0.383 (0.356) for the 400 IU Miacalcin® NS group and - 0.464 (0.359) for the placebo group.

The p-values from the between-treatment comparisions for 200 IU versus placebo from the ANOVA model of the change from baseline were <0.05 at all timepoints up to Month 60. A summary of the results are presented in Figure 7-3.

The significant reduction in the bone formation marker provides supportive evidence of the validity of the reduction in vertebral fractures observed based on similar relationships seen with other anti-resorptive therapies for PMO (Delmas 2009).

Figure 7-3 Bone alkaline phosphatase (IU/L) - means (±SEM) of change from Baseline (endpoint analysis) - ITT_E in PROOF study



SCT antibodies

Antibodies binding SCT at titers >1000 at endpoint (5-years) developed in 26.4% of patients in the SCT 100 IU group, 29.1% in the SCT 200 IU group, and 33.7% in the SCT 400 IU group. The presence of antibodies did not influence the effect of SCT on the risk reduction of new vertebral fractures.

7.1.2.2 Discussion/conclusion (PROOF STUDY)

Treatment with 200 IU Miacalcin® NS produced approximately 33% statistically and clinically significant reduction in the risk of developing a new vertebral fracture after 5 years of treatment (Relative Risk 0.674; 95% CI: 0.470-0.967; p=0.032) in the ITT population.

Fracture reduction: The analysis of the data by year of treatment shows that in the 200 IU group there was already a trend after year 1 of demonstrating a 47 % reduction (p = 0.103) in the risk of developing a new vertebral fracture. Secondary analyses of endpoints such as the occurrence of new and worsening vertebral fractures although not statistically significant demonstrate numerical trends that are consistent with a benefit from treatment with Miacalcin NS.

Lumbar spine BMD: Increases in LS-BMD relative to placebo were statistically significantly different from baseline at the early visits (years 1 and 2).

Biochemistry: Reduction in serum NTX was greatest in the first year of treatment (median reduction = 27%), the decrease was statistically significant from baseline and placebo at the early time points. A significant reduction in bone alkaline phosphatase was observed forthe 200 IU treatment arm compared with placebo from month 12 to month 60 of the study.

The PROOF study confirmed the early onset of anti-osteoporotic activity of nsSCT. The maximum BMD increase and maximum bone marker decrease is seen in the first year (i.e. in the early treatment period). This coincides with the highest reduction in vertebral fracture risk in the 200 IU group, which was sustained over 5 years.

7.1.2.3 Adequacy of the PROOF study

The results of the PROOF study have come under scrutiny by academics and Health Authorities (including the FDA). Several of the issues that have been raised regarding the evidence of fracture reduction in the PROOF study are addressed in this section.

The PROOF study was initiated in 1991, which predates the 1994 FDA draft guidelines for the treatment and prevention of PMO that requested at least 3 years of fracture data for registration purposes and up to 5 years if a statistical trend is observed at the 3 year time point ($p < 0.20$). This study served as a fulfilment to the post-approval commitment, agreed between Novartis (previously Sandoz) and FDA for the original approval of Miacalcin injectable formulation in 1986, to provide anti-fracture efficacy data of at least three years in duration.

The current US prescribing information (PI) does not make reference to the reduction in vertebral fractures that was observed in the PROOF study.

Discontinuation rates

This study is the only osteoporosis study prospectively designed as a five-year double-blind, placebo-controlled study, whereas most of the other relevant studies have a duration of three or four years. Hence, the appropriate comparison for the PROOF study with regard to discontinuations is the three year data, which is summarized below.

The 3-year discontinuation rate for the PROOF study was 37.6% (Table 7-12). This discontinuation rate is consistent within the range of discontinuation rates reported for the risedronate (VERT-NA and VERT-MN) and raloxifene (MORE) studies (Table 7-12) which were conducted during a similar timeframe. The FIT study with alendronate seems to be an exception in this respect. However, that can be attributed to the fact that FIT-1 and FIT-2 were conducted exclusively in the US, primarily involving investigational sites that were involved in the observational Study of Osteoporotic Fractures (SOF). In the sample size calculations for MORE, VERT-MN and VERT-NA, a 50% dropout rate over three years was planned for in the study designs as the modern methods available for patient retention were not accessible at the time that these studies were initiated which in some instances was before the availability of the internet.

Table 7-12 Percentage of patients who discontinued treatment before 3 years in the PROOF, VERT-MN and VERT-NA (risedronate), MORE (raloxifene), and FIT (alendronate) studies.

	PROOF (Chesnut 2000)	RIS (Harris 1999)	RIS (Reginster 2001)	MORE (Ettinger 1999)	FIT (Black 1996)
Percentage of patients who discontinued treatment before 3 years	37.6 %	42.3 %[1]	42.0%[1]	23.4 %	14 %[2]

RIS = risedronate

[1)]not taking into account the patients in the 2.5 mg group which was discontinued prematurely by an amendment.

[2)]Publication states: 87% (placebo group) and 89% (alendronate groups) of surviving patients were taking study medication at 3 years. 1985 patients were surviving at 3 years (98% of those surviving = 1946 patients). These numbers combined lead to the quoted rate of 14%.

Thus, the 3-year discontinuation rate in PROOF was comparable to the multinational clinical studies which supported successful registrations through regulatory agencies during the same time period.

A 36% statistically significant vertebral fracture risk reduction was seen in the PROOF study at 3 years with the 200 IU dose, which is also within the range of risk reductions in vertebral fracture seen in other clinical trials conducted in the same timeframe where the reduction over 3-4 years ranged between 30% at the 60 mg/day dose for raloxifene to 48% reduction observed for alendronate in the Liberman study (Liberman et al 1995). See Table 7-20 for more detailed comparisons of these studies.

Potential selection bias introduced by the discontinuation rate

Several sensitivity analyses were performed to investigate whether the drop-out rate biased the study results. The results of these additional analyses consistently showed that the estimates of the treatment effect observed in the PROOF study were independent of the method for handling dropouts and did not increase the risk reduction of vertebral fractures in favor of Miacalcin. It can therefore be concluded that positive bias in favor of the Miacalcin groups has not been observed due to the discontinuation rate.

3 year valid completer analysis

To determine what impact, if any, patients dropping out before being 3 years on treatment might have had on the primary efficacy result, a "3-year valid completer analysis" was performed. This population includes patients who had stayed on treatment for at least three years or who had experienced an incident fracture prior to 3 years, had 1-5 prevalent fractures at baseline, did not take forbidden medications and were at least 75% compliant. The results confirmed the ITT_E analysis and showed a 34% (p=0.044) decrease in new vertebral fracture risk for Miacalcin 200 IU nasal spray.

The study has been conducted and analyzed consistent with regulatory guidelines that existed at the time of the conduct and analysis of this study. Although the study was started in 1991 and concluded in April 1998, it adhered to the principles outlined in the ICH E9 guidelines, Statistical Principles for Clinical Trials. ICH E9 stresses the importance of the analysis plan

being pre-specified in the protocol and further states, "Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory". The analysis pre-specified in the protocol and used as main analysis in the report follows the Full Analysis Set concept of ICH E9, which, according to this guideline, " *... is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects*." The guidelines also rightly state that this analysis set "*… tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis …*".

ICH E9 also calls for showing the robustness of the conclusions by conducting sensitivity analyses. Multiple sensitivity analyses have been conducted for this study and there is no indication for a bias that positively impacts the efficacy demonstrated by of Miacalcin®.

Given that the primary statistical comparison resulted in a clearly statistically significant p-value, a lack of power seemed not to be a problem in the study.

In conclusion, the 3-year discontinuation rate and the 3-year fracture reduction rate were comparable to more recent studies, which have been used in successful registration procedures. In addition, the discontinuation rate, as investigated in the sensitivity analyses, did not bias the results in favor of Miacalcin. Furthermore, a 34% statistically significant reduction in vertebral fracture risk was seen in the "3-year valid completer" patients. Regarding the statistical methodology, the study adhered to the principles outlined in the ICH E9 guidelines, Statistical Principles for Clinical Trials.

7.1.2.4 Dose efficacy assessment

Efficacy of 200 IU

The PROOF study was not designed to show a dose-response effect, as noted previously from earlier studies there was some uncertainty regarding the optimal dose for the treatment of PMO hence three doses were included in the design. The primary efficacy comparison was prospectively defined to be the between-treatment comparison of the 200 IU dose of Miacalcin nasal spray and placebo. This was the only confirmatory statistical test performed in this study. It revealed a statistically significant and clinically relevant 33% fracture reduction for Miacalcin 200 IU nasal spray. Therefore, this study should be seen as a demonstration of efficacy of the 200 IU dose. All additional analyses performed on secondary comparisons, on secondary efficacy or safety parameters, or on patient subgroups, were exploratory in nature. The type one error rate for these additional tests cannot be exactly quantified, and therefore, the results of these exploratory tests must be interpreted with caution. Furthermore the results of these analyses trend towards a favorable effect of Miacalcin NS treatment on NS and do not suggest unexpected adverse effects on the skeleton.

Dose effect between 100 IU and 400 IU

No dose-response testing has been done, as the study was neither designed nor powered for this. The sample size for a reasonable, formal dose-response evaluation would have been dramatically higher than the one for this study. As an illustration, more than 2000 evaluable patients per treatment group would be required to show a statistically difference ($p < 0.05$) between 14.5% (three-year fracture rate for 200 IU) versus 17% (three-year fracture rate for 400 IU) to have a 80% power (two-sided Chi-squared test) . The primary comparison was

between 200 IU and placebo and the comparisons between 100 IU and placebo; and 400 IU and placebo were clearly exploratory in nature.

Descriptively a dose-response effect was performed on the pharmacodynamic parameters: urinary NTX, BMD and SCT antibodies.

LS-BMD increases relative to baseline in the 100 IU, 200 IU and 400 IU groups were 1.029%, 1.155% and 1.545% at 5 years, respectively, which was statistically significantly at all timepoints (p = 0.003).

It is also worth noting that the conservative ITT_E fracture analysis in all patients showed no dose effect of the 200 IU and the 400 IU groups with regard to vertebral fractures, but in the "3-year valid completers" analysis the effect seemed to have plateaued with the 200 IU dose and in the 400 IU group there was a statistical trend observed in the test versus placebo (Table 7-13).

Table 7-13 New vertebral fracture risk reduction of Miacalcin 100 IU, 200 IU, 400 IU vs. the placebo group for various populations in PROOF study.

	Risk reduction (RR, p value) Miacalcin nasal spray		
	100 IU	**200 IU**	**400 IU**
All patients, ITT_E analysis	**15%** (p=0.370)	**33%** (p=0.032)	**16%** (p=0.316)
1 - 5 prevalent fractures, ITT_E analysis	**6%** (p=0.730)	**36 %** (p=0.029)	**22%** (p=0.198)
3-year valid completers	**9%** (p=0.639)	**34%** (p=0.044)	**29%** (p=0.088)

If the 200 IU group results had been due to random chance and the non-significant 16% reduction in the "all patients" population in the 400 IU group been the true effect, one would not have seen a trend towards a 29% reduction in the "3-year valid completer" analysis, a 29% risk reduction in the 4th year and a 22% reduction in the 5th year in the 1-5 prevalent fracture population" in the 400 IU group.

The results of the "3-year valid completer" analysis in the 200 IU and 400 IU groups were similar: 34% (p=0.044) and 29% (p=0.088) risk reduction, respectively. This lack of dose-response effect between these two groups suggests that a plateau for efficacy is reached with the 200 IU dose. The NTX data support such a hypothesis.

7.1.3 PMO registration and supportive studies

Miacalcin® NS in the treatment of osteoporosis was submitted to the US FDA with a clinical data package comprising studies SMC 503, SMC 514, SMC 516, SMC 522 and SMC 524. Key elements of selected studies are summarized below.

Study SMCO 522: This was a randomized, double-blind, placebo-controlled study in women with PMO, with distal forearm BMC ≥-2 SD below normal in all but one patient, with a mean of -3 SD. The daily dosages of the Miacalcin® were 50, 100 or 200 IU/d over a 2-year period. 208 patients were randomized (mean age 70 years, mean time since menopause 21-24 years). 175 patients completed the study. 196 patients were evaluable in the intent-to-treat efficacy

analysis and 164 patients in the valid completers analysis on LS-BMD. For fracture analyses, only the patients without prevalent fractures at baseline were analyzed (114 in the Miacalcin® group and 40 in the placebo group).

Fracture determination by two different methods (Kleerekoper et al 1984 and Melton et al 1988) demonstrated that the incidence of new vertebral fractures was 66% less in the pooled Miacalcin® treatment groups (2, 0, and 3 patients had a new vertebral fracture in the 50, 100 and 200 IU groups, respectively) than in the placebo group (5 patients). This difference in fracture rates was statistically significant in the valid completers analysis for both methods of fracture determination. A trend was observed in the ITT_E analysis.

Lumbar spine bone density increased significantly more in the 200 IU than in the placebo group (+1.56% in calcitonin treated patients vs. +0.2% in the placebo group p=0.046, see Table 7-14). Improvements in the lower dosage groups were also greater than in the placebo group but these were of borderline significance. The study was small and not powered to detect effects on vertebral fracture or to determine any dose response on fracture. Therefore, this study can only be considered supportive of the efficacy of Miacalcin® on fracture.

Study SMCO 514: In this randomized, double-blind, placebo-controlled, parallel group study, 112 patients were evaluable in the intent-to-treat efficacy analysis (56 patients were <5 years, and 56 patients were >5 years postmenopausal) and 97 as valid completers. Doses of 200 IU/d or 200 IU three times a week (alternate days) were compared to placebo.

Only two patients had fractures at baseline and only three experienced a new vertebral fracture. Therefore, no conclusions with regard to anti-fracture efficacy can be drawn from this study. In the PMO population, the 200 IU daily group had an increase in BMD of 1.0% over baseline, while mean bone losses of 0.8% and 1.8% were observed in the alternate day 200 IU group and in the placebo group, respectively (no vitamin D and calcium supplementation were given) (Table 7-14). A statistically significant difference between the 200 IU/d group and placebo was observed at year 2 (p= 0.004). A similar trend was seen in femoral neck BMD. No significant changes in biomarkers were observed in any group.

Study CT 211 provides supportive BMD data (Table 7-14) from a 2-year placebo-controlled study. In this study 400 IU provided a statistically significant increase over placebo in LS-BMD after 2 years. 200 IU did not show any difference as compared to placebo. The results are confounded by a change in the DXA machine during the trial, which required post-hoc quality control.

Study SMC 503 was a randomized double blind, placebo controlled parallel group study in which administered placebo or 50 IU twice daily to women with early osteoporosis. The primary endpoint was LS BMC as assessed by DPA. The change from baseline in LS BMC at 24 months in the valid completers group was -5.8% in the placebo group (n=19) compared with +3.0% in the calcitonin treated group (n=19) demonstrating a significant in this endpoint (p<0.001). There was no significant change observed in BMC of the forearm at either proximal or distal.

Study SMCO 524 was a randomized, double blind, placebo controlled parallel group study which administered 3 doses (100, 200, and 400 IU) Miacalcin NS to women with early menopause for 24 months. The primary efficacy endpoint was LS BMD. At end of study for the valid completers in all four treatment groups, placebo (n=23), 100 IU (n=21), 200 IU (n=

22) and 400 IU (n=24), there were clinically and statistically significant declines from baseline in LS BMD ranging between -1.59 and -3.44%. There were no statistically significant differences in the mean percent decreases from baseline in any Miacalcin treatment group compared to placebo.

Studies SMCO 005 and 516 provide further supportive data in patients with 1 year treatment duration. Although the number of patients in both trials is small, a significant effect on LS-BMD is observed (Table 7-14).

Table 7-14 LS-BMD results for treatment studies in NDA for Miacalcin NS (ITT population)

Study	Duration & endpoint	Treatment groups (n= no. ITT_E pats contributing data)	Mean baseline value (g/cm^2)	Mean change at endpoint (%)	p-value vs placebo
2 yr endpoints (DXA)					
SMCO 522	2 yr	Placebo (n=51)	0.79	+0.20	---
		Mia 50 IU/d (n=47)	0.79	+1.59	0.044
		Mia 100 IU/d (n=49)	0.80	+1.36	0.088
		Mia 200 IU/d (n=49)	0.80	+1.56	0.046
CT 211	2 yr	Placebo (n=13)	0.73	+0.617	---
		Mia 200 IU/d (n=12)	0.74	-0.175	n.s.
		Mia 400 IU/d (n=11)	0.71	+1.502	n.s.
2 yr endpoints (DPA)					
SMCO 514*	2 yr	Placebo (n=22)	1.09	-1.85	---
		Mia 200 IU/d† (n=17)	1.09	-0.77	0.275
		Mia 200 IU/d (n=17)	1.09	+1.02	0.004
1 yr endpoints (DPA)					
SMCO 005	1 yr	Placebo (n=10)	0.71	+0.43	---
		Mia 50 IU/d (n=9)	0.70	+1.24	0.73
		Mia 100 IU/d (n=8)	0.70	+3.21	0.24
		Mia 200 IU/d (n=9)	0.63	+5.26	0.06
SMCO 516	1 yr	Placebo (n=20)	0.82	-0.4	---
		Mia 100 IU/d (n=20)	0.76	+3.2	0.04

† administered 3 d/week, other 200 IU treatment arm is daily administration
* Patient numbers are for the established PMO population in the trial
DXA = Dual X-ray absorptiometry; DPA = Dual photon absorptiometry

7.1.4 Other published studies with Miacalcin NS

A literature review and meta-analysis of the effect of calcitonin on bone density and fractures in postmenopausal women was published (Cranney et al 2002).

The authors searched MEDLINE and EMBASE from 1966 to 2000 and examined citations of relevant articles and the proceedings of international osteoporosis meetings. Osteoporosis investigators were contacted to identify additional studies and primary authors for unpublished data. The authors included 30 studies that randomized women to calcitonin or an alternative (placebo or calcium and/or vitamin D) and measured bone density or fracture incidence for at least 1 yr. For each trial, three independent reviewers assessed the methodological quality and abstracted data.

Calcitonin reduced the incidence of vertebral fractures, with a pooled relative risk (RR) of 0.46 [95% confidence interval (CI) 0.25-0.87, P = 0.02, n = 1404, 4 trials], while the RR from the PROOF study alone was 0.79 (95% CI 0.62-1.00, P = 0.05, n = 1108). For non-vertebral fractures, the pooled RR was 0.52 (95% CI 0.22-1.23, P = 0.14, n = 1481, 3 trials) and the PROOF study effect was less than the smaller trials (RR 0.80, 95% CI 0.59-1.09, P = 0.16, n = 1245).

For bone density of the lumbar spine, the pooled weekly dose of 250 to 2800 IU per week resulted in a significant increase in the weighted mean difference (WMD) of 3.74 (2.04-5.43, P < 0.01, n = 2260, 24 trials). The combined forearm results showed a similar effect, with a WMD of 3.02 (95% CI 0.98-5.07, P < 0.01, n = 468, 9 trials). At the femoral neck, the pooled weighted mean difference showed a non-significant trend toward benefit, WMD 3.80 (95% CI -0.32-7.91, P = 0.07, 9 trials, n = 513). Methodologically weaker studies tended to show greater effects on bone density, and the lumbar spine results suggested the possibility of publication bias.

The Authors concluded that calcitonin likely increases bone density in postmenopausal women predominantly at the lumbar spine and forearm for weekly doses of greater than 250 IU, although the true effect may be smaller than the pooled estimate would suggest. Calcitonin also likely reduces the risk of vertebral fracture; its effect on non-vertebral fracture remains uncertain.

More recently, the Quest study was completed and exploratory results were published (Chesnut et al 2005). The study evaluated the effect of Miacalcin 200 IU nasal spray daily on bone quality assessed by histomorphometry in iliac crest bone biopsies in postmenopausal women with 1 to 5 vertebral fractures, bone mineral density below mean peak value (T-score < 0) and, who were at least 5 years past menopause. This was a single center, double-blind, randomized, placebo-controlled, parallel group, 2-year study. Ninety-one patients were enrolled (46 patients treated with Miacalcin 200 IU NS and 45 patients treated with placebo NS) and 71 patients (33 patients treated with Miacalcin 200 IU NS and 38 patients treated with placebo) completed the study. All patients fulfilled the inclusion criterion of 1 to 5 vertebral fractures. The mean baseline BMD of the lumbar spine (L1 to L4) was similar in the 2 treatment groups (0.8579 g/cm^2 in the Miacalcin 200 IU NS group and 0.8306 g/cm^2 in the placebo group. Treatment with Miacalcin 200 IU NS had no effect on bone quality as evaluated by histomorphometry of an iliac crest bone biopsy. Treatment with Miacalcin 200 IU NS had little or no effect on most other parameters of bone quality assessed in the bone biopsies. The exploratory MRI-based *in vivo* histomorphometric measurements of bone quality in the wrist found statistically significant improvements in bone quality (relative to baseline) at the Month 12 and Month 24 assessments for patients treated with Miacalcin 200 IU NS compared to patients treated with placebo. Biochemical markers of bone turnover, N-telopeptide (NTX) and C-telopeptide (CTX), indicated that mean bone resorption was lower in patients treated with Miacalcin 200 IU NS than in patients treated with placebo. Safety information from the Quest study contributed to the meta-analysis presented in Section 7.2.3.

7.1.5 Investigational oral calcitonin for PMO

Efficacy data are available from two investigational oral calcitonin programs and are presented in this section. One development program (Novartis/Nordic Biosciences) also included investigations in the indication of osteoarthritis (C2301 and C2302). These osteoarthritis trials did not achieve their primary treatment goals and are included in the safety section of this document.

7.1.5.1 Phase 3 Study (A2303) Novartis / Nordic Biosciences

Study design

This was a randomized, double-blind, placebo-controlled, multi-center, Phase III study in postmenopausal women with osteoporosis, comparing treatment with 0.8 mg SMC021(oral salmon calcitonin formulation) once daily to treatment with placebo over 36 months, designed to assess reduction of the occurrence of new vertebral fractures.

At the baseline visit, patients whose eligibility was confirmed were randomized 1:1 to 0.8 mg SMC021 plus calcium and vitamin D or placebo plus calcium and vitamin D daily. Each patient was to participate in the treatment period for 36 months. The screening period was to occur within 84 days before randomization.

Population

The study population was to consist of approximately 4500 postmenopausal ambulatory women between 55 and 85 years of age with osteoporosis. The patients were not to be receiving medication that affected bone metabolism. They were to be free from any underlying condition, other than osteoporosis, that could result in abnormal bone metabolism.

Key Inclusion criteria

Patients eligible for inclusion in this study had to fulfill the following criteria:

- Postmenopausal, ambulatory women, between 55 and 85 years old.
- Either
  - A BMD T-score $\leq$ -2.5 at one or more of the following regions: lumber spine, femoral neck or total hip, and no more than 2 prevalent mild or moderate vertebral fractures according to the definition of Genant et al 1993 (No severe fracture was permitted). Inclusion was defined by absolute BMD values (g/cm^2).

or:

  - A BMD T-score $\leq$ -1.5 at one or more of the following regions: lumber spine, femoral neck or total hip, together with 1 or 2 osteoporotic fractures located at the spine according to the definition of Genant et al 1993. Inclusion was defined by absolute BMD values (g/cm^2).

Key Exclusion criteria

Patients who met any of the following criteria were to be excluded from the study:

- A BMD T-score < -3.5 (based on absolute values) at one or more of the measured sites
- More than 2 prevalent vertebral fractures
- For patients with a BMD T-score ≤ -2.5 at one or more measured sites if they have a severe vertebral fracture.
- Evidence of any clinical osteoporotic fracture and/or a history of a clinical osteoporotic fracture (excluding wrist fractures).
- A BMD T-score > -1.5 in all of the following regions: lumber spine, femoral neck or total hip.
- Malignancy (except basal cell carcinoma, cervical or breast ductal carcinoma in situ).

Patient characteristics

Treatment groups were well matched for baseline demographics and disease characteristics. The mean age of the population was 67 years, and approximately two-thirds of the population was Caucasian. Mean body weight (64 kg) and BMI (26 kg/m2) were almost identical for both treatment groups.

Disease characteristics were well matched between treatment groups (Table 7-15).

Table 7-15 Disease characteristics by treatment group (ITT analysis set) in Study A2303

Background variable	SMC021 N=2334	Placebo N=2331	Total N=4665
Main inclusion criterion			
Inclusion criterion 2	1800 (77.1)	1834 (78.7)	3634 (77.9)
Inclusion criterion 3	533 (22.8)	496 (21.3)	1029 (22.1)
Missing	1 (<0.1)	1 (<0.1)	2 (<0.1)
T-score at femoral neck - n (%)			
≤ -2.5	448 (19.2)	489 (21.0)	937 (20.1)
> -2.5 - ≤ -1.5	1153 (49.4)	1156 (49.6)	2309 (49.5)
> - 1.5	732 (31.4)	683 (29.3)	1415 (30.3)
Missing	1 (<0.1)	3 (0.1)	4 (0.1)
T-score at total hip - n (%)			
≤ -2.5	288 (12.3)	343 (14.7)	631 (13.5)
> -2.5 - ≤ -1.5	1065 (45.6)	1024 (43.9)	2089 (44.8)
> - 1.5	980 (42.0)	961 (41.2)	1941 (41.6)
Missing	1 (<0.1)	3 (0.1)	4 (0.1)
T-score at lumbar spine - n (%)			
≤ -2.5	1530 (65.6)	1545 (66.3)	3075 (65.9)
> -2.5 - ≤ -1.5	624 (26.7)	593 (25.4)	1217 (26.1)
> - 1.5	180 (7.7)	191 (8.2)	371 (8.0)

Missing	0	2 (0.1)	2 (<0.1)
Number of vertebral fractures at baseline - n (%)			
0	1582 (67.8)	1587 (68.1)	3169 (67.9)
1	377 (16.2)	397 (17.0)	774 (16.6)
≥2	105 (4.5)	141 (6.0)	246 (5.3)
Missing	270 (11.6)	206 (8.8)	476 (10.2)

The proportion of patients with no prevalent vertebral fractures at baseline was 67.9%; while 16.6% had one fracture and 5.3% of patients presented initially with more than one fracture. [Of note: In the PROOF study (after central adjudication of baseline spine radiographs,) only 269 (21.4%) had no vertebral fractures, 910 (72.5%) out of 1,255 women had one to five prevalent vertebral fractures, and 65 (5.2%) even had more than 5 fractures]. 65.9% of the study population had an osteoporotic T-score at the lumbar spine of ≤ -2.5, 20.1% had an osteoporotic T-score at the femoral neck and 13.5% had an osteoporotic T-score at the total hip (a combination of these mentioned risks allowed inclusion into the study).

Primary efficacy results

The primary study objective was to demonstrate the superiority of SMC021 relative to placebo in the proportion of study subjects with new vertebral fractures. As shown in Table 7-16, there was no significant difference in the proportion of patients with new vertebral fractures between treatment groups.

Table 7-16 Incidence of new vertebral fractures by treatment group (MITT analysis set) in study A2303

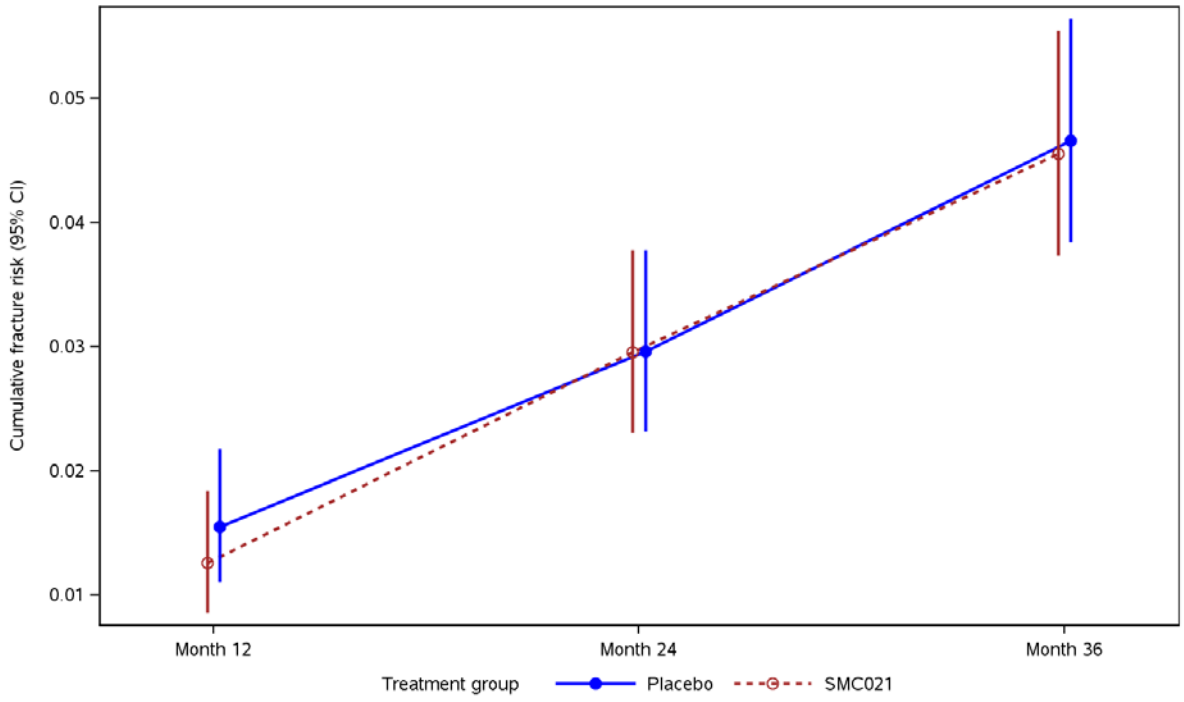
SMC021 N=2064 n (%)	Placebo N=2125 n (%)	Relative risk (95% CI)	Odds ratio (95% CI)	p-value (Chi^2)
94 (4.55)	99 (4.66)	0.98 (0.742, 1.288)	0.99 (0.740, 1.321)	0.9408

Odds ratio and p-value are from logistic regression controlling for treatment group and age at baseline, LOCF, including Month36 off-drug assessments (primary analysis for FDA)

MITT – Modified intention to treat

Kaplan-Meier estimates of the cumulative risk for a first new vertebral fracture are displayed in Figure 7-4. The cumulative risk was almost identical for the two treatment groups over the 36 month treatment period.

Figure 7-4 Cumulative risk for first new vertebral fracture by year and treatment (MITT analysis set) in Study A2303



Groups are shifted to enhance readability
Cumulative risk and 95% confidence intervals were calculated using Kaplan-Meier estimates for the discrete time points

Of the patients who experienced new vertebral fractures, the majority experienced one vertebral fracture (83, 4.0% SMC021 and 82, 3.9% Placebo patients).

Subgroup analysis of the proportion patients with at least one vertebral fracture did not show significant differences between treatment groups for subgroups related to number of prevalent fractures, type of inclusion criteria, geographical region, race/ethnicity, or T-scores at the femoral neck, total hip or lumbar spine.

Secondary efficacy results

Secondary efficacy parameters were to be tested according to a pre-defined hierarchy if a significant result had been obtained for the primary efficacy parameter. As this was not the case, any p-values for secondary efficacy analyses must be considered descriptive and, even if small, cannot result in a claim of a statistically significant difference.

A comparison between treatment groups for the incidence of new non-vertebral fractures is shown in Table 7-17. The difference between treatment groups was not significant. There was also no evidence of differences between treatments in the incidence of non-vertebral fractures by the location of fracture.

Table 7-17 Incidence of new non-vertebral fractures by treatment group (ITT analysis set) in Study A2303

SMC021 N=2334 n (%)	Placebo N=2331 n (%)	Relative risk (95% CI)	Hazard ratio (95% CI)	p-value (Chi^2)
75 (3.21)	82 (3.52)	0.91 (0.671, 1.243)	0.966 (0.7050, 1.3210)	0.8275

CI = confidence interval (profile likelihood)
Hazard ratio and p-value are from Cox regression controlling for treatment group and age at baseline

A comparison of the incidence new clinical fractures did not show a significant difference between treatment groups (Table 7-18).

Table 7-18 Incidence of new clinical fractures by treatment group (ITT analysis set) in Study A2303

SMC021 N=2334 n (%)	Placebo N=2331 n (%)	Relative risk (95% CI)	Hazard ratio (95% CI)	p-value (Chi^2)
111 (4.76)	119 (5.11)	0.93 (0.724, 1.199)	0.978 (0.7542, 1.2664)	0.8643

CI = confidence interval (profile likelihood)
Hazard ratio and p-value from Cox regression controlling for treatment group and age at baseline

While there was no significant difference between treatment groups for the incidence of new clinical fractures as a whole, fewer fractures of the hip occurred for the SMC021 group: an incidence rate of 0.1% per patient-year exposure compared to 0.7% per patient-year exposure for the placebo group. There was a statistically significant 65.8% reduction in the incidence of hip fractures (0.1% vs. 0.7%) for the SMC group vs. placebo (Cox model Hazard ratio 0.342; 95% CI: 0.1119, 0.8751; P=0.0366).

Although not statistically significant as part of the hierarchical testing procedure, as an individual measure of efficacy the increase in lumbar spine BMD for the SMC021 group was statistically significant compared to the placebo group at all timepoints (Table 7-19).

Table 7-19 Lumbar spine BMD percentage change from baseline by treatment and visit (ITT analysis set) in A2303

Visit	Treatment	n	LSM (SE)	Treatment difference (95% CI)	p-value
Month 12	SMC021	1839	1.241 (0.1000)	1.191 (0.9582, 1.4238)	<.0001
	Placebo	1981	0.050 (0.0962)		
Month 24	SMC021	1690	1.172 (0.1114)	1.105 (0.8354, 1.3744)	<.0001
	Placebo	1824	0.067 (0.1079)		
Month 36	SMC021	1860	1.018 (0.1180)	0.834 (0.5432, 1.1254)	<.0001
	Placebo	1941	0.183 (0.1154)		

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 SMC021 minus placebo.
LSM for each treatment group, treatment difference and the p-value are obtained from a repeated measures ANCOVA on the percentage change from baseline with treatment, age, baseline value, type of assessment (local or central) and visit as explanatory variables.

Total hip BMD also showed an increase for the SMC021 group compared to the Placebo group for both the ITT population and for the BMD sub-study population, although treatment comparisons were not statistically significantly different at the Month 36 treatment endpoint for the BMD substudy population (treatment difference of 0.227, 95% CI: 0.0103, 0.4432, p=0.04 for ITT population; treatment difference of 0.196, 95% CI: -0.3252, 0.7165, p=0.46 for BMD substudy population).

Femoral neck BMD showed a decrease for both treatment groups over 36 months of study, but the decrease was larger for the placebo group (Month 36 treatment difference of 0.396, 95% CI: 0.1308, 0.6613, p=0.0034 for ITT population; treatment difference of 0.424, 95% CI: -0.1409, 0.9884, p=0.1410 for BMD substudy population).

Conclusion – Oral calcitonin for PMO

The incidence of new vertebral fractures was numerically slightly lower with 94 events in the SMC021 treatment group and 99 events on placebo. Thus, the study failed to demonstrate a statistically significant treatment effect for its primary efficacy endpoint (p=0.94). This picture was also reflected in the secondary efficacy endpoints, where no statistically significant difference was seen between treatment groups for new non-vertebral fracture (p=0.83), or new clinical fracture (p=0.86). The incidence of new vertebral fractures was 4.7% in the placebo arm over three years in this trial (compared with 25.9% in the placebo arm of the PROOF study over 5 years).

There was a statistically significant treatment effect for lumbar spine BMD with a 0.83% increase in the SMC021 treatment group relative to placebo (p<0.001) at 3 years. Within new clinical fractures as a whole, fewer fractures of the hip occurred for the SMC021 group: an incidence rate of 0.1% per patient-year exposure compared to 0.7% per patient-year exposure for the placebo group.

Published phase 2 and 3 results of an investigational oral calcitonin (Tarsa Therapeutics)

The Phase 2 study (TAR01-201, Binkley et al 2012b) of an oral preparation of recombinant salmon calcitonin (oral rSCT), enrolled women (144 subjects in 7 US sites) at least 5 years postmenopausal with T-scores ≤ -1.5 and >-2.5 at the LS or total hip, femoral neck or trochanter but not ≤ -2.5 at any site, with a 10-year FRAX risk of at least 9.3% (major) or 1.2% (hip).

After a 2 week placebo run-in period participants were randomized 2:1 to receive 200 µg/day of oral rSCT or identical appearing placebo for 1 year. Vitamin D and calcium citrate (1000IU/600mg daily) were provided. Replicate DXA scans were obtained at baseline, weeks 28 and 54, and read centrally. Study medication was given h.s., until a protocol amendment changed the time of administration to dinner time.

RESULTS: 129 subjects were randomized, 114 were in the mITT population. Their mean age was 67.2yr and mean LS T-score -1.29. The mean change in LS BMD at the last visit in the treatment arm was +1.03 (delta to placebo 1.14% [95% CI: 0.14, 2.15], p=0.026). The placebo-subtracted difference in fasting CTx-1 at the exit visit compared to baseline was -20.2 % (oral rSCT vs placebo, p =0.034).

The Phase 3 ORACAL study (Binkley et al 2012a) was conducted in 565 postmenopausal women treated with orSCT, nSCT or placebo for 48 weeks. Mean age was about 66 years. Mean LS BMD T-scores were -2.80 to -2.92 among the three treatment groups. All participants received calcium and vitamin D and were randomized (4:3:2) to receive orSCT (0.2 mg per day) tablet plus placebo nasal spray, nSCT (200IU per day) plus placebo tablet or placebo (placebo tablet plus placebo nasal spray).

All women received calcium (≥1000 mg/d) and vitamin D (800 IU/d). Women randomized to oral rSCT had a mean ±SD percent increase from baseline in lumbar spine bone mineral density (BMD) (1.5%±3.2%) that was greater than those randomized to nSCT (0.78%±2.9%) or placebo (0.5%±3.2%). Lumbar spine BMD change in those receiving nasal calcitonin did not differ from placebo. Oral rSCT treatment also resulted in greater improvements in trochanteric and total proximal femur BMD than nSCT. Reductions in bone resorption markers with oral rSCT were greater than those observed in nSCT or placebo recipients. Approximately 80% of subjects in each treatment group experienced an adverse event, the majority of which were mild or moderate in intensity. Gastrointestinal system adverse events were reported by nearly one-half of women in all treatment groups and were the principal reason for premature withdrawals. Less than 10% of women experienced a serious adverse event and no deaths occurred.

The authors concluded that overall, oral rSCT was superior to nSCT and placebo for increasing BMD and reducing bone turnover. Oral rSCT was safe and as well tolerated as nSCT or placebo.

7.1.6 Efficacy observed in other approved therapies in PMO

Prior to 1994 only the demonstration of improvement in BMD was required to receive an indication for the treatment of PMO. It was not required that osteoporosis treatments demonstrate anti-fracture efficacy in order for regulatory approval to be granted. The requirement for anti-fracture efficacy data was in part due to unfavorable long-term fracture outcomes from studies of etidronate and fluoride. These agents are now understood to adversely affect mineralization of bone.

A tabular summary of the anti-fracture efficacy observed for therapies approved for the treatment of PMO is presented in Table 7-20. An overview of the key results for each therapy follows.

Alendronate

The approval of alendronate for the treatment of post-menopausal osteoporosis was obtained based on two placebo-controlled 3-year studies conducted in 881 post-menopausal women with BMD T-scores of femoral neck < -2.5 that evaluated 5, 10 and 20 mg/day vs. placebo. These studies are summarized by Lieberman (1995). After two years when additional data became available, all patients who were on 20 mg/day were switched blindly to 5 mg/day of alendronate. After 3 years, alendronate demonstrated a 48% reduction in the risk of vertebral fractures across all pooled doses relative to placebo.

Subsequently, the Fracture Intervention Trial (FIT) was conducted in two studies one in patients with prevalent vertebral fractures (FIT-I, Black et al 1996) and one in patients with Femoral neck BMD < 0.68 g/cm^2 (FIT-II, Cummings et al 1998).

FIT-I was a three-year placebo-controlled study in 2027 post-menopausal women that evaluated 5 and 10 mg/day of alendronate vs. placebo after 2 years, the 5 mg group was blinded switched to 10 mg/day. Alendronate-treated patients showed a statistically significant 47% reduction in the risk of vertebral fractures, a 20% reduction in the risk of non-vertebral fractures (not significant) and a statistically significant 51% reduction in the risk of hip fractures.

FIT-II was a 4-year placebo-controlled study in 4432 post-menopausal women that evaluated alendronate 5 mg/day over the first two years followed by 10 mg/day versus placebo. Over 4 years, alendronate demonstrated a statistically significant 44% reduction in the risk of vertebral fracture and 12% (not significant) and 21% (not significant) reductions in the risk of non-vertebral and hip fractures respectively.

Risedronate

The approval of risedronate for the treatment of PMO was based on data from two three-year placebo-controlled studies. The first study was conducted in 2458 post-menopausal women and evaluated 2.5 and 5 mg/day of risedronate relative to placebo with at least one prevalent fracture from North America (VERT-NA, Harris et al 1999). The 2.5 mg/day group was discontinued and thus the efficacy results reported are from the 5 mg/day dose only.

In VERT-MN (Reginster et al 2000), risedronate 5 mg/day demonstrated a statistically significant 41% reduction in the risk of vertebral fractures relative to placebo and a statistically significant 40% reduction in the risk of non-vertebral fractures relative to placebo. This second study was conducted outside North America in 1226 post-menopausal women with at least two prevalent vertebral fracture and evaluated 2.5 and 5 mg/day of risedronate relative to placebo. The 2.5 mg/day group was discontinued after two years and thus the efficacy results reported are from the 5 mg/day dose only. In VERT-MN, risedronate 5 mg/day demonstrated a statistically significant 49% reduction in the risk of vertebral fractures and a 33% (not significant) reduction in the risk of non-vertebral fractures

Raloxifene

The approval for the treatment of post-menopausal osteoporosis for raloxifene was obtained based on the demonstration of efficacy over 36 months in the MORE trial (Ettinger et al 1999) that was conducted in 7705 post-menopausal women that were stratified into two groups. Group 1 consisted of women without prevalent vertebral fractures who had a BMD T-score less than -2.5 at the femoral neck or for the lumbar spine. Group 2 consisted of women with lumbar spine of femoral BMD T-scores less than -2.5 and one or more severe vertebral fracture or 2 or more moderate vertebral fractures regardless of BMD. The study evaluated the efficacy of 60 and 120 mg/day of raloxifene relative to placebo.

In Group 1, 50% and 40% statistically significant reductions in risk of vertebral fractures relative to placebo over 36 months were observed for the 60 mg/day and 120/day dose groups respectively. In Group 2, 30% and 50% statistically significant reductions in risk of vertebral fractures relative to placebo over 36 months were observed for the 60 mg/day and 120/day dose groups respectively. Based on analysis pooled across both Group 1 and Group for all doses, the reduction in non-vertebral fractures was 10% relative to placebo.

Ibandronate

The initial approval of ibandronate in the treatment of post-menopausal osteoporosis was based on the daily and intermittent oral formulations. The approval of intravenous formulation and the monthly oral formulation was obtained based on bridging arguments and demonstrating significant increases in BMD that were comparable to what has been observed by the daily oral formulation.

The BONE study (Chesnut et al 2004) was a three-year placebo-controlled study in post-menopausal women that evaluated 2.5 mg/day and 20 mg every other day for 12 doses every 3 months in post-menopausal with 1-4 prevalent vertebral fractures and femoral neck BMD T-scores between -2.0 and -5.0. Statistically significant reductions in the risk of vertebral fractures of 50% and 62% relative to placebo were observed with the daily and intermittent dosing regimens respectively. Reductions in the risk of non-vertebral and hip fractures are not reported in the Chesnut publication.

Teriparatide

The approval of teriparatide for the treatment of post-menopausal osteoporosis was obtained based on a 24-month placebo-controlled study conducted in 1637 post-menopausal women that evaluated 20 and 40 µg of teriparatide vs. placebo in post-menopausal women with at least one moderate or two mild prevalent vertebral fractures, if less than 2 moderate vertebral fractures were present, a BMD T-score < -1.0 was required at least one site. Due to the non-clinical findings related to osteosarcoma, not all subjects were followed up for the full 24 month treatment period. The 20 and 40 µg dose groups showed statistically significant 65% and 69% reductions in the risk of vertebral fractures relative to placebo over a median duration of follow-up of 20 months. The reduction in non-vertebral fractures was also statistically significant with 53% and 54% reductions demonstrated for the 20 and 40 µg dose groups respectively

Zoledronic acid

The approval of zoledronic acid in the treatment of post-menopausal osteoporosis was demonstrated through data from two large placebo-controlled studies that evaluated 9863 patients. The first study, HORIZON-PFT, (Black et al 2007), was a 3-year, placebo-controlled study in 7736 postmenopausal women that evaluated the safety and efficacy of zoledronic acid 5 mg administered intravenously once every 12 months in patients who either had a femoral neck BMD T-score < -2.5 or a BMD T-score < -1.5 with at least 2 mild or 1 moderate vertebral fracture. The second study, HORIZON-RFT (Lyles et al 2007), was a placebo-controlled event-driven study that evaluated the safety and efficacy of 5 mg administered intravenously once every 12 months in 2127 men and women at least 50 years of age within 90 days of repair of a low trauma hip fracture.

In HORIZON-PFT, zoledronic acid demonstrated a 70% statistically significant reduction in the risk of vertebral fractures, a 25% reduction in the risk of non-vertebral fractures, and a 41% reduction in the risk of hip fractures. In HORIZON-RFT, zoledronic acid demonstrated a statistically 35% reduction in the risk of all clinical fractures, morphometric vertebral fractures were not evaluated in the study; however, a 46% statistically significant reduction in the risk of clinical vertebral fractures was observed as well as 27% statistically significant

reduction in the risk of non-vertebral fractures relative to placebo and a 30% (not significant) reduction in the risk of hip fractures. It was also noteworthy that this study demonstrated a 28% statistically significant reduction in the risk of death relative to placebo.

Denosumab

The approval of denosumab in the treatment of post-menopausal was demonstrated through a three-year placebo-controlled study conducted in 7868 post-menopausal women with BMD T-score between -2.5 and -4.0 at the total hip or lumbar spine that evaluated denosumab 60 mg every six months versus placebo (Cummings 2009). The study showed a 68% statistically significant reduction in the risk of vertebral fractures relative to placebo, a 20% statistically significant reduction in the risk of non-vertebral fractures relative to placebo and a 40% statistically significant reduction in the risk of hip fractures relative to placebo.

Number needed to treat

The following table shows the number of patients who need to be treated to avoid at least one fracture (vertebral or non-vertebral or hip fracture).

Table 7-20 Summary of anti-fracture efficacy for PMO therapies approved in the US

Study	Treatment/Treatment comparison	Patient population	Vertebral fractures n/m (%) RR (95%CI) NNT	Non-vertebral fractures n/m HR (95% CI) NNT	Hip fractures n/m HR (95% CI) NNT
Lieberman (1995)	Alendronate	BMD T-score < -2.5	17/526 (3.3)	N/A	N/A
	Placebo		22/355 (6.2)	N/A	N/A
	Alendronate vs. placebo		0.52 (0.28, 0.95) 35	N/A	N/A
Black (1996)	Alendronate	BMD T-score < -2 and at least one prevalent vertebral fracture	78/981 (8.0)	122/1022 (11.9)	11/1022 (1.1)
	Placebo		145/965 (15.0)	148/1005 (14.7)	22/1005 (2.2)
	Alendronate vs. Placebo		0.53 (0.41, 0.68) 15	0.80 (0.63, 1.01) 36	0.49 (0.23, 0.99) 91
Cummings (1998)	Alendronate	Femoral neck BMD < 0.68 g/cm2 without vertebral fractures	43/2057 (2.1)	261/2214 (11.8)	19/2214 (0.9)
	Placebo		78/2077 (3.8)	294/2218 (13.3)	24/2218 (1.1)
	Alendronate vs. Placebo		0.56 (0.39, 0.8) 59	0.88 (0.74, 1.04) 67	0.79 (0.43, 1.44) 500
Ettinger (1999)	Placebo	Femoral neck or Lumbar Spine BMD T-score less than -2.5 (Group 1)	68/1522 (4.5)		
	Raloxifene 60 mg/day		35/1490 (2.3)	N/A	N/A
	Raloxifene 120 mg/day		42/1512 (2.8)	N/A	N/A
	Raloxifene 60 mg vs. Placebo		0.5 (0.4, 0.8) **46**	N/A	N/A

Study	Treatment/Treatment comparison	Patient population	Vertebral fractures n/m (%) RR (95%CI) NNT	Non-vertebral fractures n/m HR (95% CI) NNT	Hip fractures n/m HR (95% CI) NNT
	Raloxifene 120 mg vs. Placebo		0.6 (0.4, 0.9) **59**	N/A	N/A
Ettinger (1999)	Placebo	Lumbar spine or Femoral neck BMD T-score < -2.5 and 1 moderate or severe vert Fx, 2 or more mild vert Fxs or 2 or more moderate vert Fx regardless of BMD	63/770 (21.2)		
	Raloxifene 60 mg/day		148/2259 (14.7)	N/A	N/A
	Raloxifene 120 mg/day		82/765 (10.7)	N/A	N/A
	Raloxifene 60 mg vs. Placebo		0.7 (0.6, 0.9) **16**	N/A	N/A
	Raloxifene 120 mg vs. Placebo		0.5 (0.4, 0.7) **10**	N/A	N/A
Harris (1999)	Placebo	At least 2 morphometric vertebral fractures or 1 morphometric vertebral fracture and lumbar spine BMD T-score < -2.0	93/678 (16.3)	52/815 (8.4)	N/A
	Risedronate		61/696 (11.3)	33/812 (5.2)	N/A
	Risedronate vs. Placebo		0.59 (0.43, 0.82) **20**	0.60 (0.39, 0.94) **32**	N/A
Reginster (2000)	Placebo	At least 2 vertebral fractures	89/346 (29.0)	51/406 (16.0)	N/A
	Risedronate		53/344 (18.1)	36/406 (10.9)	N/A
	Risedronate vs. Placebo		0.51 (0.36, 0.73) **10**	0.67 (0.44, 1.04) **20**	N/A
Neer (2001)	Placebo	At least 1 moderate or two mild morphometric vertebral	64/448 (14)	30/544 (6)	N/A

Study	Treatment/Treatment comparison	Patient population	Vertebral fractures n/m (%) RR (95%CI) NNT	Non-vertebral fractures n/m HR (95% CI) NNT	Hip fractures n/m HR (95% CI) NNT
		fractures; if less than 2 moderate vertebral fractures, BMD T-score < -1.0 required at least one site			
	PTH 20 µg		22/444 (5)	14/541 (3)	N/A
	PTH 40 µg		19/434 (4)	14/552 (3)	N/A
	PTH 20 µg vs. placebo		0.35 (0.22, 0.55) **12**	0.47 (0.25, 0.88) **34**	N/A
	PTH 40 µg vs. placebo		0.31 (0.19, 0.50) **10**	0.46 (0.25, 0.86) **34**	N/A
Chesnut (2004)	Placebo	1-4 prevalent vertebral fractures and femoral neck BMD T-scores between -2.0 and -5.0	(9.56)	N/A	N/A
	Ibandronate 2.5 mg/day		(4.68)	N/A	N/A
	Ibandronate 20 mg every other day for 12 doses every 3 months		(4.90)		
	Ibandronate daily vs. placebo		0.38 (0.25, 0.59) **21**	N/A	N/A
	Ibandronate intermittent vs. placebo		0.50 (0.34, 0.74) **22**	N/A	N/A
Black (2007)	Placebo	Femoral neck BMD T-score < -2.5 or 2 mild or 1 moderate vertebral fracture and a Femoral Neck BMD T-score less than -1.5	310/2853 (10.9)	388/3875 (10.7)	88/3875 (2.5)

Study	Treatment/Treatment comparison	Patient population	Vertebral fractures n/m (%) RR (95%CI) NNT	Non-vertebral fractures n/m HR (95% CI) NNT	Hip fractures n/m HR (95% CI) NNT
	Zoledronic acid 5 mg		92/2822 (3.3)	292/3861 (8.0)	52/3861 (1.4)
	Zoledronic acid vs. placebo		0.30 (0.24, 0.38) **14**	0.75 (0.64, 0.87) **38**	0.59 (0.42, 0.83) **91**
Lyles (2007)	Placebo	A non-traumatic hip fracture in the last 3 months	N/A	107/1062 (10.7)	33/1062 (3.5)
	Zoledronic acid 5 mg		N/A	79/1065 (7.6)	23/1065 (2.0)
	Zoledronic acid vs. placebo			0.73 (0.55, 0.98) **33**	0.70 (0.41, 1.19) **67**
Cummings (2009)	Placebo	Lumbar spine or total hip BMD T-score < -2.5	264/3691 (7.2)	293/3906 (8.0)	43/3906 (1.2)
	Denosumab		86/3702 (2.3)	238/3902 (6.5)	26/3902 (0.7)
	Denosumab vs. placebo		0.32 (0.26, 0.41) **21**	0.80 (0.67, 0.95) **67**	0.60 (0.37, 0.97) **200**

7.1.7 Summary of clinical efficacy for PMO

There is considerable evidence from studies conducted with injectable or nasal SCT that support the efficacy of calcitonin in PMO as shown by effects on bone biomarkers, increases in BMD and a reduction in vertebral fractures. The onset of effect on bone biomarkers in clinical pharmacology studies is evident within hours and in larger clinical studies in women with established PMO there are consistent positive effects on BMD and bone biomarkers at the first evaluation point (usually one year).

Sponsor studies as well as those available in the peer-reviewed literature provide substantial evidence of effectiveness of calcitonin in reducing the incidence of vertebral and non-vertebral fractures, in PMO. These findings are consistent with surrogate endpoint findings supportive of a benefit, such as significant increases in bone density of the lumbar spine and forearm. The 32.6% reduction in vertebral fracture with the approved 200 IU dose corresponds to a number needed to treat of 13 to prevent a vertebral fracture. In context, this is consistent with the other approved therapies for the treatment of PMO who have an anti-fracture efficacy claim in the prescribing information where the NNT values range from 10 for teriparatide to 22 for ibandronate. Even though the result for non-vertebral fractures from PROOF was not statistically significant (p=0.136) the number needed to treat to prevent a fracture was 36 which similar to the number needed to treat from zoledronic acid in Black et al (2007), NNT=38, and with alendronate in FIT-1 (Black et al 1996) NNT=36.

The current view of osteoporosis therapy is guided by the mandate to provide evidence of a clinically relevant outcome (i.e. prevention of fragility fractures) which is typically demonstrated in large, long-term placebo-controlled trials.

For a therapy that has demonstrated this relevant clinical outcome and with evidence to support rapid onset of effects on the skeleton, one should consider whether providing short-term treatment or no treatment will be of greater benefit for patients.

7.2 Risk – safety assessment

The risk evaluation includes an overview of safety from the clinical program (Section 7.2.1), non-clinical program (Section 7.2.2), meta-analysis results from placebo-controlled studies (Section 7.2.3), post-marketing experience (Section 7.2.4), background epidemiology on the incidence of malignancies in the PMO population (Section 7.2.5) and literature review (Section 7.2.6).

7.2.1 Clinical safety overview

Miacalcin® has been used in more than 10 million patients for more than 2 decades. When used appropriately, it is associated with minimal adverse events.

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to Miacalcin® (calcitonin-salmon) Nasal Spray and to placebo nasal spray and reported in greater than 3% of Miacalcin® Nasal Spray-treated patients are rhinitis and other nasal symptoms, which overall did not significantly differ from placebo.

Other adverse events were reported in fewer than 3% of patients during chronic therapy with Miacalcin® Nasal Spray (Appendix 1).

Common adverse reactions associated with the use of calcitonin-salmon occurred less frequently in patients treated with Miacalcin® Nasal Spray than in those patients treated with injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients treated with the nasal spray (and 1.5% for placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the nasal spray, occurs in 2%-5% of patients treated with injectable calcitonin-salmon.

The collective marketing experience with Miacalcin® Nasal Spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

For reference, the prescribing information for Miacalcin NS and Miacalcin injectable are included in Appendix 2 and Appendix 1, respectively.

7.2.2 Preclinical data with respect to malignancy risk

A comprehensive preclinical safety evaluation on mutagenicity and carcinogenicity of calcitonin under GLP standards was conducted. Key results can be summarized below:

There were no genotoxicity findings in all the *in vitro* and *in vivo* tests conducted with Miacalcin, including a bacterial gene mutation test using *Salmonella typhimurium* and *Escherichia coli*, a chromosomal aberration test, a gene (HGPRT) mutation assay in V79 cells, and a mouse micronucleus test.

Carcinogenic potential of SCT was fully evaluated in two 104-week carcinogenicity studies in Sprague-Dawley rats and CD-1 mice by once daily subcutaneous injections. The full reports of the two studies were previously submitted to FDA. The results from these studies show that SCT was not carcinogenic in mice, but caused an increased incidence of pituitary adenoma in male rats.

Pituitary adenomas were also noted in 52-week chronic toxicity studies in the rat. The follow-up mechanistic studies showed that the result of incidence of pituitary adenoma is likely a rat specific observation and are considered to have no human relevance (Gunson et al 1995; Jameson et al 1992).

There was no evidence of increase of incidences of any other neoplasm in the rat. There was no evidence of calcitonin-induced prostate cell neoplasia or hyperplasia in the carcinogenicity studies and other chronic toxicity studies.

Study design of the two carcinogenicity studies is summarized below in Table 7-21:

Table 7-21 Study design of the carcinogenicity studies with salmon calcitonin

Species (strain)	Study duration (weeks)	Route of administration	Number of animals per group	Doses (IU/kg/day)
Rat (Sprague Dawley)	104	sc (saline)	50/sex	0;0.5;1.7;5.0;10
Mouse (CD-1)	104	sc (saline)	50/sex	0;80;250;800

The incidence of pituitary adenomas in the rat carcinogenicity study (CHV2315-119) is provided below (Table 7-22). The incidence of pituitary tumors in control groups (both placebo and vehicle control groups) was very high, ranging from 21-25 out of 50 in males and 40-41 out of 50 in females. It has been reported that pituitary adenoma is the most common spontaneous neoplasm noted in Sprague-Dawley rats with the incidence of 62.2% in male rats and 84.7% in female rats (McMartin et al 1992).

Table 7-22 Summary of pituitary adenoma data in the 2-year subcutaneous carcinogenicity study in Sprague Dawley rats (CHV2315-119)

Sex	Male						Female					
SCT Dose (IU/kg/day)	0 (V)	0 (P)	0.5	1.7	5.0	10	0 (V)	0 (P)	0.5	1.7	5.0	10
No of rats examined	50	50	50	50	50	50	50	50	50	49	49	50
No of rats with pituitary adenoma	25	21	29	37*	40*	43*	40	41	46	40	42	43
P=placebo; V=Vehicle; * Significant at $p \leq 0.01$												

The treatment-related increase in the incidence of pituitary adenomas was restricted to male rats, i.e. occurred only in a single sex and a single species in the carcinogenicity study in rats. The mouse carcinogenicity study using 80-fold higher dose (800 IU/kg/day) did not result in any increase in pituitary tumors. It is important to consider that rats, particularly Sprague-Dawley rats, have a very high rate of spontaneous pituitary adenomas. The mechanism is unknown but it may be related to endocrine imbalance (e.g. declining estrogen exposure) associated with aging (McKenzie and Boorman, 1990) (Gunson et al, 1995).The pituitary adenomas noted in the rat studies were characterized as nonfunctioning α-subunit secreting tumors, which can occur spontaneously in rats (Jameson er at 1992).Further follow-up investigative studies examined differences in number, affinity or specificity of salmon calcitonin binding sites on pituitaries between human and rat (Bloom SR 1995) (Bloom SR 1996).The studies confirmed the presence of ^{125}I-salmon calcitonin binding sites in membranes prepared from rat pituitaries, but have shown only minimal binding in human pituitaries. Thus the number of calcitonin receptors in the human pituitary relative to the rat pituitary is very low. In summary, the data from the investigative studies suggest that the effect of salmon calcitonin linked to the increased incidence in pituitary tumors is a phenomenon unique to rats, which is not considered to be of clinical relevance.

To further determine whether calcitonin could promote or cause tumor progression, all the tumor data, including those spontaneous tumors, in the two carcinogenicity studies were examined thoroughly. Table 7-23 and Table 7-24 provide selected spontaneous tumor incidences from the rat and mouse 104 week subcutaneous carcinogenicity studies

In these studies, a variety of spontaneous neoplasias were present in either treated animals or control animals. A review of tumor incidence data confirmed that there was no effect of calcitonin on the incidence, time of onset and pathological changes (malignancy, invasion, and metastasis) of these frequent spontaneous tumors or on less common tumors, indicating that calcitonin had no tumor-promoting effect. Also there were no evidences that calcitonin caused tumor progression (such as increased incidence from adenoma to carcinoma). Importantly, no shift toward more malignant tumors or evidence for more invasive growth of spontaneous tumors was observed.

Table 7-23 Incidence of selected non-treatment-related benign and malignant tumors in Rat 2-year Bioassay [study CHV 2315-119]

	Males						Females					
Dose (IU/kg/day)	0	0	0.5	1.7	5	10	0	0	0.5	1.7	5	10
No. of animals examined	50	50	50	50	50	50	50	50	50	50	50	50
C-cell adenoma	5	9	6	5	3	4	6	7	9	3	8	6
C-cell carcinoma	0	2	0	0	0	0	0	1	1	0	0	1
Follicular adenoma	0	0	1	1	1	0	1	1	0	0	1	0
Follicular carcinoma	2	0	1	2	0	0	0	0	1	0	0	1
Thyroid tumors as cause of death	0	1	0	1	0	0	0	0	0	0	0	1

Table 7-24 Incidence of the selected non-treatment-related benign and malignant tumors in 2-year carcinogenicity study in mice [study CHV 2315-120]

	Males					Females				
Dose (IU/kg/day)	0	0	80	250	800	0	0	80	250	800
No. of animals examined	50	50	50	50	50	50	50	50	49	50
Bronchio-alveolar adenoma	10	4	9	5	12	5	5	9	5	9
Bronchio-alveolar carcinoma	3	6	10	3	6	3	4	5	1	1
Lung tumors as cause of death	0	1	1	0	2	1	1	2	0	2

In summary, *in vivo* nonclinical safety data do not support the association of salmon calcitonin treatment with malignancies nor add any evidence for tumor progression under treatment.

7.2.2.1 Literature review with respect to in-vitro studies on malignancy risk

This section reviews and discusses several studies which have been published regarding the effect of calcitonin on human prostate cancer cell lines. Results from these studies have been used as basis to postulate a potential role of calcitonin in tumor promotion and/or progression.

The PC-3M cells predominantly used in these research papers are poorly differentiated and have a natural potential of invasiveness and metastasis. The results from the cell culture investigations, though interesting, are not considered appropriate for assessment of carcinogenicity or tumor promotion. Also, these results are based on *in vitro* experiments with cell culture or cancer cell lines transfected with the gene of human calcitonin, or nude mice implanted with genetically modified cell lines, none of which is considered a valid approach for carcinogenicity evaluation.

(Chien and Shah 2001) observed that the highly aggressive PC-3M human prostate cancer cell line co-expresses both calcitonin and calcitonin receptors. Serum-starved LNCaP cells (another human prostate cancer cell line) responded to calcitonin secreted by PC-3M cells with increased proliferation in co-culture studies. The increase in proliferation was abolished by the addition of rabbit anti-serum to calcitonin to below the level of background proliferation, indicating a second possible mechanism for inhibition, which was not addressed. In addition, these investigators observed that human prostate cancer cells express mRNA for calcitonin and calcitonin receptors. They did not look for protein expressed in the specimens.

(Sabbisetti et al 2005) investigated the role of calcitonin-mediated protein kinase A activation, with subsequent up-regulation of cAMP. They observed that calcitonin increased the invasive potential of PC-3M cells and increased synthesis of matrix metalloproteinases-2, -9 and urokinase-type plasminogen activator, which may theoretically be linked to prostate cancer cell invasion (Sabbisetti et al 2006; Thomas et al 2007a/b; Shah et al 2008). In most of these studies, calcitonin was not added exogenously. Rather, its overexpression was forced by transfection of a plasmid containing the human calcitonin gene into the PC-3M cells. In the experiments addressing MMP-2 and MMP-9 synthesis, exogenous calcitonin was added at 10 to 10,000 nM, which are at least 3 orders of magnitude higher than the peak concentrations observed after nasal administration of Miacalcin of <20.5 pg/ml (5.8pM).

Chien et al 2001 observed an increase in calcitonin and calcitonin receptor mRNA in preserved prostate cancer specimens; the increase roughly correlated with Gleason grade. This might be a consequence of prostate cancer rather than a contributing factor to oncogenesis. Alternatively it was proposed that aberrant expression of calcitonin and its receptor by prostate cancer cells may contribute to invasiveness and metastasis through alteration of adhesion molecule expression and activation of normally silent signaling pathways (Shah et al 2008). Knock-down of calcitonin in prostate cancer cells leads to cell cycle arrest and apoptosis (Thomas et al 2007b), which speaks more strongly for calcitonin's role in maintaining the malignant phenotype, rather than for its role in transforming cells to the malignant phenotype.

The limited literature on the role of calcitonin in prostate cancer suggests that calcitonin and its receptor are aberrantly expressed by some prostate cancer cells, but normal prostate cells do not express either calcitonin or its receptor. The literature does not show a causal relationship between calcitonin and prostate cancer. Experiments demonstrating that

calcitonin stimulated proliferation of prostate cancer cells were done in serum-starved cell lines at non-pharmacological concentrations and such experiments do not mimic the clinical situation.

In consideration of the literature reviewed above, the EU PhVWP conducted a review of calcitonin and prostate cancer in 2010 which concluded that evidence was considered insufficient to establish a causal association between calcitonin and prostate cancer progression. Confirmation of cell-proliferative properties of calcitonin in animal studies is absent (see Section 7.2.2). There is no *in vivo* data from animal experimental studies available in the literature which supports the hypothesis that SCT leads to promotion or progression of malignancies when administered at pharmacologically relevant or higher doses in humans. In the absence of such data, it is not possible to draw any conclusions regarding the relevance of the published in vitro cell-culture based data which were obtained at supra-pharmacological concentrations which are never encountered *in vivo* in patients. This conclusion is in line with the absence of any signal from the prostate-specific antigen profiles obtained in an oral SCT development program (See Section 7.2.3.1)

7.2.2.2 Clinical trial data with respect to malignancy risk

In this section, the various lines of evidence that should be considered in evaluation of the observed increased risk of malignancies with calcitonin are reviewed.

As mentioned previously, a recently completed meta-analysis of all Novartis-sponsored placebo-controlled calcitonin nasal spray and oral calcitonin studies, performed in response to an increased risk observed in the oSCT osteoarthritis program, demonstrated a small but statistically significant increase in the risk of malignancies. Importantly, the meta-analysis (which is reviewed later in Section 7.2.3) indicates that:

- There was no increase in the incidence of malignancies relative to placebo observed over the first 6 months of treatment.
- The incidence rate of malignancies per 6 month time period remains relatively constant across the different calcitonin nasal spray doses through 36 months. Importantly, the relative increase in malignancy risk observed reflects the decrease in the incidence rate of malignancies in placebo-treated patients after the first 6 months (from 0.8% to 0.2% per 6 month interval).
- The increased incidence of malignancies reflects differences in a variety of malignancy types with different cellular origins
- There is no evidence of higher incidence rate of malignancies with increasing dose.

There are clear limitations to the meta-analysis. The meta-analysis only contains data for incident cases without confirmation by adjudication, obtained from summary data for the nasal calcitonin trials. Further, biological plausibility has not been demonstrated, as no mechanism has been postulated and there is no evidence of effect on malignancy from in vivo non-clinical studies. Nonetheless in view of the meta-analysis results which if true suggest an increased risk of malignancy, labelling of the possibility of risk appears to be the prudent course of action at this time.

PROOF study data with respect to malignancy risk

The cumulative number of patients in the Study CT 320 (PROOF) with malignant neoplasms was 81 (8.6%) in the pooled SCT group and 16 (5.2%) in the placebo group (Fisher's Exact Test p-value=0.065). Non-melanoma skin cancers were reported more frequently in the SCT pooled group, i.e. in 35 (3.7%) patients as compared to 3 (1.0%) patients on placebo (Fisher's Exact Test p-value = 0.012). Malignant neoplasms excluding non-melanoma skin cancers were reported by 47 (5.0%) of patients in the SCT pooled group compared with 13 (4.2%) of patients in the placebo group (Fisher's Exact Test p-value = 0.65). Among malignant neoplasms, 16 patients in the SCT pooled group reported breast cancer (1.7%) compared with 3 patients (1.0%) in the placebo group (Fisher's Exact Test p-value = 0.59). Two epidemiological reviews were prepared to evaluate further the relationship between SCT administration and non-melanoma skin cancers (Appendix 3) or breast cancers (Appendix 4); these did not support an association of SCT with these events. The lack of evidence from post-marketing surveillance experience of an association of SCT with cancer also supports the premise that the observed differences may be a chance finding.

7.2.3 Meta-analysis of malignancies in clinical trials

The meta-analysis evaluating the risk of malignancies with calcitonin that was submitted to the European Medicines Agency (EMA) as part the most recent benefit-risk review procedure in Europe was also submitted to the FDA. This meta-analysis now includes 18 placebo-controlled Miacalcin NS studies plus three placebo-controlled oral calcitonin studies.

Objectives and studies included

The objective of the meta-analysis was to evaluate the incidence of malignancy events in SCT-treated patients and placebo (i.e. non-SCT)-treated patients. The source data was tabulated from a review of all available clinical study reports using Miacalcin® NS or Miacalcin® injectable formulation or an oral calcitonin investigational product (SMC021) for which Novartis is the IND holder, and captures the number of patients and the respective specific preferred term for each treatment group in each study. All randomized, controlled, double-blind clinical trials, independent of indication were searched.

Based on the search performed, the studies included in this meta-analysis were clinical trials using the nasal spray and oral formulation only, since no randomized, controlled, double-blind clinical trials were available for Miacalcin® injectable formulations. The reason for this is that injectable formulations of Miacalcin® have been approved for use in the treatment of osteoporosis in many countries world-wide for a number of years with the first registration being in 1974. In the clinical studies originally submitted in support of the Miacalcin® registration file, the primary efficacy parameter was determined by measuring total body calcium (TBC) using neutron activation analysis (NAA). Because this method was available at only a limited number of centers, and because it involves exposure of the patient to considerable amounts of radiation, it was not possible to perform large-scale multicenter studies. In addition, at that time double-blinding of injections i.e. using sham injections was usually not performed. For example, in the US submission file dated January 1985 for injectable SCT in osteoporosis, only one study was a double-blind study using either

calcitonin or placebo injections. This study was a single-center study involving 7 patients on drug and 6 control patients without reports of malignancies.

Because of the timeframe in which the Miacalcin® NS studies were conducted, patient-level data are not available for these Miacalcin® NS studies and thus the meta-analysis was constructed from a review of the clinical study reports and literature, by extracting the number of patients exposed to each treatment, and the number of patients who experienced malignancies in each treatment group. The analysis data used to perform the meta-analysis was constructed from the information tabulated in spreadsheet format.

Meta-analyses were performed on the 18 calcitonin nasal spray studies which met the criteria for inclusion in the meta-analysis (double-blind placebo-controlled). In addition, a meta-analysis was performed including the data from the three double-blind placebo-controlled studies conducted with oral calcitonin (2 studies in patients with osteoarthritis and one study in PMO) by Novartis/Nordic Biosciences. Studies without a placebo control were excluded from the analysis as well as the open-label extension period from any double-blind controlled studies to allow for the least biased comparison of the incidence rate observed with calcitonin relative to placebo in clinical trials where placebo-treated patients were followed for the same length of time as calcitonin-treated patients.

A summary of the studies that contributed to the two meta-analyses and the patient-years exposure that they provided are presented in Table 7-25.

Table 7-25 Studies included in the malignancies meta-analysis

Study	Phase	Intervention	Patients (N)	SCT/PBO	Inclusion age (years)	Mean[Range] SCT/PBO	Study duration	Total exposure (patient years) SCT/placebo	Publication
2402	4	nSCT (200 IU) or PBO, daily	296 F (PMO)	149/147	≥ 60	70.3[59–90]/ 69.8[60–93]	6 months	64.7/60.1	n.a.
CT211[a]	2	nSCT (200 or 400 IU) or PBO, daily	46 F (PMO)	31/15	< 75	64.4[52-75]/ 65.9[53-74]	2 years	57.1/25.4	n.a.
CT310[a]	3	nSCT (100, 200 or 400 IU) or PBO, daily	279 F (PMO)	211/68	≥40	52.6[41-69]/ 53.5[41-62]	2 years	354.2/113.8	n.a
CT311[a]	3	nSCT (100, 200 or 400 IU) or PBO, daily	168 F (PMO) 155 M (glucocorticoid-induced osteoporosis)	244/79	≥35	62.2[33-86]/ 63.4[29-84]	2 years	374.3/133.2	n.a
CT312[a]	3	nSCT (200 or 400 IU) or PBO, daily	158 F (PMO) 145 M (glucocorticoid-induced osteoporosis)	201/102	≥35	61.8[32-86]/ 63.0[37-86]	2 years	321.3/160.6	n.a.
CT320 [a] (PROOF)	3	nSCT (100, 200 or 400 IU) or PBO, with calcium (1,000 mg) and vitamin D (400 IU), daily	1,255 F (PMO)	944/311	n.a.	68.4[44-94]/ 68.2[48-91]	5 years	3260.4/1050.3	Chestnut et al (2000)
MIA16[a,b]	3	nSCT (400 IU) or PBO, daily	62 F (PMO)	32/30	>60	70.7[n.a.]/ 70.1[n.a.]	2 years	n.a.	Flicker et al (1997)
SMCO005[a]	3	nSCT (50, 100 or 200	40 F (PMO)	32/10	45–75	65.8[51-75]/ 68.0[56-75]	1 year	23.9/8.2	Thamsborg et al (1991)

		IU) or PBO, daily							
SMCO503	3	nSCT 100 IU or PBO, with calcium (500 mg), daily	52 F (healthy, early menopause)	26/26	45–56	52.3[40-59]/ 53.0[40-59][c]	2 years	48.8/46.4	Overgaard et al (1989)
SMCO504[a]	3	nSCT 100 IU or calcium (500 mg), daily	58 F (healthy, early menopause)	29/29	45–58	54.3[40-69]/ 53.8[40-59][c]	2 years	44.3/48.8	n.a.
SMCO506[a]	3	Calcium (500 mg) with or without nSCT 50 IU, 5 days/wk	288 F (bone loss in early menopause)	147/141	n.a.	51.6[30-69]/ 52.3[30-69][c]	3 years	373/372.3	Reginster et al (1994)
SMCO511[a]	3	nSCT 100 IU or calcium (1000 mg), daily	120 F (bone loss, peri-menopause)	60/60	>40	45.5[40-59]/ 45.0[30-59][c]	3 years	189.6/183.5	n.a.
SMCO514[a]	3	nSCT 200 IU or PBO, daily or 3 days/wk	117 F (PMO)	71/46	35–65	55.7[48-64]/ 56.1[48-64][c]	2 years	135.9/85.9	Ellerington et al (1996)
SMCO517	2	nSCT (50 or 200 IU) or calcium (500 mg), 5 days/wk	251 F (healthy, early menopause)	168/83	45–62	52.8[38-61]/ 53.0[37-60]	2 years	290.6/145.8	Reginster et al (1995)
SMCO520	3	nSCT (100 or 200 IU) or calcium (1000 mg), daily	97 F (healthy, early menopause	65/32	46–60	54.0[40-69]/ 54.0[40-69][c]	2 years	107/55	n.a.
SMCO522[a]	3	nSCT (50, 100 or 200 IU) or PBO, with calcium (500 mg), daily	208 F (PMO)	156/52	68–72	70.0[68-72]/ 69.8[68-72]	2 years	265.5/86.2	Overgaard et al (1992)

SMCO524[a]	3	nSCT (100, 200 or 400 IU) or PBO, with calcium (500 mg), daily	134 F (healthy, early menopause)	100/33	45–56	52.2[47-56]/ 51.8[47-56][c]	2 years	185/62	Overgaard et al (1994)
QUEST	4	nSCT (200 IU) or placebo daily	91 F (PMO)	46/45	n.a.	67.3 67.6	2 years	82.3/75.1	Chesnut et al (2005)
A2303[a]	3	oSCT (0.8 mg) or PBO, once daily, with calcium (800−1000 mg) and vitamin D (400−800 IU)	4,665 F (PMO)	2334/ 2331	55–85	66.5[55-86]/ 67.0[50-85]	3 years	5250.3/5660.7	n.a.
C2301[a]	3	oSCT (0.8 mg) or PBO, twice daily	1,169 (799 F and 370 M) (knee OA[e])	585/584	51–80	64.1[50-80]/ 63.9[50-79]	2 years	872.1/983.0	n.a.
C2302[a]	3	oSCT (0.8 mg) or PBO, twice daily	1,028 (625 F and 403 M) (knee OA[e])	520/508	51–80	63.9[51-80]/ 63.7[51-80]	2 years	769.9/818.8	n.a.

SCT, salmon calcitonin; PBO, placebo; nSCT, nasal salmon calcitonin; PMO, postmenopausal; n.a., not available; wk, week; F, female; M, male; oSCT, oral salmon calcitonin; OA, osteoarthritis

[a] In these studies, at least one patient with any malignancy was reported

[b] Nandrolone co-treatment arms in the study were not included in the analysis

[c] Age range obtained from age category from the Clinical Study Report

Statistical methods

At the study level, only those studies that had at least one malignancy in one of the treatment groups were included in the meta-analyses performed using the Peto method which is consistent with the approach used in the meta-analyses performed as part of systematic reviews done by the Cochrane collaboration.

To account for the small number of events in individual treatment groups at the study level, the likelihood of calcitonin increasing the occurrence of malignancies relative to placebo/control was evaluated by computing the Peto odds-ratio of each type of malignancy event for each study (calcitonin vs. placebo) as well as for all studies combined.

Two continuity correction approaches were applied to the Peto method as sensitivity analyses.

- Constant correction (CC): add 0.5 to event and no-event cells, i.e., increasing the sample size by 1 for each treatment arm
- Treatment arm correction (TA): add a value proportional to the reciprocal of the size of the opposite treatment group

In addition, the odds ratios were estimated using the Mantel-Haenszel method where continuity correction was applied to both treatment arms when there were zero events in any treatment arm.

With the Peto method without continuity correction as the main method referenced in this section, the following six additional sensitivity analyses were performed:

1. Peto_CC: Peto method with constant correction (zero events in both treatment arms)
2. Peto_TA: Peto method with treatment arm correction (zero events in both treatment arms)
3. MH_CC: Mantel-Haenszel method with constant correction (zero events in any treatment arm)
4. MH_TA: Mantel-Haenszel method with treatment arm correction (zero events in any treatment arm)
5. MH_TA, Random: Mantel-Haenszel with treatment arm correction for odds-ratio in each study, and DerSimonian-Laird random-effect for the pooled odds ratio
6. The Poisson exposure-adjusted exact method

Peto and Mantel-Haenszel methods were based on fixed-effect models. A random-effect (DerSimonian-Laird) model was also evaluated to estimate the odds ratios for completeness.

Analyses are presented for all malignancies as well as for basal cell carcinomas (BCC, the most common malignancy type) and non-BCC events.

Forest plots are provided to give a graphical display of the odds ratios by study and overall with the corresponding 95% confidence intervals. The graphical display allows for a visual interpretation of how each study influences the overall meta-analysis result.

Forest plots by study and overall are also provided by dose of calcitonin in the nasal sprays studies as well as for the patients who experienced basal cell carcinoma events which were the most common cancer type.

In order to evaluate the degree of heterogeneity across studies, Cochran's Q (Conover 1999), and I^2 statistic (equal to 100×(Q-degree of freedom)/Q) (Higgins 2003) are presented. A p-

value from the Q-test <0.05 or a high I^2 value would suggest heterogeneity across the studies included in the meta-analysis.

Rationale for choice of statistical methods

It is recognized in the literature that the Peto method is biased and more sensitive to unequal allocation of subjects to treatment groups. For this reason, the Mantel-Haenszel estimate of odds ratio was performed as one of the sensitivity analyses.

It is also recognized that in fitting a fixed effects model that it is being assumed that we are estimating the same treatment effect (odds ratio) in each study. To justify this choice of model, a random effects model is also included as sensitivity analysis.

When the possibility exists that the duration of exposure is different across the treatment groups, a Poisson exposure-adjusted model will generally give the most accurate estimate of the relationship between experimental treatment and control. However, in this meta-analysis, information on patient exposure from the nasal spray studies is obtained exclusively from the information available from summary tables in the individual CSRs as there is no electronic patient-level data. It is for this reason that the Poisson exposure-adjusted exact method is not the primary approach used in the comparing the incidence between calcitonin and placebo.

Results

Calcitonin nasal spray-treated patients had a 2.21% higher incidence rate of malignancy when compared to placebo-treated patients. All calcitonin (nasal + oral)-treated patients had a 1.23% higher incidence of malignancy compared to placebo-treated patients. A summary of the results is presented in Table 7-26. Please note that the denominators presented here include those studies in the denominator where malignancies did not occur in any of the treatment groups. The overall estimates in the Forest Plots include only those studies with events as the studies without malignancy events do not contribute to the magnitude of the treatment effect. Thus, event rates presented in Figure 7-5 and Figure 7-6 differ from what is presented in Table 7-26.

Table 7-26 Absolute incidence rates of any malignancy

Nasal calcitonin			Nasal+Oral		
	SCT	Placebo		SCT	Placebo
# of studies	n/N (%)	n/N (%)	# of studies	n/N (%)	n/N (%)
18	122/2712 (4.50%)	30/1309 (2.29%)	21	254/6151 (4.13%)	137/4732 (2.90%)

The odds-ratios and 95% confidence intervals in Table 7-27 imply that Miacalcin® NS has a higher risk of malignancy compared to placebo for all meta-analysis methods applied. Only the lower limit of the 95% confidence interval for the random effects model (MH_TA, Random) is less than 1, and the lower limit for that model is 0.99. Further evidence of the robustness of the results is indicated by the overall estimate of the odds ratio from the Peto method being identical to the odds ratio obtained from the Poisson exposure-adjusted model (Odds-ratio = 1.54), for the comparison of Miacalcin NS vs. placebo.

Table 7-27 Odds ratio (95% CI) on any malignancy

	Nasal calcitonin vs. Placebo	Nasal+Oral vs. Placebo
Peto	1.54 (1.06, 2.23)	1.33 (1.07, 1.64)
Peto_CC	1.50 (1.04, 2.16)	1.32 (1.07, 1.63)
Peto_TA	1.52 (1.06, 2.19)	1.32 (1.07, 1.64)
MH_CC	1.47 1.00, 2.15)	1.31 (1.06, 1.62)
MH_TA	1.54 (1.04, 2.27)	1.33 (1.07, 1.65)
MH_TA, Random	1.49 (0.99, 2.22)	1.28 (1.03, 1.60)
Poisson, exposure-adjusted	1.54 (1.02, 2.38)	1.39 (1.12, 1.74)

MH: Mantel-Haenszel; CC: constant correction; TA: treatment arm correction

When testing for heterogeneity between the clinical studies included in the meta-analysis, none of the Cochran Q-statistics achieved statistical significance for any of the meta-analysis populations indicating low heterogeneity. Details of these comparisons are available in the Appendix 5.

A summary of the odds ratio results by study and overall are presented graphically in the Forest Plot shown in Figure 7-5 for the Miacalcin nasal spray studies and Figure 7-6 for the meta-analysis including both the nasal spray and oral calcitonin studies.

Figure 7-5 Incidences and odds ratio for any malignancy by Peto method (Calcitonin NS studies)

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Figure 4.1a (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.27(0.16– 9.95)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.18– 2.32)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.77(0.57– 5.51)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.62(1.00– 2.61)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 45.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 522	4.0/ 156.0 (2.56)	0.0/ 52.0 (0.00)	3.87(0.40– 37.81)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.76(0.04– 353.5)
Total	122.0/2304.0 (5.30)	30.0/1021.0 (2.94)	1.54(1.06– 2.23)

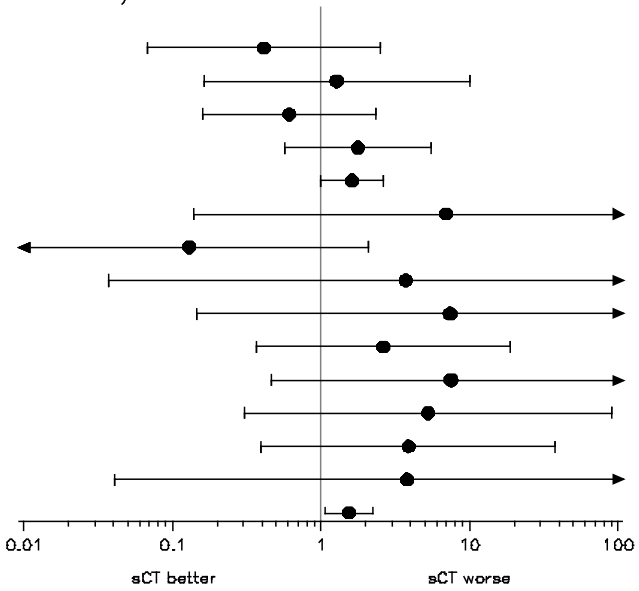

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Figure 7-6 Incidences and odds ratios for any malignancy by Peto method (Calcitonin NS + oral studies)

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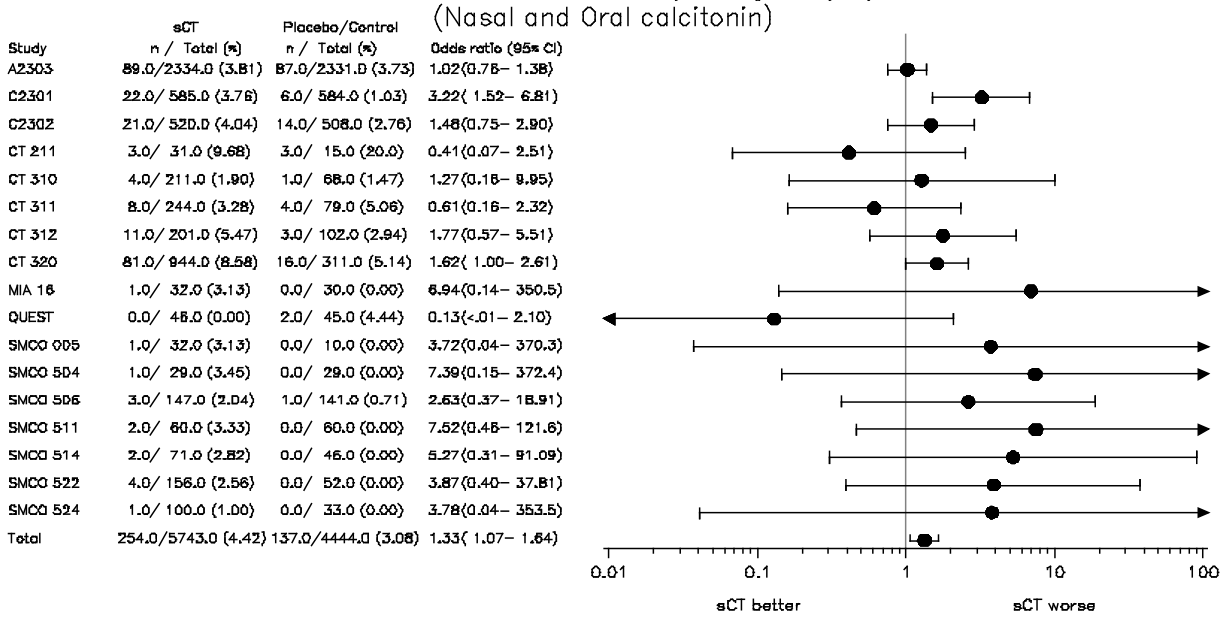
Figure 4.2a (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto
(Nasal and Oral calcitonin)



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The study-level results when considering nasal spray and oral calcitonin studies in Figure 7-6 show that odds ratios calculated at the study level were greater than one in 14 of the 17 studies where there was at least one malignancy event in either the calcitonin or placebo treatment groups. These results indicate a higher likelihood of malignancy for calcitonin in those studies compared to placebo. However, the increase in risk only achieves statistical significance in CT 320 (PROOF) with the nasal spray (lower limit of 95% confidence interval = 1.00) and in Study C2301 (lower limit of 95% confidence interval = 1.52). The CT 320 result differs from what was reported in the clinical study report where Fisher's Exact Test was used to test the hypothesis of association between treatment and malignancy. When considering only the nasal spray studies for calcitonin in the meta-analysis, the number needed to harm (NNH) is approximately 46 and increases to 82 when the oral calcitonin studies are added to the meta-analysis. This implies that, based on the controlled clinical trial data, approximately 46 patients would need to be treated with calcitonin nasal spray before a malignancy was detected.

Most of the malignancy cases with calcitonin NS were reported in study CT 320. According to the study report, there were 84 cancer events and 81 cases observed among 944 patients in the three arms treated with SCT (out of which 31 cases were BCCs plus 7 additional non-melanoma skin cancer cases) while 16/311 cancer observations (out of which 3 cases were BCCs) were reported for the placebo arm.

Since none of the calcitonin studies had been designed to prospectively assess malignancy incidence, the information for the meta-analysis was compiled from adverse event documentation (spontaneous reporting at trial visits). During the subsequent reconciliation of each event, especially to determine time of onset, one BCC in the CSR had to be amended for the following reasons: Pt. No. 13018 was listed in the database as a basal cell carcinoma, but narrative indicates only skin cancer.

All malignancy cases in study CT 320 were judged by the Investigators as not related to SCT.

Study CT 320 had unique characteristics when compared to all other studies such as a longer duration (it was a 5 year study while all other studies were ≤ 24 months) and a specific patient population (Caucasian population with fair skin type, elderly women mean age about 68 years with PMO). Due to these characteristics, the patients in this study were prone to develop BCCs and other non-melanoma skin cancers. Of note, all BCC cases were judged by the investigator as not related to SCT. An epidemiologic comparison to an untreated population with similar characteristics revealed that these numbers are within the expected range of cases developing non-melanoma skin cancers (Appendix 3). These findings were discussed at the time when the study report was submitted and do not reveal a new safety signal.

Meta-analysis of tumor types

Among the tumor types, basal cell carcinoma was the most common type of tumor. Other types included breast cancer and non-melanoma skin cancers. The complete list of the types of malignancies is available as Appendix 8.

Basal cell carcinoma

A summary of the basal cell carcinoma results are presented using the same methods, excluding the Poisson exposure-adjusted model, that were used for the meta-analysis of all malignancies. These results are presented in Table 7-28 and in the Forest Plots by study and overall in Figure 7-7 and Figure 7-8.

Table 7-28 Odds ratio (95% CI) on BCC malignancies

	Nasal calcitonin vs. Placebo	Nasal+Oral vs. Placebo
Peto	1.95 (0.99, 3.88)	1.99 (1.22, 3.25)
Peto_CC	1.44 (0.80, 2.59)	1.88 (1.06, 2.60)
Peto_TA	1.66 (0.92, 2.99)	1.80 (1.15, 2.83)
MH_CC	1.41 (0.75, 2.63)	1.64 (1.02, 2.65)
MH_TA	1.77 (0.91, 3.45)	1.88 (1.15, 3.09)
MH_TA, Random	1.53 (0.74, 3.15)	1.72 (1.02, 2.90)
Poisson, exposure-adjusted	2.80 (1.17, 8.09)	2.88 (1.63, 5.36)

MH: Mantel-Haenszel; CC: constant correction; TA: treatment arm correction

* With study in the Poisson model, quasi-complete separation of data points was detected and the maximum likelihood estimate may not exist. The results for basal cell carcinoma meta-analysis did not consider 'study' in the model.

The results for the different methods of meta-analysis show that when one considers all 21 nasal spray and oral studies that there is a consistent statistically significant increase in the risk of BCC with calcitonin compared to placebo. When considering just the nasal spray studies the increase in risk is not statistically significant for any of the methods except for the Poisson exposure-adjusted method which accounts for patient exposure in the individual studies.

Figure 7-7 Incidences and odds ratio for any basal cell carcinoma by Peto method (Calcitonin NS studies)

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Figure 4.3a (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto
(Nasal calcitonin)

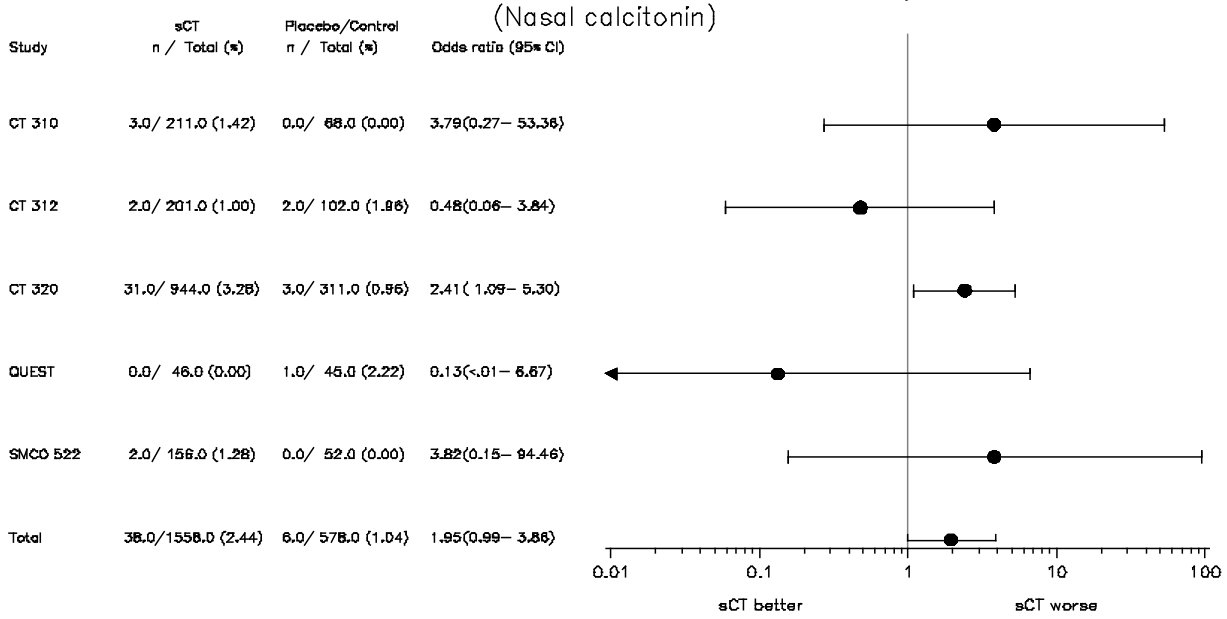

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Figure 7-8 Incidences and odds ratio for basal cell carcinoma (BCC) by Peto method (Calcitonin NS + oral studies)

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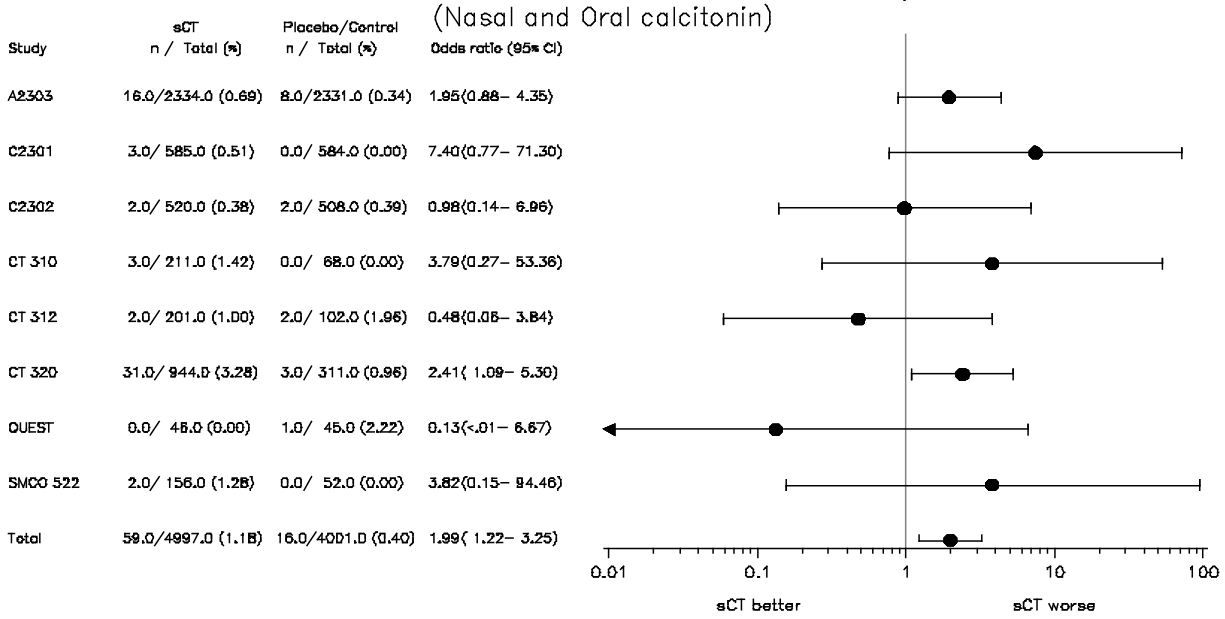
Figure 4.4a (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto
(Nasal and Oral calcitonin)



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When considering calcitonin nasal spray there is approximately a twofold greater likelihood of calcitonin-treated patients experiencing a BCC event. This result was greatly influenced by the more than threefold greater incidence of basal cell carcinoma in CT 320 (3.28% vs. 0.96%). With oral calcitonin in the PMO study (A2303) there was approximately a twofold greater incidence of BCC with oral calcitonin relative to placebo (0.67% vs. 0.33%).

Non-BCC malignancies

A summary of the malignancy results excluding BCC events are presented using the same methods excluding the Poisson exposure-adjusted model that were used for the meta-analysis of all malignancies. These results are presented in Table 7-29 and in the Forest Plots by study and overall in Figure 7-9 and Figure 7-10.

Table 7-29 Odds ratio (95% CI) on malignancies excluding BCC events

	Nasal calcitonin vs. Placebo	Nasal+Oral vs. Placebo
Peto	1.34 (0.88, 2.04)	1.20 (0.95, 1.51)
Peto_CC	1.30 (0.88, 1.96)	1.19 (0.95, 1.50)
Peto_TA	1.32 (0.87, 2.00)	1.20 (0.95, 1.50)
MH_CC	1.24 (0.82, 1.87)	1.17 (0.93, 1.48)
MH_TA	1.31 (0.88, 1.99)	1.19 (0.95, 1.50)
MH_TA, Random	1.25 (0.81, 1.92)	1.16 (0.91, 1.46)
Poisson, exposure-adjusted	1.31 (0.83, 2.13)	1.26 (0.99, 1.60)

MH: Mantel-Haenszel; CC: constant correction; TA: treatment arm correction

The different meta-analysis methods show a consistent increase in the likelihood of malignancies with or without inclusion of the oral calcitonin placebo-controlled studies. Only the Poisson model that contains both the nasal spray and oral studies approaches statistical significance (Lower bound of 95% CI = 0.99)

Figure 7-9 Incidences and odds ratios for any malignancy excluding BCC by Peto method (Nasal calcitonin)

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Figure 4.6a (Page 1 of 1)
Incidences and odds ratio for any malignancy excluding BCC by Peto
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.18– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 45.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.76(0.04– 353.5)
Total	88.0/2304.0 (3.82)	26.0/1021.0 (2.55)	1.34(0.88– 2.04)

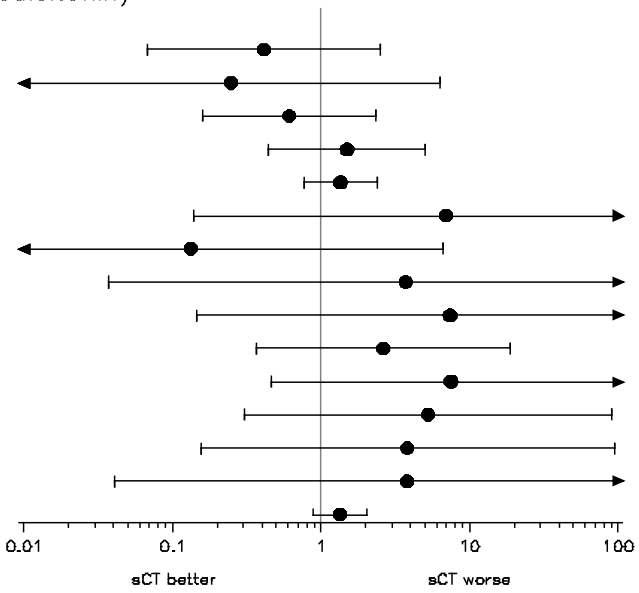

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Figure 7-10 Incidences and odds ratios for any malignancy excluding BCC by Peto method (Nasal+oral calcitonin)

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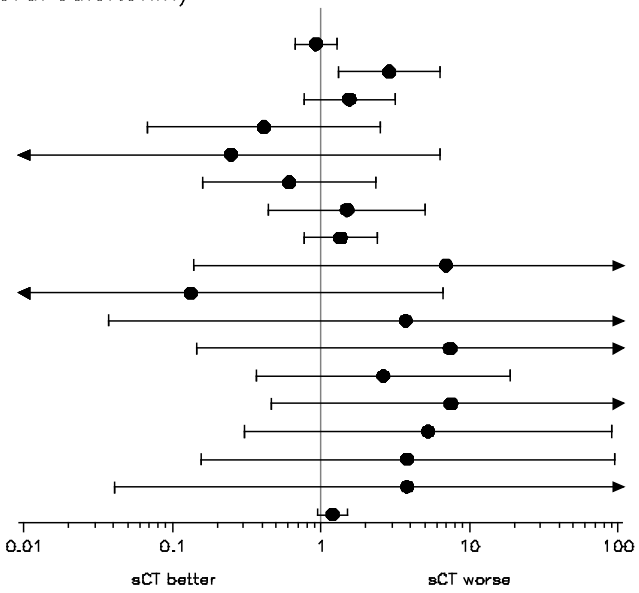
Figure 4.7a (Page 1 of 1)
Incidences and odds ratio for any malignancy excluding BCC by Peto
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
A2303	73.0/2334.0 (3.13)	79.0/2331.0 (3.39)	0.92(0.67– 1.27)
C2301	19.0/ 585.0 (3.25)	6.0/ 584.0 (1.03)	2.89(1.31– 6.37)
C2302	19.0/ 520.0 (3.65)	12.0/ 508.0 (2.36)	1.55(0.78– 3.18)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.45– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	199.0/5743.0 (3.47)	123.0/4444.0 (2.77)	1.20(0.95– 1.51)



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Assessment of dose response

As the dosage used in nasal and oral calcitonin trials was different, evaluating dose-response was restricted to the nasal calcitonin trials. In order to assess the relationship between dose and the rate of malignancy, separate meta-analyses were performed for each dose group comparison (100IU, 200IU, and 400IU against placebo) from the nasal calcitonin clinical trials.

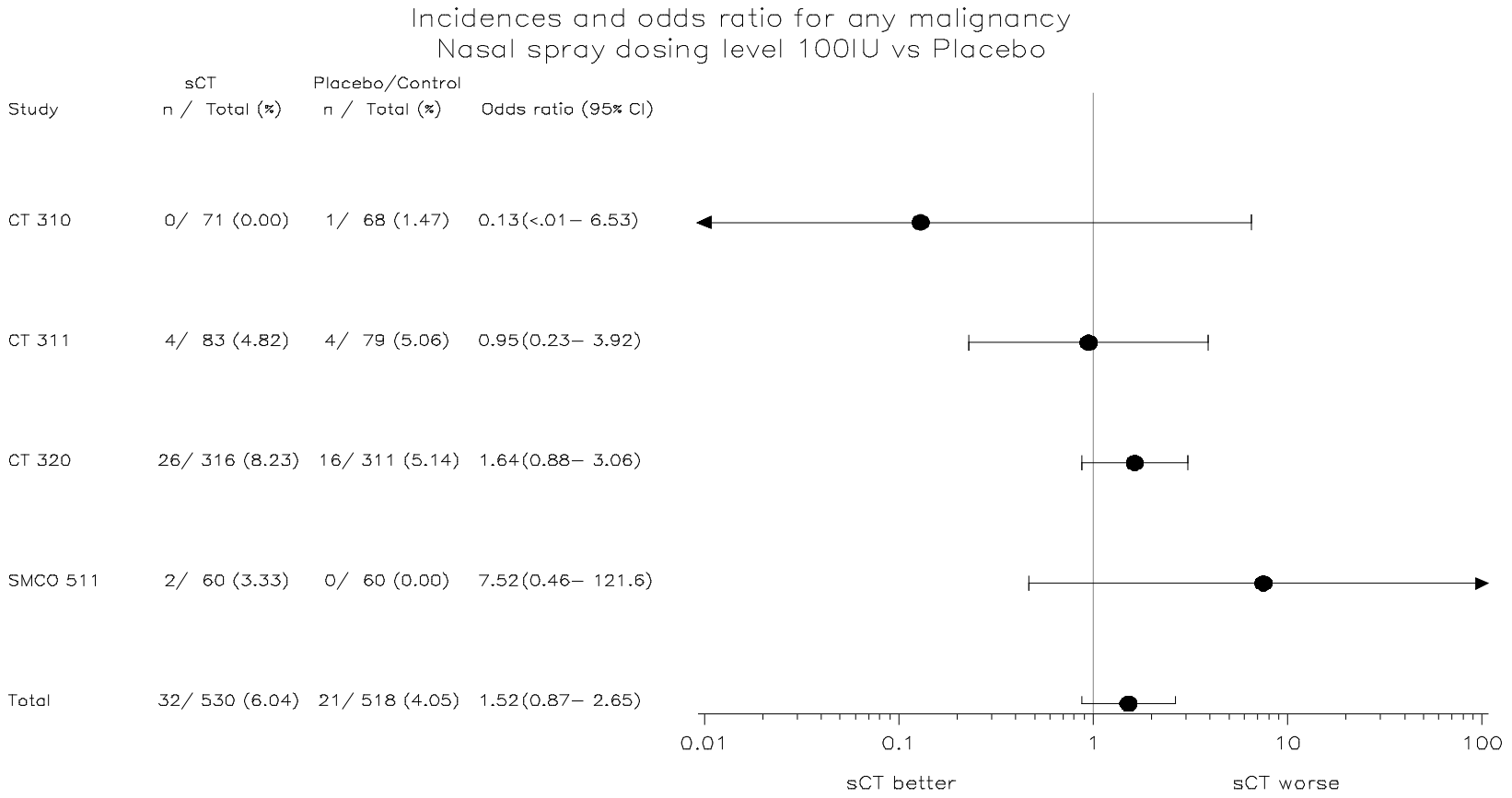
As shown in Table 7-30, there is no evidence of a dose response relationship with calcitonin nasal spray as the odds ratios for all dose groups are nearly identical.

Table 7-30 Summary of odds ratios (95% CI) for dose-response relationship for malignancy by dose level (nasal spray calcitonin studies)

	100IU vs. Placebo	200IU vs. Placebo	400IU vs. Placebo
Any malignancy	1.52 (0.87, 2.65)	1.52 (0.95, 2.44)	1.51 (0.92, 2.48)

The Forest Plots showing the by study results and overall results by dose of calcitonin nasal spray are provided in Figures 7-11, 7-12 and 7-13.

Figure 7-11 Incidences and odds ratio for any malignancy by Peto method comparing Calcitonin NS 100 IU to placebo



Odds ratio (sCT vs Placebo/Control) obtained by Peto method.
Arrows represent estimates outside of axis range.
Odds ratio estimate in Total row only includes studies with at least one event in either treatment group.
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Figure 7-12 Incidences and odds ratio for any malignancy by Peto method comparing Calcitonin NS 200 IU to placebo

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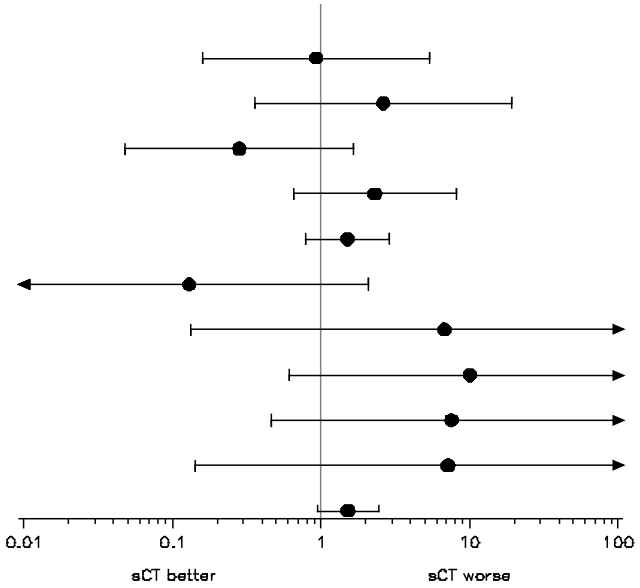
Incidences and odds ratio for any malignancy (Nasal spray dosing level 200IU vs Placebo)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 211	3.0/ 16.0 (18.8)	3.0/ 15.0 (20.0)	0.93(0.16– 5.35)
CT 310	3.0/ 72.0 (4.17)	1.0/ 68.0 (1.47)	2.62(0.38– 19.04)
CT 311	1.0/ 82.0 (1.22)	4.0/ 79.0 (5.06)	0.26(0.05– 1.66)
CT 312	7.0/ 102.0 (6.86)	3.0/ 102.0 (2.94)	2.31(0.65– 8.21)
CT 320	24.0/ 316.0 (7.59)	16.0/ 311.0 (5.14)	1.51(0.79– 2.86)
QUEST	0.0/ 46.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 11.0 (9.09)	0.0/ 10.0 (0.00)	6.75(0.13– 341.5)
SMCO 514	2.0/ 36.0 (5.56)	0.0/ 46.0 (0.00)	10.04(0.60– 166.7)
SMCO 522	2.0/ 52.0 (3.85)	0.0/ 52.0 (0.00)	7.54(0.46– 122.1)
SMCO 524	1.0/ 34.0 (2.94)	0.0/ 33.0 (0.00)	7.17(0.14– 361.7)
Total	44.0/ 767.0 (5.74)	29.0/ 761.0 (3.81)	1.52(0.95– 2.44)



Odds ratio obtained by Peto method.
Only includes studies with at least one event in either treatment group.

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Figure 7-13 Incidences and odds ratio for any malignancy by Peto method comparing Calcitonin NS 400 IU to placebo

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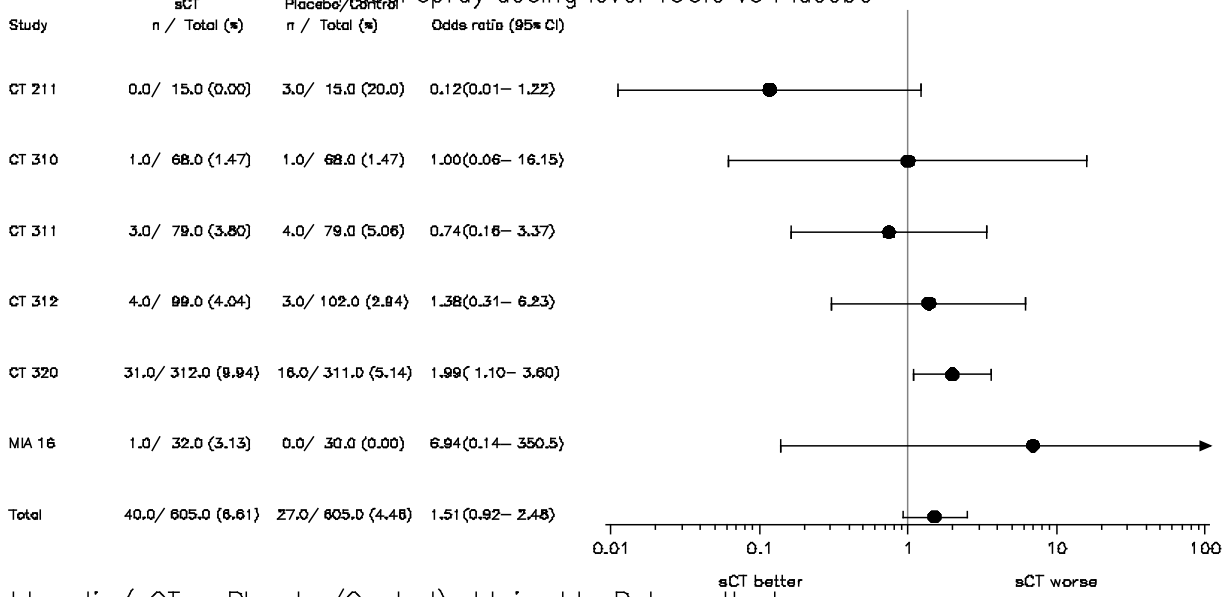
Figure 3.3c1 (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal spray dosing level 400IU vs Placebo



Odds ratio (sCT vs Placebo/Control) obtained by Peto method.
Arrows represent estimates outside of axis range.
Odds ratio estimate in Total row only includes studies with at least one event in either treatment group.
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Assessment of duration of treatment

Because patient-level data are not available for the calcitonin nasal spray clinical studies, Kaplan-Meier curves cannot be presented. Time to malignancy event was assessed by presenting the summary and the number of malignant cases in each 6-month period for the treatment and placebo groups.

To evaluate the exposure-adjusted risk ratios with study level data, Poisson meta-analysis is presented, accounting for total exposure (the sum of exposures from all patients in a treatment group of a trial is used rather than the number of patients)

From the number of malignancies in each 6-month period, nasal calcitonin and placebo group have a similar incidence rate in the first 6 months. However, beginning in the 2nd 6-month period the nasal calcitonin group has a higher incidence rate (1.2%) of malignancies compared to placebo (0.2%) during the 6-12 month exposure period and beyond. From Month 6 to 36 the differences in incidence rates can potentially be attributed to the apparent decrease in event rate observed in the placebo group between Month 12 and Month 36 while the nasal calcitonin incidence rate remain constant over this time period. After Month 36 the results should be interpreted with caution given the substantially higher dropout rate during this time period.

Oral calcitonin and placebo have similar incidence rates of malignancy within the first year. For periods longer than 6 months (time point used in the clinical trial), oral calcitonin has a slightly higher incidence rate compared to placebo.

A summary of the incidence of malignancy by time period is presented in Table 7-31.

Table 7-31 Incidence of first malignancy by time period in studies included in the meta-analyses

	Time period (months)							
	0	>0-6	>6-12	>12-18	>18-24	>24-36	>36-48	>48-60
Nasal calcitonin(#)								
Number at risk	2680	2419	2112	1919	1803	742	495	383
Malignancy		22	25	14	10	24	7	15
%		0.9%	1.2%	0.7%	0.6%	3.2%	1.4%	3.9%
Placebo								
Number at risk	1278	1146	942	863	821	334	154	128
Malignancy		9	2	3	3	4	1	5
%		0.8%	0.2%	0.2%	0.3%	1.2%	0.6%	3.9%
Oral calcitonin								
Number at risk (^)	3439	2876	2664	2507	2094	427		
Malignancy		20	21	30	21	38*		
%		0.7%	0.8%	1.2%	1.0%	8.9%		
Placebo								
Number at risk (^)	3423	3092	2887	2757	2290	404		
Malignancy		17	22	20	18	30**		
%		0.5%	0.8%	0.7%	0.8%	7.4%		
All calcitonin								
Number at risk	6119	5295	4776	4426	3897	1169	495	383
Malignancy		42	46	44	31	62	7	15
%		0.8%	1.0%	1.0%	0.8%	5.3%	1.4%	3.9%
Placebo								
Number at risk	4701	4238	3829	3620	3111	738	154	128
Malignancy		26	24	23	21	34	1	5
%		0.6%	0.6%	0.6%	0.7%	4.6%	0.6%	3.9%

-For multiple malignancies within a patient, only the first occurred malignancy is considered.

N: Number of patients who entered into the time period (number of patients at risk)

-Eight missing values existed for time to malignancy event (5 for calcitonin group, 3 for placebo group) for nasal calcitonin trials.

-Two elevated PSA cases without time to event information (both in calcitonin group).

-Percentage is calculated based on the completers at each period.

* including two patients with time-to-event >36 months.

** including four patients with time-to-event >36 months.

(#) the data by time period is not available for study MIA16.

(^) the number of patients remaining in the study at 182 (6 months), 365 (12 months), 547 (18 months), 730 (24 months), 1095 (36 months) days is used.

- One duration of treatment in QUEST in placebo group is missing.

Deaths

The numbers of deaths and those associated with malignancy in the trials which were included in the meta-analysis are presented in Table 7-32.

Table 7-32 Numbers of deaths in clinical trials

	Placebo			Calcitonin		
Study Number	N	Deaths (%)	Malignancy Deaths (%)	N	Deaths (%)	Malignancy Deaths (%)
2402	147	0	0	149	0	0
CT211	15	0	0	31	0	0
CT310	68	0	0	208	0	0
CT311	79	6	0	244	13	0
CT312	102	10	0	201	21	1
CT320	211	7	0	944	18	3
MIA16	30	2	0	63	3	0
SMCO005	10	0	0	32	1	0
SMCO503	26	0	0	26	0	0
SMCO504	29	0	0	29	0	0
SMCO506	141	0	0	147	3	1
SMCO511	60	0	0	60	2	2
SMCO514	46	2	0	71	0	0
SMCO517	83	0	0	168	0	0
SMCO520	32	0	0	65	0	0
SMCO522	52	0	0	156	0	0
SMCO524	33	0	0	101	0	0
QUEST	46	0	0	45	0	0
A2303	2331	16	1	2334	19	3
C2301	584	2	0	585	2	2
C2302	508	1	1	520	3	0
Total	4633	49 (1.06)	2 (0.043)	6179	86 (1.39)	12 (0.19)

Deaths due to malignancy were reported for 14 patients from 7 of the 21 studies in the meta-analysis. Overall deaths occurred in 1.06% of patients receiving placebo and 1.39% of calcitonin-treated patients. Two deaths due to malignancy were reported in patients receiving placebo and 12 patients receiving calcitonin. The numbers within individual trials are small and the types of malignancy are varied. Overall the death rates in the placebo and calcitonin treated groups are similar.

7.2.3.1 Data on from oral calcitonin trials (Nordic Biosciences/Novartis) on prostate cancer and Prostate-specific antigen (PSA) profiles

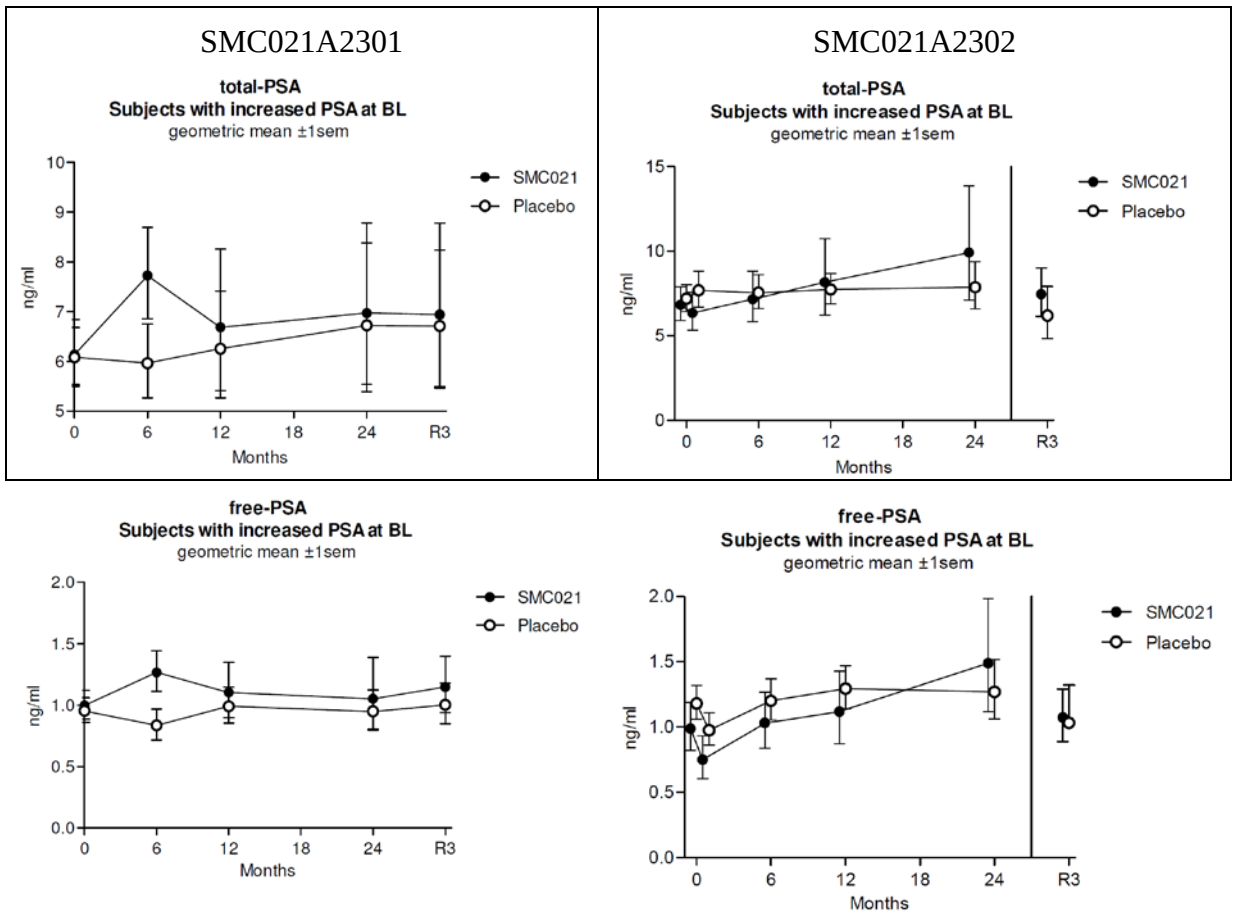
The oSCT program included male patients in the two osteoarthritis trials C2301 and C2302. Triggered by the initially reported imbalance of prostate cancer events (4 in oSCT vs. 0 in placebo groups), clinical follow-up was intensified. Eventually, full analysis of all observed

prostate cancer cases (12 vs. 10 confirmed events), as well as PSA profiles, showed no correlation between the use of calcitonin and prostate cancer.

During the two osteoarthritis trials C2301 and C2302 (clinicaltrials.gov numbers, NCT00486434 and NCT00704847), prostate-specific antigen (PSA) values were collected from male patients over time (baseline and after 1-2 and 3 years of exposure). The observation of an imbalance of prostate cancer reports in study C2301 triggered a wider screening for PSA elevations and clinical follow up.

Full analysis of observed prostate cancer cases and PSA profiles showed no correlation of calcitonin use with elevated PSA levels or their progression over time. As shown in Figure 7-14 there is no consistent pattern of change in PSA values (total or free) for men with elevated PSA at baseline that were treated with oSCT compared with placebo. The (age-related) increase of PSA levels over the study period was comparable in both study arms in each study. Of note, these studies were done in patients receiving oral calcitonin twice daily, while oral calcitonin for PMO was administered once daily. These data do not support a trophic effect of salmon calcitonin on the prostate and are not consistent with the hypothesis of calcitonin causing tumor promotion / progression (see also preclinical Section 7.2.2).

Figure 7-14 Total and free PSA over time in subjects with increased PSA at baseline in Osteoarthritis Studies SMC021A2301 and A2302



PSA, Prostate-specific antigen
R3, unscheduled follow-up visit

7.2.4 Post-marketing data with respect to malignancy risk

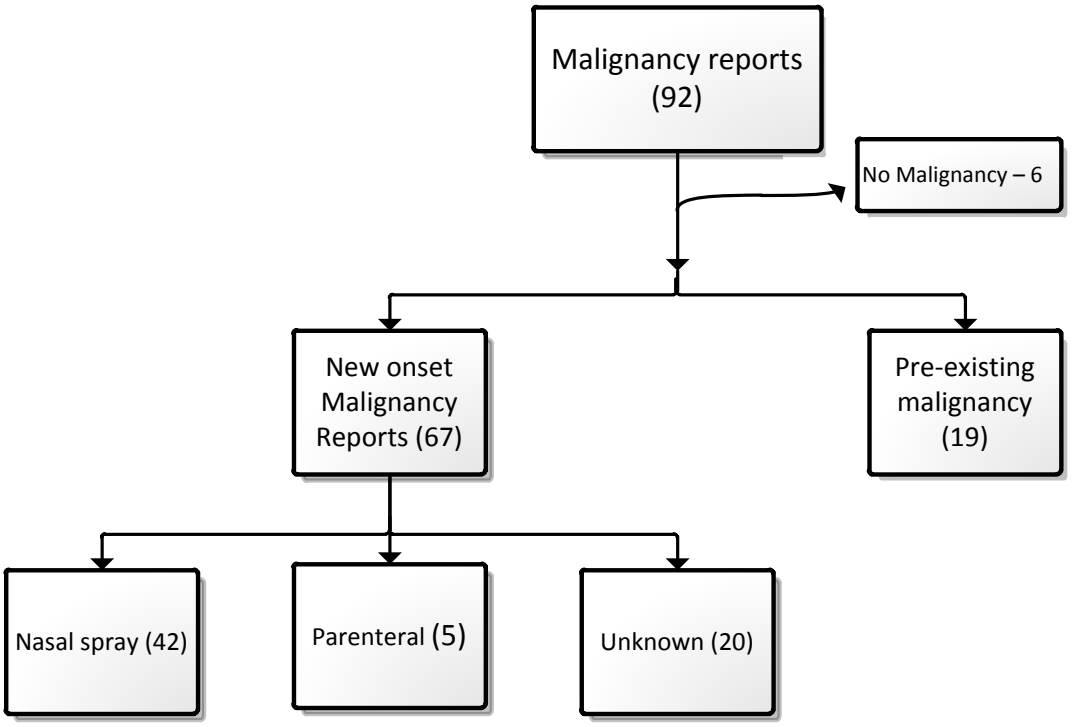
7.2.4.1 Cases from Novartis Global Safety Database

A Novartis safety database search was performed since product's launch with a data lock point of 31 Dec 2012. The search strategy included the Standard MedDRA Query (SMQ) – "Malignancies" and SMQ "Tumors of unspecified malignancy" (search scope: broad) from the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. These SMQs include terms for all types of malignant or unspecified tumors, malignancy-related conditions, malignancy-related therapeutic and diagnostic procedures, and tumor markers. Some cases retrieved by this strategy may not represent actual cases of new onset malignancy, so these were identified and excluded from analysis.

7.2.4.1.1 Results

The above search retrieved 92 spontaneously reported cases including 33 healthcare professional (HCP) and 59 non-HCP case reports. Twenty-five cases were excluded from analysis either because they did not report malignancy (n=6) or because they reported malignancy as a pre-existing condition, present before the initiation of therapy with calcitonin (n=19). This is reflected in Figure 7-15.

Figure 7-15 Case reports of malignancies from post-marketing reports

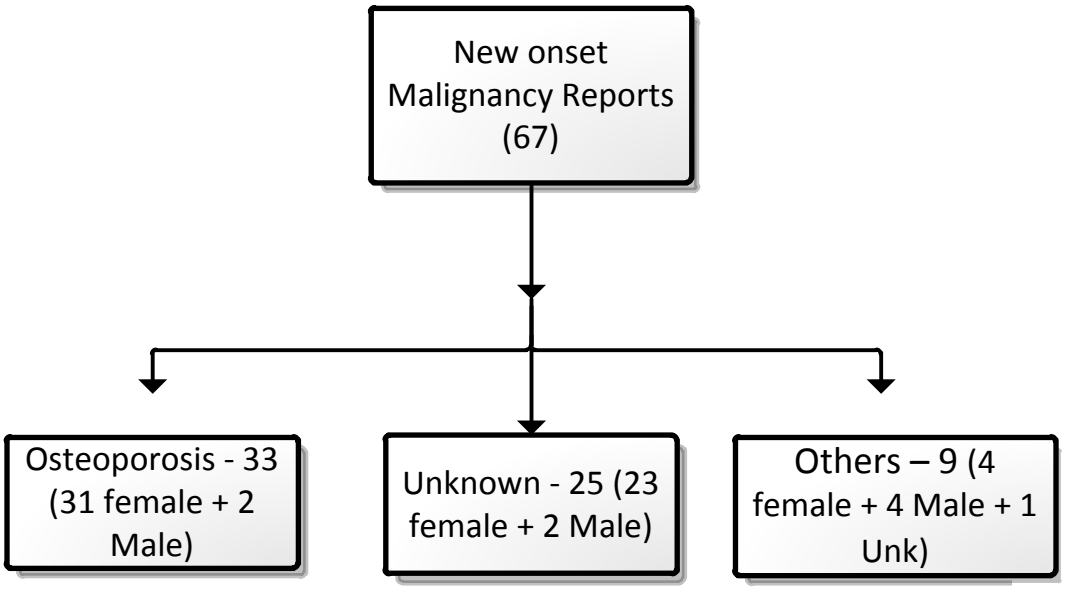


7.2.4.2 New-onset malignancy reports

In total, 67 reports were retrieved from the post-marketing safety database, which reported new events of malignancy while receiving calcitonin. It includes 16 HCP and 51 non-HCP reports. Of the 67 cases with new-onset malignancies, 33 patients (31 women, 2 men) were treated with calcitonin for an indication of osteoporosis, 25 patients (23 women, 2 men) were treated for unknown indications, and 9 patients (4 women, 4 men, 1 unknown) were treated for other indications (nonspecific reaction [n=2], hypercalcemia [n=2], Paget's Disease [n=2], complex regional pain syndrome [n=1], osteopenia [n=1], and arthralgia [n=1]).

According to available data (from January 1998 to December 2012), the cumulative sales of calcitonin corresponds to a patient exposure of at least 11 million patient-treatment-years (PY) in the period, indicating a post-marketing reporting rate for new-onset malignancies of approximately 0.6 case per 100,000 PY. Also according to the distribution of cases in the post-marketing database, 80% of the total exposure corresponds to postmenopausal osteoporosis indication.

Figure 7-16 Case summaries of new-onset malignancy based on indication from post-marketing reports



The distribution of the malignancy adverse event terms by indication is presented in Table 7-33. The table reflects the count of adverse event terms, so there may be a higher count of terms than case reports, as a patient from an individual case may report more than one malignancy term.

Table 7-33 Malignancy patterns based on indication from post-marketing reports

Osteoporosis	Unknown	Other indications
Breast cancer (8)	Breast cancer (5)	Neoplasm NOS (3)
Thyroid neoplasm (5)	Neoplasm NOS (5)	Malignant melanoma (1)
Colon cancer (3)	Lung neoplasm malignant (2)	Multiple myeloma (1)
Gastrointestinal carcinoma (3)	Skin cancer (2)	Mycosis fungoides (1)
Hepatic neoplasm malignant (3)	Basal cell carcinoma (1)	Pancreatic carcinoma (1)
Lung cancer (3)	Bladder cancer (1)	
Neoplasm NOS (3)	Bone neoplasm malignant (1)	
Ovarian cancer (3)	Gastric cancer (1)	
Gastric cancer (2)	Hepatic neoplasm malignant (1)	
Pancreatic carcinoma (2)	Leukemia (1)	
Cervix carcinoma (1)	Lymphoma (1)	
Gallbladder cancer (1)	Multiple myeloma (1)	
Lip neoplasm (1)	Pancreatic carcinoma (1)	
Nasal neoplasm (1)	Rectal cancer (1)	
	Sarcoma osteogenic (1)	
	Uterine cancer (1)	

7.2.4.2.1 New onset malignancies in patient receiving calcitonin for osteoporosis

In total, 33 reports were identified in patients receiving calcitonin for osteoporosis (Table 7-34). The most commonly reported malignancies were breast cancer (n=8), thyroid neoplasm (n=5), gastrointestinal carcinoma (n=4), colon cancer (n=3), hepatic neoplasm malignant (n=3), lung cancer (n=3), ovarian cancer (n=3), and unspecified neoplasm (n=3). The following reports from the Novartis safety database were included in the analysis and are summarized in Table 7-34.

Table 7-34 Malignancy-related events in patients treated for osteoporosis from post-marketing reports

Case No Gender/age	Dose TTO	Adverse Event Terms	Comment
Nasal spray (n=27)			
PHBS1998DK17947 F/71	Unk 184	Breast cancer female	Poorly documented
PHEH2004US07494 F/61	Unk 426	Breast cancer female	Poorly documented
PHEH2004US12894 F/73	200 IU 489	Mastectomy Breast cancer	Limited information makes causality unassessable
PHFR2012GB004896 F/64	Unk 4380	Breast cancer	Poorly documented
PHHY2012BR060074 F/46	Unk Unk	Breast cancer, Gastrointestinal carcinoma	Poorly documented
PHEH1997US01304 F/63	Unk 63	Thyroid neoplasm, Fibrocystic breast disease	Poorly documented
PHEH2001US02428 F/61	200 IU Unk	Thyroid neoplasm	Poorly documented
PHEH2001US07793 F/Unk	200 IU 1095	Thyroid neoplasm	Poorly documented
PHEH2004US02117 F/68	200 IU 13 years	Thyroid neoplasm	Poorly documented
PHEH2005US13004 F/75	200 IU 1500	Thyroid neoplasm	Poorly documented
PHBS2002PE15034 F/86	200IU 914	Colon cancer, Metastasis	Poorly documented
PHEH1998US13966 F/74	Unk Unk	Colon cancer	Poorly documented
PHHO1998DK08669 F/78	Unk 1171	Colon cancer	Poorly documented
PHHO1998AU08703 F/68	Unk 588	Lung cancer	Poorly documented
PHBS1998DK19458 F/71	Unk 503	Lung neoplasm malignant	Poorly documented
PHHY2012ES117586 F/80	200 IU 924	Lung adenocarcinoma	Poorly documented
PHBS2006BR02991 M/Unk	Unk Unk	Neoplasm malignant	Poorly documented
PHEH1997US00061 F/49	1 DF 60	Neoplasm NOS	Poorly documented
PHEH1998US01209 F/87	1 DF 365	Neoplasm malignant	Poorly documented
PHEH2008US09543	Unk	Ovarian cancer	Poorly documented

Case No Gender/age	Dose TTO	Adverse Event Terms	Comment
F/Unk	Unk		
PHBS1998FR17871	50 IU	Malignant ovarian cyst	Poorly documented
F/Unk	Unk		
PHBS2002PE08773	200 IU	Ovarian cancer, Gastric cancer	Secondary (metastatic) ovarian carcinoma from primary gastric carcinoma; long history of gastritis
F/74	411		
PHHO1998DK08673	Unk	Pancreatic carcinoma	Poorly documented
F/70	30		
PHHO2004EC04618	Unk	Pancreatic cancer metastatic, Hepatic cancer metastatic, Gastrointestinal cancer metastatic	Poorly documented
F/91	50		
PHEH2007US15191	Unk	Nasal cavity cancer Papilloma	Considering TTO and location of the tumor, causality cannot be excluded
F/Unk	730		
PHEH2004US12754	200 IU	Nasal neoplasm, Lip neoplasm malignant (unspecified)	Poorly documented
M/80	6483		
PHEH2003US08211	200 IU	Cervix carcinoma	Poorly documented
F/70	1095		
Parenteral (n=1)			
PHBS1998DE15922	Unk	Hepatic neoplasm malignant	Poorly documented
F/70	Unk		
Unknown (n=5)			
PHEH1998US13967	Unk	Breast cancer	Poorly documented
F/68	Unk		
PHHO2006CL12373	Unk	Breast cancer stage III, Malignant breast lump removal	Poorly documented
F/67	183		
PHHO1998FR08437	Unk	Gastrointestinal carcinoma, Metastases to liver	Poorly documented
F/35	Unk		
PHHO2004CL15910	Unk	Gastric cancer	Poorly documented
F/74	184		
PHHY2009BR20225	Unk	Gallbladder cancer	Poorly documented
F/85	610		

TTO = time to onset (in days, unless otherwise specified); Unk = unknown; DF = dosage form

Of the 33 reports, 31 reports were poorly documented and hence inconclusive. No information was available on time to onset, action taken with suspect drug, event outcome, co-medication and medical history.

In 1 report (PHEH2007US15191), considering the time to onset and anatomical location of the tumor (nasal cavity), causality cannot be excluded for calcitonin nasal spray. Another patient (PHBS2002PE08773) was diagnosed with secondary ovarian carcinoma (metastatic) from a primary gastric carcinoma, which could have been confounded by long history of

gastritis treated with antihistamines. There are no other reports, however, for similar malignancies in the database.

7.2.4.2.2 New onset malignancies in patients receiving calcitonin for unknown indication

In total, 25 reports were identified with no reported indication for calcitonin (Table 7-35). Given that postmenopausal osteoporosis is the most common indication in the post-marketing database, all these cases are considered for analysis to evaluate the risk of malignancy in this indication. The most commonly reported malignancies were breast cancer (n=5), neoplasm not otherwise specified (n=5), lung neoplasm malignant (n=2) and skin cancer (n=2).

Table 7-35 Malignancy-related events in patients treated for unknown indication from post-marketing reports

Case No Gender/age	Dose TTO	Adverse Event Terms	Comment
Nasal Spray (n=14)			
PHEH2008US08588 F/69	Unk Unk	Breast cancer	Poorly documented
PHEH2009US04312 F/Unk	Unk Unk	Breast lump removal	Poorly documented
PHHO2002CA10838 F/Unk	Unk Unk	Breast cancer metastatic	Poorly documented
PHHY2010US38169 F/73	Unk Unk	Breast cancer	Poorly documented
PHHO2002CA10879 F/unk	Unk Unk	Breast cancer, Bone neoplasm malignant	Poorly documented
PHHY2004CL005202 F/Unk	Unk Unk	Bone neoplasm malignant	Poorly documented
PHHO2001BR10660 F/53	200 IU Unk	Neoplasm malignant	Poorly documented
PHEH2011US02126 F/80	200 IU Unk	Neoplasm malignant	Poorly documented
PHEH1998US09441 F/70	1 OT 364	Neoplasm skin	Poorly documented
PHEH2004US05941 F/Unk	Unk < 365	Skin neoplasm excision, Basal cell carcinoma	Considering temporality and anatomical location of the tumor (nasal bridge), causality cannot be excluded
PHEH2012US023465 F/88	Unk Unk	Neuroendocrine skin carcinoma Lung neoplasm malignant	Poorly documented
PHEH2007US00585 F/58	200 IU 351	Rectal cancer	Poorly documented
PHHO2001BR10645 F/63	200 IU Unk	Uterine cancer	Poorly documented
PHHO2006CL05621	Unk	Multiple myeloma	Poorly documented

Case No Gender/age	Dose TTO	Adverse Event Terms	Comment
F/68	Unk		
Parenteral (n=2)			
PHEH1998US13927 F/79	100 IU 210	Lung neoplasm malignant	Poorly documented
PHEH2008US11304 M/Unk	Unk 4 days	Hepatic neoplasm malignant	Poorly documented
Unknown (n=9)			
PHEH2005US10504 F/Unk	Unk Unk	Neoplasm malignant	Poorly documented
PHHO2005CL00646 F/Unk	Unk Unk	Neoplasm malignant	Poorly documented
PHHO2005CL01375 F/Unk	Unk Unk	Metastatic neoplasm	Poorly documented
PHEH1998US12408 F/69	100 IU Unk	Gastric cancer	Poorly documented
PHEH2002US06692 F/77	Unk 1095	Lymphoma, Tumor flare	Considering temporality and anatomical location of the tumor (orbital lymphoma), causality cannot be excluded
PHEH2008US09901 F/76	Unk Unk	Pancreatic carcinoma	Poorly documented
PHHO1998GB08436 F/21	Unk Unk	Sarcoma	Poorly documented
PHHO2004CL06640 F/79	Unk Unk	Leukemia	Poorly documented
PHHO2005CL17452 M/83	Unk Unk	Bladder cancer	Poorly documented

Of these, 23 reports were poorly documented and hence inconclusive. No information was available on the event time to onset, action taken with suspect drug, event outcome, co-medication and/or medical history.

Considering the temporality and anatomical location of the tumor, in 2 reports (PHEH2002US06692 [orbital lymphoma] and PHEH2004US05941 [basal cell carcinoma of nasal bridge]), causality to calcitonin cannot be excluded. There are, however, no further similar reports in the database.

7.2.4.2.3 New onset malignancies in patients receiving calcitonin for other indications

In total, 9 reports were identified in patients receiving calcitonin with known indication other than osteoporosis (Table 7-36).

Table 7-36 Malignancy-related events in patients treated for other indications (non-osteoporosis) from post-marketing reports

Case No Gender/age	Dose TTO	Indication	Adverse Term Events	Comment
PHBS1998DE15904 F/Unk	100 IU 3	Complex regional pain syndrome	Neoplasm malignant	Poorly documented
PHEH1996US01589 F/Unk	Unk Unk	Nonspecific reaction	Neoplasm	Poorly documented
PHHY2008BR05494 F/82	Unk 21	Arthralgia	Neoplasm malignant	Poorly documented
PHHY2011ES79441 F/60	Unk Unk	Osteopenia	Multiple myeloma	Poorly documented
PHHY2011ES79440 M/38	Unk 3	Hypercalcemia	Multiple myeloma, Calcification metastatic	Pre-existing multiple myeloma was diagnosed during therapy with calcitonin/
PHBS1995DE00785 M/59	Unk Unk	Nonspecific reaction	Mycosis fungoides	History of eczema that was later diagnosed as mycosis fungoides
PHBS1998CH20994 M/73	Unk 300	Paget's disease	Malignant melanoma	Poorly documented
PHBS1998DE15873 Unk/65	Unk Unk	Paget's disease	Pancreatic carcinoma	Poorly documented
PHHY2011RU96872 M/38	Unk 365	Hypercalcemia	Adrenal neoplasm	Poorly documented

Of these 9 reports, 7 were poorly documented and hence inconclusive. No information was available on the event time to onset, action taken with suspect drug, event outcome, co-medication and/or medical history.

In case PHHY2011ES79440, considering the short time to onset (3 days) a pre-existing multiple myeloma appears to be diagnosed during therapy with calcitonin. In another report (PHBS1995DE00785), the patient was diagnosed with mycosis fungoides that was initially diagnosed as eczema after initiation of therapy with calcitonin and hence appears to be an incidental finding.

7.2.4.3 Discussion

The most commonly observed malignancies associated with osteoporosis and unknown indications were breast cancer, gastrointestinal tract malignancies, lung carcinoma, and thyroid neoplasms.

Breast cancer cases in osteoporosis and "unknown" indications

There were 13 cases reporting breast cancer for the osteoporosis and unknown indication. The mean and median ages for these patients were 66 and 67 years respectively. There was no

clear support for a causal relationship in these cases, other than the diagnosis of breast cancer during calcitonin therapy. As evident by epidemiology data, breast cancer is a common malignancy in the osteoporosis population. Risk factors seen in patients receiving therapy with calcitonin include female gender, advanced age, family history, late age of menopause, late age of first term pregnancy/nulliparity, use of combined estrogen/progesterone hormone-replacement therapy, adult weight gain, sedentary lifestyle, and alcohol consumption that could have independently contributed for the risk of breast cancer.

Gastrointestinal tract cancer cases in osteoporosis and 'unknown" indications

There were 10 cases reporting gastrointestinal tract cancers [colon cancer (n=3), gastrointestinal carcinoma (n=3), gastric cancer (n=3), and rectal cancer (n=1)] for osteoporosis and unknown indications. The mean and median ages for these patients were 69 and 74 years. There was no clear support for a causal relationship in these cases, other than the diagnosis of a gastrointestinal tract cancer during calcitonin therapy. Risk factors in these patients include advancing age, diet high in animal fat, smoking, obesity, excessive alcohol consumption, diet containing high amounts of salted, cured, or poorly preserved foods, and/or chronic pancreatitis.

Lung carcinoma cases in osteoporosis and 'unknown" indications

There were 5 cases reporting lung cancer for osteoporosis and unknown indications. The mean and median ages for these patients were 77 and 79 years. There was no clear support for a causal relationship in these cases, other than the diagnosis of lung cancer during treatment with calcitonin. Lung carcinoma is observed in people with similar demographics and risk factors include smoking/second hand smoking, exposures to radon or asbestos, radiation therapy and family history of lung cancer.

Thyroid neoplasm cases in osteoporosis and 'unknown" indications

There were 5 cases reporting thyroid neoplasms in the osteoporosis and unknown indication. The mean and median ages for these patients were 67 and 65 years. There was no clear support for a causal relationship in these cases, other than the diagnosis of thyroid nodules during the calcitonin therapy. For unclear reasons thyroid cancers, like almost all diseases of the thyroid, occur about three times more often in women than in men. Risk factors include a diet low in iodine, radiation, and hereditary conditions, and family history.

7.2.4.4 Conclusion on post-marketing cases

The pattern of distribution of malignancies in the post-marketing analysis, regardless of malignancy type and causality, is consistent with what would be expected in a population with similar demographics. During the standard periodical pharmacovigilance monitoring, the frequency of spontaneously reported malignancy cases has remained stable and very low (less than 1 case per 100,000 PY of exposure). The risk of developing malignancies during calcitonin therapy is continuously monitored through routine pharmacovigilance activities.

7.2.5 Background on epidemiology of malignancy incidence in the PMO population

Data from National Cancer Institute's Surveillance and Epidemiological End Results websites for the years 1992-2009 show that the incidence of cancer is about 15-fold higher in those over 50, compared to people under 50, across all racial and ethnic groups (data for both sexes are shown). For women alone, the difference in incidence is about 10-fold and for men alone, the difference in incidence is over 20-fold (source: http://seer.cancer.gov). Therefore, the population most likely to use Miacalcin® is also the population in which cancers are most likely to occur and also to be fatal.

This is particularly important when considering that across all of the Miacalcin studies there were only 7 fatal cases of cancer, in a population where similar or higher rates might be expected.

Figure 7-17 Malignancy background rates < 50 years of age from SEER

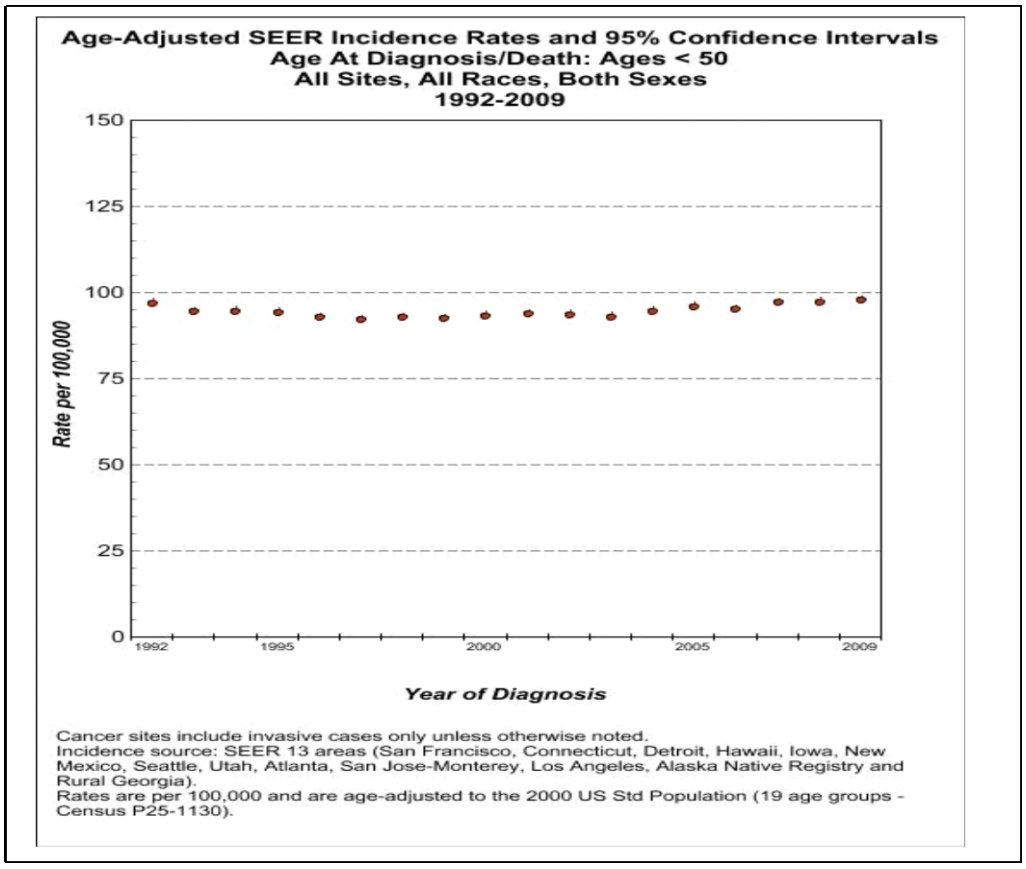
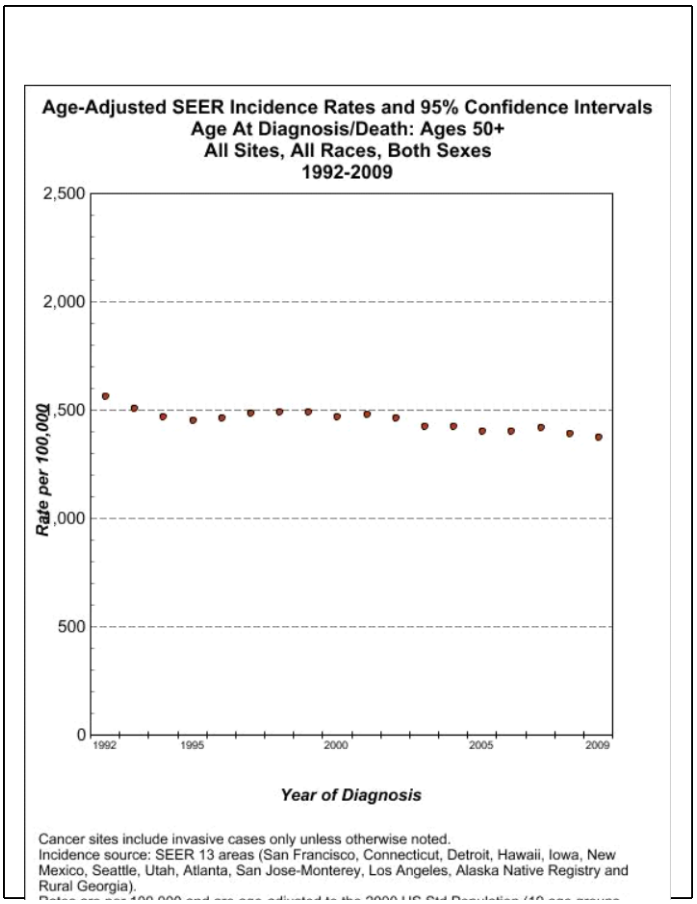


Figure 7-18 Malignancy background rates >= 50 years of age from SEER



(Data from http://seer.cancer.gov/faststats/selections.php?#Output; accessed 12/30/2012)

The age-adjusted incidence rate of overall cancer in the US population of women of 50 years of age and older was 1190.7 per 100,000 women per year (95% CI 1,188.6-1,192.9), the age-specific rates show rapid increase with age (Table 7-37).

In the same period, the incidence rates of specific cancer sites in women 50 years and older were as follow: breast cancer 356.7 per 100,000 women per year (95% CI 355.5-357.9), colon cancer 111.1 per 100,000 women per year (95% CI 110.4-111.7), ovary cancer 38.8 per 100,000 women per year (95% CI 38.4-39.2), pancreatic cancer 35.1 per 100,000 women per year (95% CI 34.7-35.5), and thyroid 19.3 per 100,000 women per year (95% CI 19.1-19.6).

Table 7-37 Incidence rates of overall cancer (excluding non-melanoma skin cancer) in US population of women aged 50 years and older, 1992-2009

Age	Incidence rate per 100,000 women/year*	95% Confidence Interval	
45-49 years	415.8	413.3	418.3
50-54 years	582.2	578.9	585.4
55-59 years	792.7	788.5	796.9
60-64 years	1,056.5	1,051.1	1,061.9
65-69 years	1,359.7	1,353.1	1,366.4
70-74 years	1,631.3	1,623.6	1,638.9
75-79 years	1,850.8	1,842.0	1,859.6
80-84 years	1,980.6	1,970.2	1,991.0
≥85 years	1,897.4	1,887.1	1,907.7
Overall ≥50 years	1,190.7	1,188.6	1,192.9

*Rates are per 100000 and age-adjusted to the 2000 US Std Population (single ages to 84 - Census P25-1130) standard. Rates exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Research Data, Nov 2011 Sub, Vintage 2009 Pops (1992-2009) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012, based on the November 2011 submission.

Direct comparison of incidence rates of malignancies observed in calcitonin trials with that reported from population-based cancer registries poses some challenges when, differences in age and sex distribution are not taken into account. Indirect standardization was used to compare the observed number of malignancies (excluding non-melanoma skin cancer) with that in a reference population. Age-sex-specific incidence rates in the US population obtained from SEER Program for the period 1992-2009 were used as reference and applied to the age-specific person-years of follow-up of the study population. This allows to estimate the expected number of malignancies (excluding non-melanoma skin cancers) in the study population had the patients been diagnosed at the same age-specific rate as individuals in the reference population (Table 7-38).

Table 7-38 Expected number of malignancies (excluding non-melanoma skin cancer) in studies included in the meta-analysis

Studies included in Meta-analysis					SEER 1992-2009	Expected
Study	Group	Age range	Sex	P-Y	IR per 100,000[a]	Malignancies
2402	nSCT	59-85+	F	64.7	1515.31	0.9804
	PBO	60-85+	F	60.1	1547.92	0.9303
CT211	nSCT	52-75	F	57.1	1071.41	0.6118
	PBO	53-74	F	25.4	1083.31	0.2752
CT310	nSCT	41-69	F	354.2	661.75	2.3439
	PBO	41-62	F	113.8	546.98	0.6225
CT311	nSCT	33-85+	M/F	374.3	810.40	3.0333
	PBO	29-84	M/F	133.2	690.23	0.9194
CT312	nSCT	32-85+	M/F	321.3	788.66	2.5340
	PBO	37-85+	M/F	160.6	910.74	1.4626
CT320	nSCT	44-85+	F	3260.4	1014.14	33.0649
PROOF	PBO	48-85+	F	1050.3	1137.78	11.9501
MIA16	nSCT	60-85+	F	64[b]	1547.92	0.9907
	PBO	60-85+	F	60[b]	1547.92	0.9288
SMCO005	nSCT	51-75	F	23.9	1039.95	0.2485
	PBO	56-75	F	8.2	1206.91	0.0990
SMCO503	nSCT	40-59	F	48.8	483.63	0.2360
	PBO	40-59	F	46.4	483.63	0.2244
SMCO504	nSCT	40-69	F	44.3	640.91	0.2839
	PBO	40-59	F	48.8	483.63	0.2360
SMCO506	nSCT	30-69	F	373	470.91	1.7565
	PBO	30-69	F	372.3	470.91	1.7532
SMCO511	nSCT	40-59	F	189.6	483.63	0.9170
	PBO	30-59	F	183.5	343.14	0.6297
SMCO514	nSCT	48-64	F	135.9	728.39	0.9899
	PBO	48-64	F	85.9	728.39	0.6257
SMCO517	nSCT	38-61	F	290.6	471.12	1.3691
	PBO	37-60	F	145.8	441.35	0.6435
SMCO520	nSCT	40-69	F	107	640.91	0.6858
	PBO	40-69	F	55	640.91	0.3525
SMCO522	nSCT	68-72	F	265.5	1523.79	4.0457
	PBO	68-72	F	86.2	1523.79	1.3135
SMCO524	nSCT	47-56	F	185	561.88	1.0395
	PBO	47-56	F	62	561.88	0.3484
QUEST	nSCT	50-85+[c]	F	82.3	1203.41	0.9904
	PBO	50-85+[c]	F	75.1	1008.50	0.7574
A2303	oSCT	55-85+	F	5250.3	1376.88	72.2906

	PBO	50-85+	F	5660.7	1203.41	68.1216
C2301	oSCT	50-80	M/F	872.1	1306.70	11.3958
	PBO	50-79	M/F	983	1287.84	12.6595
C2302	oSCT	51-80	M/F	769.9	1357.16	10.4488
	PBO	51-80	M/F	818.8	1357.16	11.1125

SCT: salmon calcitonin; PBO: placebo; nSCT: nasal salmon calcitonin; oSCT: oral salmon calcitonin; F: female, M: male; P-Y: patient-years; SEER: Surveillance Epidemiology and End Results

a Rates exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Rates are per 100000 and age-adjusted to the 2000 US Standard Population (single ages to 84 - Census P25-1130). Source: Surveillance Epidemiology and End Results (SEER) Program (www,seer,cancer,gov) SEER*Stat Database: Incidence - SEER 13 Regs Research Data Nov 2011 Sub Vintage 2009 Pops (1992-2009) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U,S, 1969-2010 Counties National Cancer Institute DCCPS Surveillance Research Program Surveillance Systems Branch released April 2012 based on the November 2011 submission

b P-Y estimated based on number of patients in study group and study duration

The Standardized Incidence Ratio (SIR), namely the ratio of the observed number of malignancies in the study population over the number of cases expected after standardization, was calculated for the treated patients and for patients on placebo. Ninety five percent confidence intervals for the SIRs were calculated assuming a Poisson distribution with the Mid-P method (Kulkami, Tripathi, Michalek 1998).

SEER incidence rates of malignancies used to estimate the expected number of malignancies do not include non-melanoma skin cancers and only include primary incident malignancies. In order to calculate the SIR, cases of basal cell and squamous cell carcinomas of the skin, as well as those cases identified from the available case narratives as recurrent malignancies, were excluded from the total count of observed malignancies. Overall, 97 non-melanoma skin cancers, 69 in the treatment and 28 in the placebo groups, were excluded. Skin cancers of unspecified type, 3 in the treatment and 2 in the placebo groups, were not excluded. Four cases of recurrent malignancy, 2 in treatment and 2 placebo groups, were also excluded.

Overall, the estimated number of expected malignancies (excluding non-melanoma skin cancer) in all calcitonin patients was 150 (vs. 183 observed) and in placebo group 116 (vs. 117). The corresponding SIRs show that compared to a reference general population of similar age and sex the incidence of malignancies (excluding non-melanoma skin cancer) was higher for calcitonin (SIR=1.22, 95% CI 1.05-1.41) and similar for placebo group (SIR=1.01, 95% CI 0.84-1.2220) (Table 7-39).

Table 7-39 SIRs based on number of observed malignancies excluding BCC, SCC, and recurrent/second malignancy*

	Malignancies				
	Observed	Expected	SIR	95% CI**	
All SCT	183	150	1.22	1.05	1.41
nSCT	77	56	1.38	1.09	1.71
oSCT	106	94	1.13	0.93	1.36
PBO	117	116	1.01	0.84	1.20

*Source documents used [Data on file]:

SCT: salmon calcitonin; PBO: placebo; nSCT: nasal salmon calcitonin; oSCT: oral salmon calcitonin; NMSC: non-melanoma skin cancer; SIR: standardized incidence ratio; CI: confidence interval

**Mid-P exact CI.

There are some limitations that have to be considered when interpreting these results. First, the incidence rates used as reference are from the US population, which may differ from that of other countries from where the clinical trial population originated. Second, the data used in this analysis was obtained from clinical study reports, therefore lacks the detail (e.g. person-time distribution by age and sex) desired to perform a robust SIR analysis. Finally, the identification of non-melanoma skin cancers and non-incident or recurrent malignancies was possible as far as documented in the clinical study reports.

Non-melanoma skin cancers are the most frequent cutaneous cancers, the incidence of these types of skin cancer show high geographic variability, and a steady increase in the last decades (Hayes et al 2007; Holme, Malinovszky and Roberts 2000; Karagas et al 1999; Birch-Johansen et al 2010). Patients with non-melanoma skin cancer are at increased risk to develop new primary cancer (Wassberger et al 1999, Frisch et al 1996, Hemminki and Dong 2000, Friedman and Tekawa 2000, Efird et al 2002). Further, the risk of developing a subsequent skin cancer after a prior non-melanoma skin cancer is high, for basal cell carcinoma it is estimated a 10-fold increased risk after 3 years of first tumor compared with the rate in a comparable general population (Marcil and Stern 2000).

The systematic collection of data on non-melanoma skin cancers in the population is challenging and few cancer registries register these types of cancers. Crude age-specific incidence rates of basal cell carcinoma in women in postmenopausal age reported in some publications show a rapid increase with age (Table 7-40).

Table 7-40 Age-specific crude incidence rates of basal cell carcinoma in women aged 45 years or older from different geographic areas

Reference	Population Period	Age	Incidence rate per 100,000 persons per year
Chuang et al (1990)	Rochester, Minn, USA 1976-1984	45-54 years	165.8
		55-64 years	279.6
		65-74 years	430.8
		75-84 years	598.7
		≥85 years	927.8
Karagas et al (1999)	New Hampshire, USA 1993-1994	45-54 years	244.6
		55-64 years	388.5
		65-74 years	729.0
		≥75 years	1,090.8
Holme et al (2000)	South Wales (UK) 1998	45-49 years	145.3
		50-54 years	235.7
		55-59 years	379.9
		60-64 years	205.2
		65-69 years	575.7
		70-74 years	565.1
		75-79 years	910.9
		80-84	730.0
		≥85 years	785.4
Staples et al (2006)	Australia 2002	40-49 years	1,316
		50-59 years	2,067
		60-69 years	2,510
		≥70 years	3,880
Bath-Hextall et al (2007)	The Health Improvement Network database, UK 1996-2003	45-49 years	66
		50-54 years	113
		55-59 years	167
		60-64 years	178
		65-69 years	292
		70-74 years	355
		75-79 years	441
		≥80 years	491
De Vries et al (2012)	Finish Cancer Registry, Finland, 2009	45-69 years	162
		≥70 years	591
	Maltese Cancer Registry, Malta, 2009	45-69 years	129
		≥70 years	321
	Eindhoven Cancer Registry, The Netherlands, 2009	45-69 years	310
		≥70 years	665
	Scottish Cancer Registry, Scotland, 2006	45-69 years	157
		≥70 years	468

The crude incidence rate of basal cell carcinoma among all SCT patients in the clinical trials included in the meta-analysis was 59 cases in 1313.4 person-years of follow-up or 449.2 cases per 100,000 person-years (95% CI 345.1-575.4), among all SCT patients and 17 cases in

10,235.1 person-years of follow-up or 166.1 cases per 100,000 person-years (95% CI 100.0-260.5) in placebo group. These incidences appear to be within the limits of rates reported in general population considering that the study population was mostly female patients with a mean age in the range of 45 to 70 years.

Concerning deaths due to malignancy these were reported for 14 patients from 7 of the 21 studies in the meta-analysis, 12 in SCT treatment patients and 2 in placebo group, which corresponds to a mortality rate 190 per 100,000 and 43 per 100,000, respectively. Although the numbers are small and subject to high variability, the cancer death rates would be within the range of death rates for cancer reported in general population (Siegel 2013).

Conclusion

The epidemiological analysis showed that the overall observed incidence of malignancies (excluding non-melanoma skin cancers) in SCT treated patients was higher than would have been expected based on general population incidence rates. The difference between observed and expected was small and marginally significant. Among placebo patients the observed incidence was within the expected in the reference population.

The estimated incidence of basal cell carcinoma in the calcitonin treatment group appears to be within the range of rates reported in general population.

7.2.6 Literature with respect to malignancy risk.

In a late breaker abstract submitted to American Society for Bone and Mineral Research (ASBMR) annual meeting in 2012, the ORACAL trial (Phase 3 global) and TAR01-201 (Phase 2 US) trials of oral rSCT were reviewed with regard to malignancy events (Krause, et al 2012). Treatment duration was approximately 1 year. Subjects randomized to oral rSCT received the same dose, 200 µg (1200 IU) per day in these trials; this dose of rSCT (200 µg) was approximately 6 fold greater than present in nasal SCT formulations (33 µg). Neither trial specifically excluded individuals with cancer, but the presence of uncontrolled acute or chronic medical conditions was exclusionary. Subjects were seen at the clinical site 4 times after randomization in ORACAL and 5 times after randomization in 201. At each visit, as well as during regularly scheduled intervening phone calls, adverse events (AEs) were solicited and recorded. The safety databases from the two studies were integrated and AEs in the "Neoplasms benign, malignant and unspecified" system organ class were reviewed for AEs consistent with cancer. RESULTS: 678 women constitute the safety population. The mean age was approximately 67y, >95% of subjects were White. Adverse events consistent with cancer are displayed in the table. There was no malignancy event in the nasal SCT group, no increased risk in the oral SCT population compared with placebo and no deaths occurred.

Overall duration of exposure in these trials was about 1 year and there was no imbalance in the numbers of incident malignancies reported through adverse events (Table 7-41). The table below includes 1 case of basal cell carcinoma in the placebo group that was included on the poster (Appendix 9) presentation at the ASBMR meeting in 2012 but not in the abstract (the information was confirmed by Tarsa Therapeutics, via inter-company communication).

Table 7-41 Malignancies in ORACAL trials

	Oral rsCT N= 349	NsSCT N= 182	Placebo N= 147
Breast cancer	2	0	1
Skin cancer (unspecified)	0	0	1
Melanoma	1	0	0
Basal cell carcinoma	0	0	1
Thyroid cancer	1	0	1
Total (%)	4 (1.1)	0 (0.0)	4 (2.7)

7.2.7 Safety conclusions

Conclusions with respect to malignancy risk

Novartis post-marketing safety database gives no indication of increased incidence of malignancy. In the nonclinical toxicity studies, no genotoxic potential was found by the accepted tests (Ames assay, etc.). In 104-week carcinogenicity studies conducted in rats and mice, no evidence of treatment-related prostate hyperplasia or neoplasia was found and there was no evidence for effects on tumor progression or invasiveness. There was an increased incidence of pituitary adenoma in male rats that was considered rat-specific and not relevant to human safety.

Based on meta-analysis performed across all available controlled clinical trials conducted with nasal spray calcitonin, there is a 54% greater likelihood of a subject experiencing a malignancy when treated with nasal spray calcitonin. Based on increase incidence of malignancy for nasal spray calcitonin vs. placebo one would need to treat 46 patients before the harm of a potential malignancy is observed. The increased likelihood of a malignancy is also observed for basal carcinomas and for all malignancies excluding basal cell carcinomas. If exposure is limited to 12 months, one would need to treat approximately 91 subjects before the harm of a potential malignancy is observed.

Despite the increased risk of malignancy found in the meta-analysis, the increased incidence of malignancy does not appear to be associated with the dose administered as all doses studied in the PROOF trial had similar malignancy incidence rates.

The observed difference relative to placebo which begins to appear from 12 months onward can possibly be attributed to the multi-fold decrease in the malignancy event rate for placebo-treated patients between Month 12 and Month 36 while the rate by time period for calcitonin remained relatively constant. The lack of dose response and the absence of increased incidence over time do not seem consistent with a causal association between treatment with calcitonin and malignancy.

The overall mortality rates are similar for those on calcitonin vs. those on placebo.

Although the meta-analysis is clearly limited by several factors, most notably the fact that incident cases are not confirmed by adjudication, Novartis believes that revisions in treatment recommendations are warranted and they are discussed further in the overall discussion of benefit risk in Section 8.

7.3 General safety aspects of anti-osteoporotic treatment

Table 7-42 presents an overview of the safety aspects for currently approved products by drug class.

7.3.1 Treatment options

Cadarette et al 2008 reviewed the relative efficacies of approved drugs for osteoporosis and concluded no single therapy was superior for this disease. This highlights the continued need for a broad array of treatment options for PMO, Paget's disease, and hypercalcemia associated with cancer to satisfy the patient population needs. Since the PMO population will grow as the US population ages, it is important to keep many effective treatment options available for future patients.

These available treatment options described in the guidelines have safety limitations that are included in their respective prescribing information and further exemplified in Section 8.1.

Table 7-42 Overview of safety concerns by drug class

Bisphosphonates	Oral bisphosphonates may cause upper GI disorders such as dysphagia, esophagitis, and esophageal and gastric ulcer, All bisphosphonates carry precautions on hypocalcemia and renal impairment. Patients who receive IV ibandronate or zoledronic acid should have serum creatinine measured before administration of each dose. A concern exists regarding possible over-suppression of bone turnover with long-term bisphosphonate therapy, resulting in a more brittle skeleton. - unusual, poorly healing fractures of the subtrochanteric femur region - osteonecrosis of the jaw (AFF and ONJ)
Selective estrogen-receptor modulators	A significant increase in venous thromboembolic (VTE) events was noted in the MORE trial. Grady 2004 However, a secondary analysis of the MORE trial data (Barrett-Connor et al 2002) found no overall significant differences in the number of coronary or cerebrovascular events between placebo and raloxifene. Raloxifene therapy may be associated with an increase in vasomotor symptoms and leg cramps. Ettinger et al (1999), Grady et al (2004) Bone loss often resumes when raloxifene therapy is stopped. Neele et al (2002), Siris et al (2005)
PTH Teriparatide (recombinant human PTH 1-34), marketed as Forteo,	In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures to teriparatide ranging from 3 to 60 times the exposure in humans given a 20-mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, prescribe FORTEO® only for patients for whom the potential benefits are considered to outweigh the potential risk. FORTEO should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult patients with open epiphyses, or prior external beam or implant radiation therapy involving the skeleton) [see Warnings and Precautions (5.1), Adverse Reactions (6.2), and Nonclinical Toxicology (13.1)]. Forteo Package Insert, December 2012. Drug-related adverse effects include muscle cramps and infrequent hypercalcemia, nausea, and dizziness. Teriparatide should not be administered to postmenopausal women with hypercalcemia, bone metastases, disorders that predispose them to bone tumors such as Paget's disease, or those who received prior skeletal irradiation. PTH is indicated for no longer than 24 months in the United States and for no longer than 18 months in Canada. When PTH therapy has been stopped, substantial bone loss has occurred within the first year. Black et al (2005)
Systemic estrogen (ET) or estrogen plus progestogen (EPT)	The optimal time to initiate ET/EPT and the optimal duration of therapy have not been established, but ET/EPT is largely utilized in the early years after menopause. The primary indication for systemic ET/EPT is for women experiencing moderate to severe menopause symptoms (e.g., vasomotor symptoms, vaginal atrophy). Approved in the United States and Canada for prevention, but not treatment, of PMO. For postmenopausal women ages 65 to 79 followed for a mean of 4.0 years, the Women's Health Initiative Memory Study Shumaker et al (2003) found a statistically significant increase in probable dementia for those who were receiving EPT. After a mean follow-up of 5.2 years, there was a nonsignificant

	trend for increased probable dementia among women allocated to ET alone. NAMS recommends use of ET/EPT at the lowest effective dose consistent with treatment goals. (The North American Menopause Society 2008). Lower doses of ET/EPT than used in the WHI, however, have not been examined with regard to fracture efficacy.
Denosumab	Serious infections, Pre-existing hypocalcemia, Over-suppression of bone turnover with long-term therapy, resulting in a more brittle skeleton with unusual, poorly healing fractures of the subtrochanteric femur region or osteonecrosis of the jaw (AFF and ONJ) Effect of denosumab is rapidly reversible on cessation of therapy (Brown et al 2012)

8 Benefit/risk assessment for treatment of osteoporosis

8.1 Medical need and Alternative Therapies

The PMO population is large and growing (due to better health care and longer life expectations), and often has multiple co-morbid conditions. There is a medical need for a variety of alternative therapies to serve this diverse population. Potent anti-resorptive drugs, such as bisphosphonates and denosumab have potential safety concerns associated with long-term use and can therefore generally be used only for a portion of the expected patient lifespan.

As summarized in the current (American College of Obstetrics and Gynecology guidelines 2012), the following adverse events and contraindications need to be considered in making an informed choice in the care of patients with PMO:

Bisphosphonates

Adverse events with bisphosphonates include musculoskeletal aches and pains, gastrointestinal irritation, and esophageal ulceration. Potential risks reported after marketing include osteonecrosis of the jaw, seizures, atypical fractures of the femoral shaft, and esophageal cancer. A precise understanding of the true risk of these events has been difficult to determine because of the lack of data on the incidence of these problems in the general population. Although rare cases of osteonecrosis of the jaw have been reported in patients using bisphosphonates for osteoporosis, it has been seen most commonly after dental extractions in those being treated with large intravenous doses of bisphosphonates in association with supportive cancer therapy. There is no requirement to discontinue bisphosphonates for dental procedures. However, temporarily discontinuing bisphosphonate therapy for a dental procedure should be considered, given the long duration of action of bisphosphonates.

Zoledronic acid is contraindicated in patients with acute renal failure or creatinine clearance of less than or equal to 35 mL/min. Patients should be screened for renal disease before zoledronic acid infusion because renal failure has occurred after infusion in patients with compromised renal function. Caution with regard to renal function should be exercised with other drugs in this class as noted in the product information sheets. Hypocalcemia should be corrected before the use of these drugs.

An advisory panel to the U.S. Food and Drug Administration reviewed the issue of treatment interruption (drug holidays) and duration of therapy and recommended that labeling should be more specific with regard to duration of use. Based on the review of data across the class of bisphosphonates it was recommended that treatment be limited to 3-5 years based on the risk of individual patient (Whitaker et al 2012).

Partial estrogen agonists and antagonists

Adverse effects of raloxifene include venous thromboembolism, leg cramps, and death from stroke (not increased risk of stroke). A medical history of stroke should be carefully weighed when considering use of this drug. Women close to menopause may experience vasomotor symptoms for a while after initiating therapy.

PTH Teriparatide

Teriparatide should not be administered to postmenopausal women with hypercalcemia, bone metastases, disorders that predispose them to bone tumors such as Paget's disease, or those who received prior skeletal irradiation. PTH is indicated for no longer than 24 months in the United States and for no longer than 18 months in Canada.

Denosumab

A higher rate of infections that required hospitalization was seen in the clinical trials. However, concerns about suppression of the immune system leading to increased rates of cancer were not substantiated.

Osteonecrosis of the jaw and atypical fractures have also been associated with denosumab therapy (Appendix 7, Prolia Prescribing Information).

Calcitonin

Adverse effects include flushing and nausea with subcutaneous injection and local irritation with nasal spray. Calcitonin has no identified safety issues with regard to potential complications of bone turnover (atypical fractures and ONJ), renal insufficiency or failure, cardiovascular or cerebrovascular events, or immunological suppression and can bridge periods of medical need when other treatment options are not suitable.

8.2 Benefit/risk Conclusions

Several pharmacologic options are available for osteoporosis therapy; no studies have prospectively compared these therapies for anti-fracture efficacy or safety in a statistically well powered study. (Cadarette et al 2008) reviewed these retrospectively and concluded no single treatment for PMO is superior. Alternatives to SCT all have limitations with regard to underlying diseases or specific adverse events, as indicated above; suggesting that a broad array of appropriately labeled products is needed to fulfill the medical needs of the spectrum of patients with postmenopausal osteoporosis.

Novartis concurs that a potential for increased risk of malignancy should be taken seriously. However, with respect to the use of calcitonin in PMO, the strength of the signal and unclear plausibility of the finding needs to be weighed against the benefit in patients who are unable

or refuse to use other treatment options. Part of this evaluation should include a consideration as to whether adequate labeling can be developed to inform physicians and patients of the possible risks and guide appropriate use.

Miacalcin has established anti-fracture efficacy in the PMO population based on the 36% reduction in the risk of vertebral fractures with the 200 IU dose relative to placebo over 3 years. This corresponds to a number needed to treat of 13. In addition, 37% reduction in non-vertebral fractures with number needed to treat of 36 puts SCT in line with the other approved PMO treatment options. This can be combined with supporting evidence of rapid onset of favorable effects on the skeleton based on changes in bone biomarkers and increases in BMD.

There is a continued clinical need for Miacalcin treatment, for at least short-term use, in patients at high risk of fracture for whom other treatment options are contraindicated, not suitable, or not tolerated.

This might include patients with high risk of osteoporotic fractures and:

- Immunosuppression due to HIV/organ transplant/IL-1 inhibitor or TNF-alpha inhibitor treatment
- Requiring dental surgery who may be at risk for osteonecrosis of the jaw
- Suffering from renal impairment or failure
- Refusing other approved therapies (e.g. refusal of estrogen therapy by a postmenopausal woman or refusal to comply with dosing instructions for oral bisphosphonates

Physicians should be allowed to perform an individual benefit-risk assessment in making a decision to prescribe Miacalcin, taking into account the specific patient's fracture risk and potential for experiencing adverse events.

Novartis is committed to ensuring that appropriate patients can safely benefit from the use of Miacalcin in PMO and supports prescribing information changes to highlight the possible risk of malignancy. These changes include

- A summary of the meta-analysis findings,
- Recommendations for limiting use to patients who cannot tolerate other options,
- Recommendations for use for the shortest duration possible as a bridge to, or from, other treatment options.

Other options for ensuring safe use, such as a Medication Guide, may also be of benefit.

Novartis welcomes discussion and input from the Committee regarding options to further enhance the safe use of Miacalcin and looks forward to working with the FDA to communicate possible risk while maintaining PMO treatment choices.

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10 Appendices

Appendix 1 US PI insert for Miacalcin® Injectable dated July 2012

Appendix 2 US PI insert for Miacalcin® Nasal Spray dated July 2012

Appendix 3 Epidemiological Assessment of Non-Melanoma Skin Cancer Cases in the Clinical Trial Nº 320 (Miacalcin® Salmon Calcitonin). Miret M, Gutierrez LP, Perez-Gutthann S (1998)

Appendix 4 Epidemiological Assessment of Breast Cancer Cases in the Clinical Trial Nº 320 (Miacalcin® Salmon Calcitonin). Gutierrez LP, Miret M (1998)

Appendix 5 Meta-analysis tests for heterogeneity

Appendix 6 Forest plots of meta-analysis results for Miacalcin® malignancy risk

Appendix 7 Prolia (Denosumab) Prescribing Information

Appendix 8 Type of malignancies reported in the nSCT and oSCT clinical trial included in the meta-analysis

Appendix 9 Tarsa Malignancy poster

Appendix 1

Appendix 1 US PI insert for Miacalcin® Injectable dated July 2012

NOVARTIS

Miacalcin®

(calcitonin-salmon)

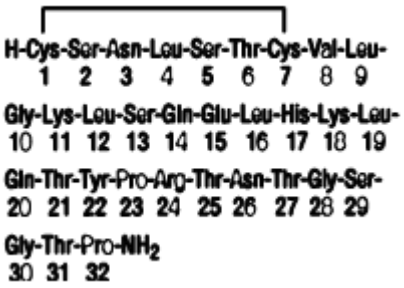
Injection, Synthetic

Rx only

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

Miacalcin® (calcitonin-salmon) Injection, Synthetic is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in sterile solution for subcutaneous or intramuscular injection. Each milliliter contains: calcitonin-salmon 200 I.U., acetic acid, USP, 2.25 mg; phenol, USP, 5.0 mg; sodium acetate trihydrate, USP, 2.0 mg; sodium chloride, USP, 7.5 mg; water for injection, USP, qs to 1.0 mL.

The activity of Miacalcin Injection is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute for Biological Standards and Control, Holly Hill, London.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action. The actions of calcitonin on bone and its role in normal human bone physiology are still incompletely understood.

Bone: Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of

bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. Decreased osteocytic resorption may also be involved. There is some evidence that initially bone formation may be augmented by calcitonin through increased osteoblastic activity. However, calcitonin will probably not induce a long-term increase in bone formation.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. This reduces the transfer of calcium from bone to blood and tends to return blood calcium to the normal level. The importance of this process in humans has not been determined. In normal adults, who have a relatively low rate of bone resorption, the administration of exogenous calcitonin results in only a slight decrease in serum calcium. In normal children and in patients with generalized Paget's disease, bone resorption is more rapid and decreases in serum calcium are more pronounced in response to calcitonin.

Paget's Disease of Bone (osteitis deformans): Paget's disease is a disorder of uncertain etiology characterized by abnormal and accelerated bone formation and resorption in one or more bones. In most patients, only small areas of bone are involved and the disease is not symptomatic. In a small fraction of patients, however, the abnormal bone may lead to bone pain and bone deformity, cranial and spinal nerve entrapment, or spinal cord compression. The increased vascularity of the abnormal bone may lead to high output congestive heart failure.

Active Paget's disease involving a large mass of bone may increase the urinary hydroxyproline excretion (reflecting breakdown of collagen-containing bone matrix) and serum alkaline phosphatase (reflecting increased bone formation).

Calcitonin-salmon, presumably by an initial blocking effect on bone resorption, causes a decreased rate of bone turnover with a resultant fall in the serum alkaline phosphatase and urinary hydroxyproline excretion in approximately 2/3 of patients treated. These biochemical changes appear to correspond to changes toward more normal bone, as evidenced by a small number of documented examples of: 1) radiologic regression of Pagetic lesions, 2) improvement of impaired auditory nerve and other neurologic function, 3) decreases (measured) in abnormally elevated cardiac output. These improvements occur extremely rarely, if ever, spontaneously (elevated cardiac output may disappear over a period of years when the disease slowly enters a sclerotic phase; in the cases treated with calcitonin, however, the decreases were seen in less than one year.)

Some patients with Paget's disease, who have good biochemical and/or symptomatic responses initially, later relapse. Suggested explanations have included the formation of neutralizing antibodies and the development of secondary hyperparathyroidism, but neither suggestion appears to explain adequately the majority of relapses.

Although the parathyroid hormone levels do appear to rise transiently during each hypocalcemic response to calcitonin, most investigators have been unable to demonstrate persistent hypersecretion of parathyroid hormone in patients treated chronically with calcitonin-salmon.

Circulating antibodies to calcitonin after 2-18 months' treatment have been reported in about half of the patients with Paget's disease in whom antibody studies were done, but calcitonin treatment remained effective in many of these cases. Occasionally, patients with high antibody

titers are found. These patients usually will have suffered a biochemical relapse of Paget's disease and are unresponsive to the acute hypocalcemic effects of calcitonin.

Hypercalcemia: In clinical trials, calcitonin-salmon has been shown to lower the elevated serum calcium of patients with carcinoma (with or without demonstrated metastases), multiple myeloma, or primary hyperparathyroidism (lesser response). Patients with higher values for serum calcium tend to show greater reduction during calcitonin therapy. The decrease in calcium occurs about 2 hours after the first injection and lasts for about 6-8 hours. Calcitonin-salmon given every 12 hours maintained a calcium lowering effect for about 5-8 days, the time period evaluated for most patients during the clinical studies. The average reduction of 8-hour post-injection serum calcium during this period was about 9%.

Kidney: Calcitonin increases the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. In some patients, the inhibition of bone resorption by calcitonin is of such magnitude that the consequent reduction of filtered calcium load more than compensates for the decrease in tubular reabsorption of calcium. The result in these patients is a decrease rather than an increase in urinary calcium.

Transient increases in sodium and water excretion may occur after the initial injection of calcitonin. In most patients, these changes return to pretreatment levels with continued therapy.

Gastrointestinal Tract: Increasing evidence indicates that calcitonin has significant actions on the gastrointestinal tract. Short-term administration results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated.

Metabolism: Information from animal studies with calcitonin-salmon and from clinical studies with calcitonins of porcine and human origin ~~suggest~~suggests that calcitonin-salmon is rapidly metabolized by conversion to smaller inactive fragments, primarily in the kidneys, but also in the blood and peripheral tissues. A small amount of unchanged hormone and its inactive metabolites are excreted in the urine.

The absolute bioavailability of salmon calcitonin is approximately 66% and 71% after intramuscular (i.m.) or subcutaneous (s.c.) injection, respectively. After subcutaneous administration, peak plasma levels are reached in approximately 23 minutes. The terminal half-life is approximately 58 minutes for i.m. administration and 59-to 64 minutes for s.c. administration. The apparent volume of distribution is 0.15-0.3 L/kg.

It appears that calcitonin-salmon cannot cross the placental barrier and its passage to the cerebrospinal fluid or to breast milk has not been determined.

INDICATIONS AND USAGE

Miacalcin® (calcitonin-salmon) Injection, Synthetic is indicated for the treatment of symptomatic Paget's disease of bone, for the treatment of hypercalcemia, and for the treatment of postmenopausal osteoporosis.

Paget's Disease: Miacalcin Injection should be used only in patients who do not respond to alternative treatments or for whom such treatments are not suitable (e.g. patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other

therapies). At the present time, effectiveness has been demonstrated principally in patients with moderate to severe disease characterized by polyostotic involvement with elevated serum alkaline phosphatase and urinary hydroxyproline excretion.

In these patients, the biochemical abnormalities were substantially improved (more than 30% reduction) in about 2/3 of patients studied, and bone pain was improved in a similar fraction. A small number of documented instances of reversal of neurologic deficits have occurred, including improvement in the basilar compression syndrome, and improvement of spinal cord and spinal nerve lesions. At present, there is too little experience to predict the likelihood of improvement of any given neurologic lesion. Hearing loss, the most common neurologic lesion of Paget's disease, is improved infrequently (4 of 29 patients studied audiometrically).

Patients with increased cardiac output due to extensive Paget's disease have had measured decreases in cardiac output while receiving calcitonin. The number of treated patients in this category is still too small to predict how likely such a result will be.

The large majority of patients with localized, especially monostotic disease do not develop symptoms and most patients with mild symptoms can be managed with analgesics. There is no evidence that the prophylactic use of calcitonin is beneficial in asymptomatic patients, although treatment may be considered in exceptional circumstances in which there is extensive involvement of the skull or spinal cord with the possibility of irreversible neurologic damage. In these instances, treatment would be based on the demonstrated effect of calcitonin on Pagetic bone, rather than on clinical studies in the patient population in question.

Hypercalcemia: Miacalcin Injection is indicated for early treatment of hypercalcemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium is required, until more specific treatment of the underlying disease can be accomplished. It may also be added to existing therapeutic regimens for hypercalcemia such as intravenous fluids and furosemide, oral phosphate or corticosteroids, or other agents.

Postmenopausal Osteoporosis: Miacalcin Injection 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 Injection should be reserved for patients ~~who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated~~for whom alternative treatments are not suitable (e.g. patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies). Use of Miacalcin Injection is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass. No evidence currently exists to indicate whether or not Miacalcin Injection decreases the risk of vertebral crush fractures or spinal deformity. A recent controlled study, which was discontinued prior to completion because of questions regarding its design and implementation, failed to demonstrate any benefit of salmon calcitonin on fracture rate. No adequate controlled trials have examined the effect of salmon calcitonin injection on vertebral bone mineral density beyond 1 year of treatment. Two placebo-controlled studies with salmon calcitonin have shown an increase in total body calcium at 1 year, followed by a trend to decreasing total body calcium (still above baseline) at 2 years. The minimum effective dose of Miacalcin Injection for prevention of vertebral bone mineral density loss has not been established. It has been suggested that those postmenopausal patients having increased rates of bone turnover may be more likely to respond to anti-resorptive agents such as Miacalcin Injection.

CONTRAINDICATIONS

Clinical allergy to synthetic calcitonin-salmon.

WARNINGS

Allergic Reactions

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock), *including very rare reports* of death attributed to anaphylaxis. The usual provisions should be made for the emergency treatment of such a reaction should it occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of Miacalcin® (calcitonin-salmon) Injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

Malignancies

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 (see ADVERSE REACTIONS). 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, however, it cannot be excluded that an increased risk also applies when calcitonin is administered long-term subcutaneously, intramuscularly or intravenously. The benefits for the individual patient should be carefully evaluated against possible risks (see ADVERSE REACTIONS).

The incidence of osteogenic sarcoma is known to be increased in Paget's disease. Pagetic lesions, with or without therapy, may appear by X-ray to progress markedly, possibly with some loss of definition of periosteal margins. Such lesions should be evaluated carefully to differentiate these from osteogenic sarcoma.

PRECAUTIONS

Drug Interactions

Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

General

The administration of calcitonin possibly could lead to hypocalcemic tetany under special circumstances although no cases have yet been reported. Provisions for parenteral calcium administration should be available during the first several administrations of calcitonin.

Laboratory Tests

Periodic examinations of urine sediment of patients on chronic therapy are recommended.

Coarse granular casts and casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no other evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Urine sediment abnormalities have not been reported by other investigators.

Instructions for the Patient

Careful instruction in sterile injection technique should be given to the patient, and to other persons who may administer Miacalcin® (calcitonin-salmon) Injection, Synthetic.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

An increased incidence of pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley rats administered calcitonin-salmon at dosages of 20 and 80 I.U./kg/day and in Fisher 344 rats given 80 I.U./kg/day. The relevance of these findings to humans is unknown. Calcitonin-salmon was not mutagenic in tests using *Salmonella typhimurium, Escherichia coli,* and Chinese Hamster V79 cells. *In vivo* nonclinical safety data do not support an association of malignancies with calcitonin-salmon treatment and do not provide any evidence for tumor progression.

Pregnancy: Teratogenic Effects

Category C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given in doses 14-56 times the dose recommended for human use. Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Miacalcin Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

Pediatric Use

Disorders of bone in children referred to as juvenile Paget's disease have been reported rarely. The relationship of these disorders to adult Paget's disease has not been established and experience with the use of calcitonin in these disorders is very limited. There is no adequate data to support the use of Miacalcin Injection in children.

ADVERSE REACTIONS

Gastrointestinal System

Nausea with or without vomiting has been noted in about 10% of patients treated with calcitonin. It is most evident when treatment is first initiated and tends to decrease or disappear with continued administration.

Dermatologic/Hypersensitivity

Local inflammatory reactions at the site of subcutaneous or intramuscular injection have been reported in about 10% of patients. Flushing of face or hands occurred in about 2-5% of patients. Skin rashes, nocturia, pruritus of the ear lobes, feverish sensation, pain in the eyes, poor appetite, abdominal pain, edema of feet, and salty taste have been reported in patients treated with calcitonin-salmon. Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock), *including very rare reports* of death attributed to anaphylaxis. (see WARNINGS).

Malignancies

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 patients treated with placebo. A mechanism for this observation has not been identified (see WARNINGS).

In addition, the following adverse events were reported with Miacalcin Injection.

Body as a Whole – General Disorders: influenza-like symptoms, fatigue, edema (facial, peripheral, and generalized),

Musculoskeletal/Collagen: arthralgia, musculoskeletal pain

Cardiovascular: hypertension

Gastrointestinal: abdominal pain, diarrhea,

Immune System Disorders: hypersensitivity, anaphylactic and anaphylactoid reactions, anaphylactic shock

Urinary System: polyuria

Central and Peripheral Nervous System: dizziness, headache, tremor

Vision: visual disturbance

OVERDOSAGE

A dose of l000 I.U. subcutaneously may produce nausea and vomiting as the only adverse effects. Doses of 32 units per kg per day for 1-2 days demonstrate no other adverse effects.

Data on chronic high-dose administration are insufficient to judge toxicity.

DOSAGE AND ADMINISTRATION

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

Paget's Disease: The recommended starting dose of Miacalcin® (calcitonin-salmon) Injection, Synthetic in Paget's disease is 100 I.U. (0.5 mL) per day administered subcutaneously (preferred for outpatient self-administration) or intramuscularly. The duration of treatment depends on the therapeutic indication and the patient's response. Drug effect should be monitored by periodic measurement of serum alkaline phosphatase and 24-hour urinary hydroxyproline (if available) and evaluations of symptoms. A decrease toward normal of the biochemical abnormalities is usually seen, if it is going to occur, within the first few months. Bone pain may also decrease during that time. Improvement of neurologic lesions, when it occurs, requires a longer period of treatment, often more than one year. Therefore, the benefits and risks to each individual patient should be evaluated when considering long-term treatment of neurologic lesions.

In many patients, doses of 50 I.U. (0.25 mL) per day or every other day are sufficient to maintain biochemical and clinical improvement. At the present time, however, there are insufficient data to determine whether this reduced dose will have the same effect as the higher dose on forming more normal bone structure. It appears preferable, therefore, to maintain the higher dose in any patient with serious deformity or neurological involvement.

In any patient with a good response initially who later relapses, either clinically or biochemically, the possibility of antibody formation should be explored. The patient may be tested for antibodies by an appropriate specialized test or evaluated for the possibility of antibody formation by critical clinical evaluation.

Patient compliance should also be assessed in the event of relapse.

In patients who relapse, whether because of antibodies or for unexplained reasons, a dosage increase beyond 100 I.U. per day does not usually appear to elicit an improved response.

Hypercalcemia: The recommended starting dose of Miacalcin Injection in hypercalcemia is 4 I.U./kg body weight every 12 hours by subcutaneous or intramuscular injection. If the response to this dose is not satisfactory after one or two days, the dose may be increased to 8 I.U./kg every 12 hours. If the response remains unsatisfactory after two more days, the dose may be further increased to a maximum of 8 I.U./kg every 6 hours.

Postmenopausal Osteoporosis: The minimum effective dose of Miacalcin Injection for the prevention of vertebral bone mineral density loss has not been established. Data from a single one-year placebo-controlled study with salmon calcitonin injection suggested that 100 I.U. (subcutaneously or intramuscularly) every other day might be effective in preserving vertebral bone mineral density. Baseline and interval monitoring of biochemical markers of bone resorption/turnover (e.g., fasting AM, second-voided urine hydroxyproline to creatinine ratio) and of bone mineral density may be useful in achieving the minimum effective dose. Patients should also receive supplemental calcium such as calcium carbonate 1.5 g daily and an adequate vitamin D intake (400 units daily). An adequate diet is also essential.

If the volume of Miacalcin Injection to be injected exceeds 2 mL, intramuscular injection is preferable and multiple sites of injection should be used.

Miacalcin vials should be inspected visually. If the solution is not clear and colorless, or contains any particles, or if the vial is damaged, do not administer the solution.

HOW SUPPLIED

Miacalcin® (calcitonin-salmon) Injection, Synthetic is available as a sterile solution in individual 2 mL vials containing 200 I.U. per mL .....NDC 0078-0149-23

Store in refrigerator between 2°C- to 8°C (36°F- to 46°F).

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2012-~~106~~144
~~April 2012~~July 2012

Appendix 2

Appendix 2 US PI insert for Miacalcin® Nasal Spray dated July 2012

NOVARTIS

Miacalcin®

(calcitonin-salmon)

Nasal Spray

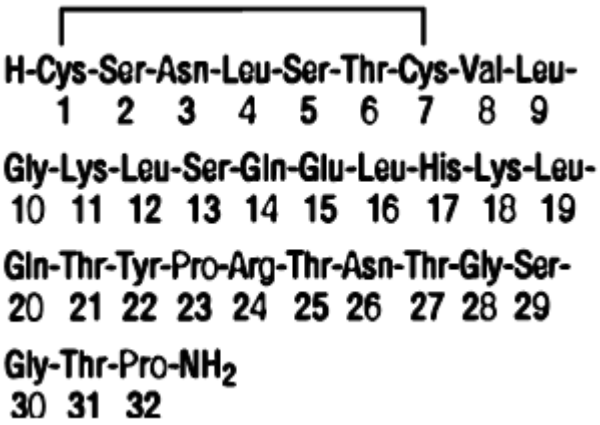
Rx only

Prescribing Information

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

Miacalcin® (calcitonin-salmon) Nasal Spray is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in a 3.7 mL fill glass bottle as a solution for nasal administration. This is sufficient medication for at least 30 doses.

Active Ingredient: calcitonin-salmon 2200 I.U. per mL (corresponding to 200 I.U. per 0.09 mL actuation).

Inactive Ingredients: sodium chloride, benzalkonium chloride, hydrochloric acid (added as necessary to adjust pH) and purified water.

The activity of Miacalcin Nasal Spray is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute of Biologic Standards and Control, Holly Hill, London.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action.

The information below, describing the clinical pharmacology of calcitonin, has been derived from studies with *injectable* calcitonin. The mean bioavailability of Miacalcin® (calcitonin-salmon) Nasal Spray is approximately 3% of that of injectable calcitonin in normal subjects and, therefore, the conclusions concerning the clinical pharmacology of this preparation may be different.

The actions of calcitonin on bone and its role in normal human bone physiology are still not completely elucidated, although calcitonin receptors have been discovered in osteoclasts and osteoblasts.

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. *In vitro* studies have shown that calcitonin-salmon causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of calcitonin-salmon from the test system. There is some evidence from the *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. This reduces the transfer of calcium from bone to blood and tends to return blood calcium towards the normal level. The importance of this process in humans has not been determined. In normal adults, who have a relatively low rate of bone resorption, the administration of exogenous calcitonin results in only a slight decrease in serum calcium in the limits of the normal range. In normal children and in patients with Paget's disease in whom bone resorption is more rapid, decreases in serum calcium are more pronounced in response to calcitonin.

Bone biopsy and radial bone mass studies at baseline and after 26 months of daily injectable calcitonin indicate that calcitonin therapy results in formation of normal bone.

Postmenopausal Osteoporosis

Osteoporosis is a disease characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk as patients approach or fall below a bone mineral density associated with increased frequency of fracture. The most common type of osteoporosis occurs in postmenopausal females. Osteoporosis is a result of a disproportionate rate of bone resorption compared to bone formation which disrupts the structural integrity of bone, rendering it more susceptible to fracture. The most common sites of these fractures are the vertebrae, hip, and distal forearm (Colles' fractures). Vertebral fractures occur with the highest frequency and are associated with back pain, spinal deformity and a loss of height.

Miacalcin Nasal Spray, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

Calcium Homeostasis

In two clinical studies designed to evaluate the pharmacodynamic response to Miacalcin Nasal Spray, administration of 100-1600 I.U. to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 I.U. did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal females.

Kidney

Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been carried out with Miacalcin Nasal Spray.

Gastrointestinal Tract

Some evidence from studies with injectable preparations ~~suggest~~ suggests that calcitonin may have significant actions on the gastrointestinal tract. Short-term administration of injectable calcitonin results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated. These studies have not been conducted with Miacalcin Nasal Spray.

Pharmacokinetics and Metabolism

The bioavailability of Miacalcin Nasal Spray relative to intramuscular administration is between 3 and 5%. Miacalcin Nasal Spray is absorbed by the nasal mucosa with a mean Tmax of about 13 minutes. The terminal half-life of calcitonin-salmon has been calculated to be around 18 minutes and no evidence of accumulation was observed with multiple dosing. Plasma exposure was higher following administration of 400 IU nasal spray compared to that after 200 IU dose. As is the case with other polypeptide hormones, there is very little value in monitoring plasma levels of salmon calcitonin since these are not directly predictive of the therapeutic response. Hence, Miacalcin activity should be evaluated by using clinical parameters of efficacy.

INDICATIONS AND USAGE

Postmenopausal Osteoporosis

Miacalcin® (calcitonin-salmon) Nasal Spray 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 Nasal Spray should be reserved for patients ~~who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated~~for whom alternative treatments are not suitable (e.g. patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies). Use of Miacalcin Nasal Spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per

day) and vitamin D (400 I.U. per day) intake to retard the progressive loss of bone mass. The evidence of efficacy is based on increases in spinal bone mineral density observed in clinical trials.

Two randomized, placebo-controlled trials were conducted in 325 postmenopausal females (227 Miacalcin Nasal Spray-treated and 98 placebo-treated) with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females. These studies conducted over two years demonstrated that 200 I.U. daily of Miacalcin Nasal Spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 years postmenopause. Miacalcin Nasal Spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as 6 months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of Miacalcin Nasal Spray on cortical bone of the forearm or hip were demonstrated. However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after 1 year of treatment changing to a trend at 2 years that was no longer statistically significant.

CONTRAINDICATIONS

Clinical allergy to calcitonin-salmon.

WARNINGS

Allergic Reactions

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. A few cases of serious allergic-type reactions have been reported in patients receiving Miacalcin® (calcitonin-salmon) Nasal Spray, including cases of anaphylaxis and anaphylactic shock.. With injectable calcitonin-salmon there have been a few reports of serious allergic-type reactions (e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock), including very rare reports of death attributed to anaphylaxis. The usual provisions should be made for the emergency treatment of such a reaction should it occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of Miacalcin® Injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

Malignancies

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 (see ADVERSE REACTIONS). 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 (see ADVERSE REACTIONS).

PRECAUTIONS

Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with Miacalcin® (calcitonin-salmon) Nasal Spray ingredients.

Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

The effects of prior use of diphosphonates in postmenopausal osteoporosis patients have not been assessed; however, in patients with Paget's disease, prior diphosphonate use appears to reduce the anti-resorptive response to Miacalcin Nasal Spray.

Periodic Nasal Examinations

Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended.

The development of mucosal alterations or transient nasal conditions occurred in up to 9% of patients who received Miacalcin Nasal Spray and in up to 12% of patients who received placebo nasal spray in studies in postmenopausal females. The majority of patients (approximately 90%) in whom nasal abnormalities were noted also reported nasally related complaints/symptoms as adverse events. Therefore, a nasal examination should be performed prior to start of treatment with nasal calcitonin and at any time nasal complaints occur.

In all postmenopausal patients treated with Miacalcin Nasal Spray, the most commonly reported nasal adverse events included rhinitis (12%), epistaxis (3.5%), and sinusitis (2.3%). Smoking was shown not to have any contributory effect on the occurrence of nasal adverse events. One patient (0.3%) treated with Miacalcin Nasal Spray who was receiving 400 I.U. daily developed a small nasal wound. In clinical trials in another disorder (Paget's disease), 2.8% of patients developed nasal ulcerations.

If severe ulceration of the nasal mucosa occurs, as indicated by ulcers greater than 1.5 mm in diameter or penetrating below the mucosa, or those associated with heavy bleeding, Miacalcin Nasal Spray should be discontinued. Although smaller ulcers often heal without withdrawal of Miacalcin Nasal Spray, medication should be discontinued temporarily until healing occurs.

Information for Patients

Careful instructions on pump assembly, priming of the pump, and nasal introduction of Miacalcin Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient. Patients should notify their physician if they develop significant nasal irritation.

Patients should be advised of the following:

- Store new, unassembled bottles in the refrigerator between 2℃-8°C (36℉-46°F).

- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.
- Store bottle in use at room temperature between 15°C-30°C (59°F-86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.
- See DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump for complete instructions on priming the pump and administering Miacalcin Nasal Spray.

You should keep track of the number of doses used from the bottle.

After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

An increased incidence of nonfunctioning pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 I.U. per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body surface area). The findings suggest that calcitonin-salmon reduced the latency period for development of pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process. *In vivo* nonclinical safety data do not support an association of malignancies with calcitonin-salmon treatment and do not provide any evidence for tumor progression.

Calcitonin-salmon was tested for mutagenicity using *Salmonella typhimurium* (5 strains) and *Escherichia coli* (2 strains), with and without rat liver metabolic activation, and found to be non-mutagenic. The drug was also not mutagenic in a chromosome aberration test in mammalian V79 cells of the Chinese Hamster *in vitro*.

Laboratory Tests

Urine sediment abnormalities have not been reported in ambulatory volunteers treated with Miacalcin Nasal Spray. Coarse granular casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given injectable calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Periodic examinations of urine sediment should be considered.

Pregnancy

Teratogenic Effects

Category C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by injection in doses 8-33 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area.

Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women with calcitonin-salmon. Miacalcin Nasal Spray is *not* indicated for use in pregnancy.

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

Pediatric Use

There are no data to support the use of Miacalcin Nasal Spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is very limited.

Geriatric Use

In one large multicenter, double-blind, randomized clinical study of Miacalcin Nasal Spray, 279 patients were less than 65 years old, while 467 patients were 65 to 74 years old and 196 patients were 75 and over. Compared to subjects less than 65 years old, the incidence of nasal adverse events (rhinitis, irritation, erythema, and excoriation) was higher in patients over the age of 65, particularly those over the age of 75. Most events were mild in intensity. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to Miacalcin® (calcitonin-salmon) Nasal Spray (N=341) and to placebo nasal spray (N=131) and reported in greater than 3% of Miacalcin Nasal Spray-treated patients are presented below in the following table. Most adverse reactions were mild to moderate in severity. Nasal adverse events were most common with 70% mild, 25% moderate, and 5% severe in nature (placebo rates were 71% mild, 27% moderate, and 2% severe).

Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically

Adverse Reaction	Miacalcin® (calcitonin-salmon) Nasal Spray N=341 % of Patients	Placebo N=131 % of Patients
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

†Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of nose.

Malignancies

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 patients treated with placebo. A mechanism for this observation has not been identified (see WARNINGS).

In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with Miacalcin Nasal Spray. Adverse events reported in 1%-3% of patients are identified with an asterisk (*). The remainder occurred in less than 1% of patients. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to Miacalcin Nasal Spray has not been established.

Body as a Whole – General Disorders: influenza-like symptoms*, fatigue*, edema (facial, peripheral, and generalized), fever

Integumentary: erythematous rash*, skin ulceration, eczema, alopecia, pruritus, increased sweating

Musculoskeletal/Collagen: arthrosis*, myalgia*, arthritis, polymyalgia rheumatica, stiffness

Respiratory/Special Senses: sinusitis*, upper respiratory tract infection*, bronchospasm*, pharyngitis, bronchitis, pneumonia, coughing, dyspnea, taste perversion, parosmia, nasal congestion, sneezing, , allergic rhinitis, nasal odor, mucosal excoriation, rhinitis ulcerative

Cardiovascular: hypertension*, angina pectoris*, tachycardia, palpitation, bundle branch block, myocardial infarction

Gastrointestinal: dyspepsia*, constipation*, abdominal pain*, nausea*, diarrhea*, vomiting, flatulence, increased appetite, gastritis, dry mouth

Liver/Metabolic: cholelithiasis, hepatitis, thirst, weight increase

Endocrine: goiter, hyperthyroidism

Urinary System: cystitis*, pyelonephritis, hematuria, renal calculus

Central and Peripheral Nervous System: dizziness*, paresthesia*, vertigo, migraine, neuralgia, agitation, tremor

Hearing/Vestibular: tinnitus, hearing loss, earache

Vision: abnormal lacrimation*, conjunctivitis*, blurred vision, vitreous floater, visual disturbance

Vascular: flushing, cerebrovascular accident, thrombophlebitis

Hematologic/Resistance Mechanisms: lymphadenopathy*, infection*, anemia

Psychiatric: depression*, insomnia, anxiety, anorexia

Immune system disorders: Hypersensitivity, anaphylaxis and anaphylactic shock

Common adverse reactions associated with the use of injectable calcitonin-salmon occurred less frequently in patients treated with Miacalcin Nasal Spray than in those patients treated with

injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients treated with the nasal spray (and 1.5% of those receiving placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the nasal spray, occurs in 2%-5% of patients treated with injectable calcitonin-salmon. Although the administered dosages of injectable and nasal spray calcitonin-salmon are comparable (50-100 units daily of injectable versus 200 units daily of nasal spray), the nasal dosage form has a mean bioavailability of about 3% (range 0.3%-30.6%) and therefore provides less drug to the systemic circulation, possibly accounting for the decrease in frequency of adverse reactions.

The collective foreign marketing experience with Miacalcin Nasal Spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

OVERDOSAGE

No instances of overdose with Miacalcin® (calcitonin-salmon) Nasal Spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of Miacalcin Nasal Spray up to 1600 I.U., doses up to 800 I.U. per day for 3 days and chronic administration of doses up to 600 I.U. per day have been studied without serious adverse effects. A dose of 1000 I.U. of Miacalcin injectable solution given subcutaneously may produce nausea and vomiting. A dose of Miacalcin injectable solution of 32 I.U. per kg per day for 1 or 2 days demonstrated no additional adverse effects.

There have been no reports of hypocalcemic tetany. However, the pharmacologic actions of Miacalcin Nasal Spray suggest that this could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

DOSAGE AND ADMINISTRATION

The recommended dose of Miacalcin® (calcitonin-salmon) Nasal Spray in postmenopausal osteoporotic females is one spray (200 I.U.) per day administered intranasally, alternating nostrils daily.

Due to the association between occurrence of malignancies and long term calcitonin use (see WARNINGS), the treatment duration should be limited to the shortest period of time possible and using the lowest effective dose.

Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of Miacalcin Nasal Spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to Miacalcin Nasal Spray therapy in these patients.

Priming (Activation) of Pump

Before the first dose and administration, Miacalcin Nasal Spray should be at room temperature. To prime the pump, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle until a full spray is produced. The pump is primed once the first full

spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the head in the upright position, and the pump firmly depressed toward the bottle. The pump should not be primed before each daily dose.

HOW SUPPLIED

Miacalcin® (calcitonin-salmon) Nasal Spray

Available as a metered dose clear solution in a 3.7 mL fill clear glass bottle. It is available in a dosage strength of 200 I.U. per activation (0.09 mL per spray). A screw-on pump is provided. The pump, following priming, will deliver 0.09 mL of solution. Miacalcin Nasal Spray contains 2200 I.U. per mL calcitonin-salmon and is provided in an individual box containing one glass bottle and one screw-on pump ..... NDC 0078-0311-54

Store and Dispense

Store unopened bottle in refrigerator between 2°C to 8°C (36°F to 46°F). Protect from freezing.

Store bottle in use at room temperature between 15°C to 30°C (59°F to 86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Information for the Patient

Miacalcin®

(calcitonin-salmon)

Nasal Spray

What is MIACALCIN® [MEE-uh-KAL-sin] Nasal Spray?

MIACALCIN® Nasal Spray is a medication used for the treatment of osteoporosis after menopause (postmenopausal osteoporosis) in women more than 5 years after menopause with low bone mass who refuse or cannot tolerate ~~estrogens~~alternative treatments, or in whom ~~estrogens~~ alternative treatments are not an option. Patients who use MIACALCIN® Nasal Spray should be sure to ingest adequate amounts of calcium and vitamin D along with therapy.

How much calcium and vitamin D do I need each day?

When taking MIACALCIN® Nasal Spray, it is recommended that you get at least 1000 mg of calcium and 400 I.U. (International Units) of vitamin D each day. Check with your doctor or healthcare provider to see if you are getting enough calcium and vitamin D in your diet. If not, he or she may recommend that you start taking calcium and vitamin D supplements.

What is osteoporosis after menopause? What causes it?

Postmenopausal osteoporosis is a condition associated with frail, brittle bones. It usually occurs when “old” bone cells are removed from bones faster than they can be replaced by “new” bone cells. As a result, bones get weak and may become susceptible to fractures.

Osteoporosis occurs most frequently in women who have gone through menopause. At menopause, a woman’s body goes through many changes, including a substantial decrease in the amount of estrogen produced. Estrogen in your body helps keep bones strong -- without it, they may become weak.

Postmenopausal osteoporosis begins without notice; however, over time symptoms develop such as:

- Curved spine
- Rounded shoulders
- Loss of height

Untreated, postmenopausal osteoporosis can be painful and disabling. Some women with postmenopausal osteoporosis suffer from broken hips and fractured wrists. Fortunately, osteoporosis after menopause is treatable. Your doctor or healthcare provider can prescribe a medication, like MIACALCIN® Nasal Spray, to treat your condition.

How does MIACALCIN® Nasal Spray work?

The active ingredient in MIACALCIN® Nasal Spray is calcitonin, a man-made protein similar to one found in people, other mammals, and some types of fish and birds.

The way calcitonin affects bone is still being studied, but it is believed to work in the following ways:

- Calcitonin reduces the activity of osteoclasts [AHS-tee-oh-clasts], the cells that remove “old” bone
- Because bone building continues while bone removal is slowed down, the result is an increase in bone mass

When you spray MIACALCIN® Nasal Spray into your nostril, it is rapidly absorbed by the blood vessels lining your nasal passages. It then travels into your bloodstream and on to your bones where it works to stop bone loss and helps your bones become stronger.

How do I use MIACALCIN® Nasal Spray?

The recommended dose of MIACALCIN® Nasal Spray is one spray daily in alternated nostrils -- unless directed otherwise by your healthcare provider. Start with a spray in the left nostril on your first day, followed by a spray in the right nostril on the second day. Continue to alternate nostrils every day. There are at least 30 "doses" of MIACALCIN® Nasal Spray in each bottle.

You should keep track of the number of doses used from the bottle.

Do not use more MIACALCIN® Nasal Spray than advised by your doctor.

Your doctor will tell you exactly how long you need to use MIACALCIN® Nasal Spray. You should not use it longer than advised by your doctor.

After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.

Who should not take MIACALCIN® Nasal Spray?

MIACALCIN® Nasal Spray should not be used by patients who are allergic to the protein calcitonin-salmon, or by women who are pregnant or nursing.

You should be aware of these warnings and precautions when taking MIACALCIN® (calcitonin-salmon) Nasal Spray.

- No formal studies designed to test drug interactions with calcitonin-salmon have been done; however, no drug interactions have been observed with the use of MIACALCIN® Nasal Spray. You should inform your doctor and pharmacist about the other prescription and nonprescription medications you are taking.
- In clinical studies, nasal symptoms occurred in approximately 9% of postmenopausal patients taking MIACALCIN® Nasal Spray. For this reason, it is recommended that a nasal examination be performed prior to the start of treatment and at any time nasal complaints occur.
- Rare instances of nasal ulceration have occurred with MIACALCIN® Nasal Spray. In some cases, your doctor may decide to temporarily discontinue treatment with MIACALCIN® Nasal Spray until symptoms subside.
- Because calcitonin-salmon is a protein, the possibility of a systemic allergic reaction exists. Patients who are allergic to calcitonin-salmon should not use MIACALCIN® Nasal Spray.
- MIACALCIN® Nasal Spray is safe to use in elderly patients. A slight increase in nasal symptoms has been observed in patients over 65 years of age, however the symptoms are usually mild. No other unusual side effects have been seen in patients over 65 years of age.
- In clinical studies where calcitonin was used for a long time, a small increased risk for cancer was observed.

Possible side effects

Most patients tolerate treatment with MIACALCIN® Nasal Spray very well; however, like all prescription drugs, MIACALCIN® Nasal Spray may cause some side effects in some people. These side effects are usually mild and generally do not lead to discontinuation of treatment with MIACALCIN® Nasal Spray. The most commonly reported side effects are:

- Nasal symptoms such as runny nose, crusting, or nasal bleeding
- Back/joint pain

- Headache

Anytime you have a medical problem you think may be related to MIACALCIN® Nasal Spray, talk to your doctor or healthcare provider.

Your doctor or pharmacist can demonstrate how to assemble, prime, and use MIACALCIN® Nasal Spray. In addition, detailed directions can be found in your MIACALCIN® Nasal Spray box. Please read them carefully before assembling and using the spray.

This medication is prescribed for a particular condition. Do not use it for another condition or give the drug to others. Keep MIACALCIN® Nasal Spray and all medicines out of reach of children. This leaflet provides a summary of information about MIACALCIN® Nasal Spray. If you have any questions or concerns about either MIACALCIN® Nasal Spray or osteoporosis, talk to your doctor. In addition, talk to your pharmacist or other healthcare provider.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

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~~April 2012~~July 2012/~~July 2011~~July 2012

HOW TO ASSEMBLE AND USE

Miacalcin® NASAL SPRAY

(calcitonin-salmon) Nasal Solution

ONE SPRAY, ONCE A DAY

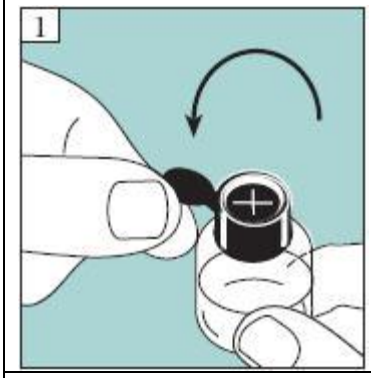
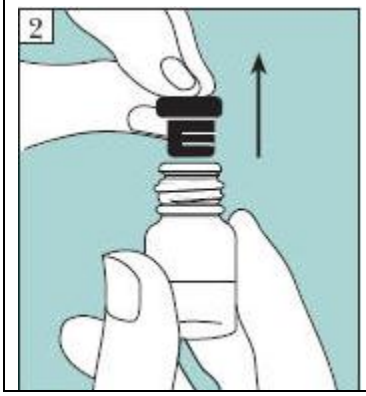
BEFORE USING MIACALCIN® (calcitonin-salmon) NASAL SPRAY

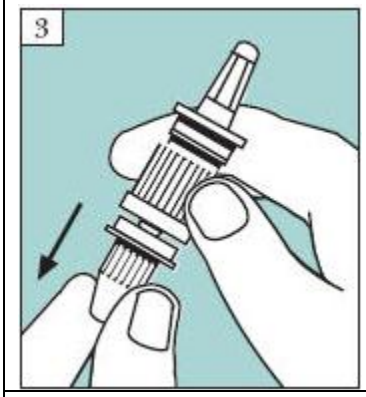
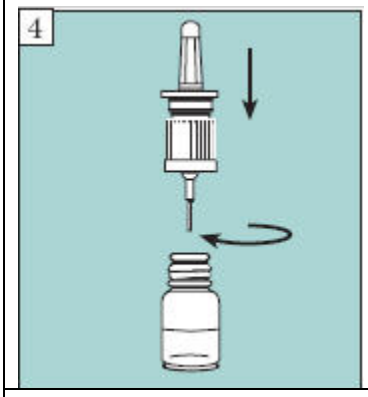
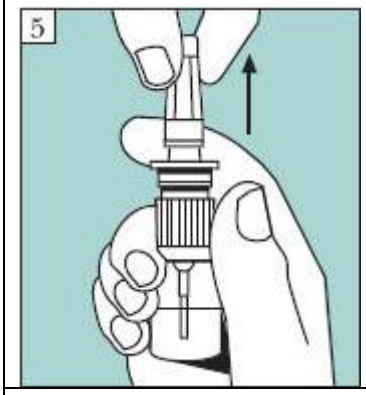
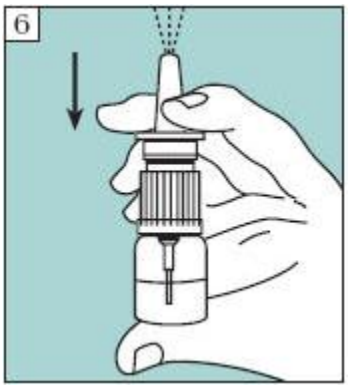
This package contains one bottle of MIACALCIN® (calcitonin-salmon) Nasal Spray and one screw-on pump.

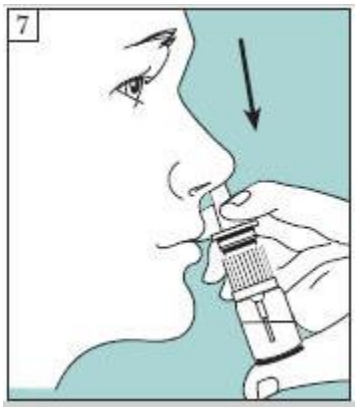
Important Facts About Your Medication:

- The bottle contains the proper amount of medication — be aware that the entire bottle will not be filled with liquid.
- Before opening and assembling your medication bottle, keep it in your refrigerator between 2°C- to 8°C (36°F- to 46°F). Do not freeze.
- After opening and assembling a new medication bottle, keep it at room temperature between 15°C- to 30°C (59°F- to 86°F) in an upright position.

HOW TO USE MIACALCIN® (calcitonin-salmon) NASAL SPRAY

Putting the Nasal Spray Pump Unit Together 	1. If your bottle and pump unit were already assembled by your pharmacist, go to Step 6. If not, remove the bottle from your refrigerator and allow it to reach room temperature before assembling. Lift up the blue plastic tab and carefully pull the metal safety seal off the bottle.
	2. Keeping the bottle upright, remove the rubber stopper from the bottle.

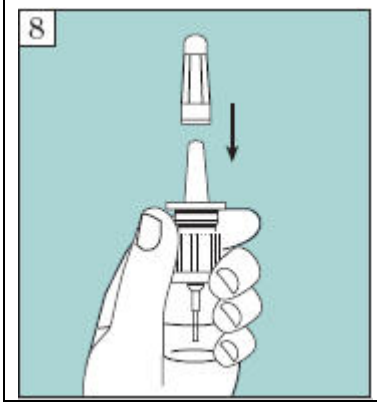
	3. Holding the pump unit, gently remove the opaque plastic protective cap from the bottom of the unit. Note: Do not depress pump when it is not attached to the bottle.
	4. Holding the bottle upright, insert the nasal spray pump unit into the bottle. Then turn the pump clockwise, and tighten it until it is securely fastened to the bottle.
	5. Holding the bottle upright with your index finger on top of one of the two side arms of the pump, gently remove the clear protective cap from the top of the nozzle.
Priming a New Bottle 	6. **To ensure proper delivery of medication, a newly opened and assembled bottle <u>must</u> be primed before you use it for the <u>first</u> time. <u>If your pharmacist assembled the unit for you</u>**, check to see if it has already been primed by pumping the unit once. If a full spray is emitted, the unit has already been primed. If no spray is emitted, you must prime the unit. Holding the bottle upright with your index and middle fingers on the two side arms of the pump, and your thumb on the bottom of the bottle, press the arms down fully **until you see a full spray**. Now the nasal spray is ready for use. **Do not re-prime the pump before each daily use because this will waste your medication.**
Using the Medication	7. The recommended dose of MIACALCIN® (calcitonin-

<table>
<tr><td> 
</td><td>salmon) Nasal Spray is one spray once a day in one nostril.

Keep your head upright and carefully place the nozzle in one nostril.

Tilt the bottle until it is in a straight line with the nasal passage.

Firmly press down on the pump once to spray the medication into your nose. It is not necessary to inhale while this is being done. Please note: Because the mist is so fine, you may not feel it inside your nose. Also, some medication may drip out of your nose. However, in either case, the medication is absorbed. IMPORTANT: Do not “test” the spray unit or prime it before you use your daily dose because this will waste your medication.</td></tr>
<tr><td colspan="2">Cleaning the Pump

Once or twice a week, wipe the nozzle with a clean, damp cloth. Dry the nozzle before replacing the clear protective cap.</td></tr>
<tr><td>Storing the Unit
 
</td><td>8. Holding the bottle with two fingers under the two side arms of the pump, gently replace the protective cap on the nasal spray unit. Be careful not to depress the pump while this is being done. Once the pump is primed, the unit must be kept at room temperature between 15°C - to 30°C (59°F - to 86°F) in the upright position until the medication is finished.</td></tr>
</table>

IMPORTANT

- Do not refrigerate the unit between doses.
- Do not store the unit on its side.

Bottles left at room temperature (opened or unopened) for more than 35 days must be discarded.

Refrigerated bottles are good until the expiration date stamped on the bottle and box.

Alternate Nostrils Daily

The first day, start with one spray in the left nostril. The next day, use one spray in the right nostril, and so on.

It is important to receive the correct daily amount of calcium and vitamin D, as directed by your healthcare provider.

IMPORTANT

- **Use MIACALCIN® (calcitonin-salmon) Nasal Spray daily as prescribed by your physician.**

~~To ensure proper treatment, it is important to use your MIACALCIN® (calcitonin-salmon) Nasal Spray daily even if you have no symptoms of postmenopausal osteoporosis.~~

What is the Correct Dose of MIACALCIN ®(calcitonin-salmon) Nasal Spray?

A single spray of MIACALCIN® (calcitonin-salmon) Nasal Spray contains one daily dose, which is 200 I.U. of calcitonin-salmon. The fine mist is actually 0.09 mL (milliliter) of solution. Your bottle of MIACALCIN® Nasal Spray contains at least 30 doses. Priming the pump as described in Step 6 does not alter the total number of doses available in a bottle of MIACALCIN® Nasal Spray. The bottle need only be primed once after assembly. Do not re-prime or "test spray" your bottle before you use your daily dose of MIACALCIN® Nasal Spray. This will waste your medication.

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Please see your healthcare provider for complete product information for MIACALCIN® Nasal Spray.

~~July 2011~~July 2012

Appendix 3

Appendix 3 Epidemiological Assessment of Non-Melanoma Skin Cancer Cases in the Clinical Trial Nº 320 (Miacalcin® Salmon Calcitonin). Miret M, Gutierrez LP, Perez-Gutthann S (1998)

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Epidemiological Assessment of Non-Melanoma Skin Cancer Cases in the Clinical Trial Nº 320 (Miacalcin® Salmon Calcitonin)

Clinical Safety and Epidemiology

Global Epidemiology

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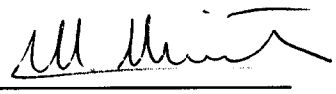

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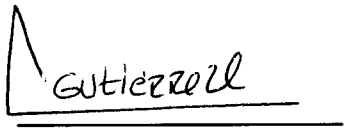

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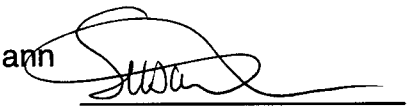

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March 22, 1999

Date

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1. Summary

The Mialcalcin® (salmon calcitonin) Study N° 320 is a multicenter trial conducted in the United States and the United Kingdom with the objective of investigating the efficacy of three doses of Mialcalcin® Nasal Spray (NS) versus placebo in the prevention of osteoporotic vertebral fractures. A total of 1255 postmenopausal women were randomized into four treatment groups. At the end of the study period, 29 women had been diagnosed a primary non-melanoma skin cancer (NMSC): 26 in the Miacalcin®NS groups and 3 in the placebo group. Additionally, 10 patients with prior history of either a squamous cell carcinoma (SCC) or a basal cell carcinoma (BCC) had a subsequent skin cancer. This document reports the results of the indirect standardization and analyses conducted to evaluate the occurrence of SCC and BCC among participants in the clinical trial.

After application of the indirect standardization method the expected number of BCC cases (13.11) was lower than the actual observed BCC cases (23) among the Miacalcin®NS treated patients. The expected number of SCC cases (8.92) was found to be higher than the observed number of incident cases (3) in the Miacalcin® Study 320. However, these results have to be interpreted with caution in the case of BCC because the reference population incidence rates corresponded to the period 1976-84.

In the cohort analysis a relative risk (RR) of 2.5 for developing a BCC was found. When treated patients were compared to patients on placebo, the results of the cumulative dose and duration of exposure analyses did not support a positive association between Miacalcin intake and BCC.

To further examine NMSC occurrence with more recent data, all incident, recurrent and subsequent events were analysed with the indirect standardization method using data from a reference population of New Mexico corresponding to 1989-91. Both for BCC and for SCC, the number of expected events was lower than the number of observed events.

Concluding, an increased number of BCC cases has been diagnosed in the Miacalcin NS treatment arms versus placebo. However, the trends in NMSC in external population suggest that the risk might have been overestimated. Results of the analysis by dose and duration of treatment suggest the effect of a potential detection bias rather than a BCC initiator or promoter role of Miacalcin.

2. Background

2.1 The Miacalcin® NS Study Nº 320

Salmon calcitonin has been used in the prevention of osteoporosis for more than two decades. No signs of an increase in the number of cancers with the use of salmon calcitonin have been detected. A new formulation of salmon calcitonin administered via a nasal spray was studied

in the Miacalcin® NS Study N° 320, a multicentered, double-blind, placebo-controlled randomized study conducted in forty-two centers in the United States and seven centers in the United Kingdom, from February 1991 to April 20 1998. The study aimed to determine the efficacy and safety of three dose levels of Miacalcin®NS in reducing the rates of incident vertebral fractures in postmenopausal women with established osteoporosis. Patients were randomized to receive 100 IU, 200 IU, 400 IU Miacalcin®NS or placebo once daily in the morning for 5 years and were additionally requested to ingest at least 1,500 mg calcium and 400 IU Vitamin D daily. There were no significant baseline differences between treatment groups with respect to age, weight, height, race, lumbar bone mineral density, body mass index, history of smoking/alcohol use, personal biographical data or gynecological history. The majority of patients were Caucasian (97%) and more than 5 years postmenopausal (98%). The patients' ages at entry ranged from 44 to 94 years (mean 68 years).

At the end of the study (04/30/98) 39 non-melanoma skin cancers had been diagnosed during the study in 36 women. Out of these 39, 29 were first time (incident) malignancies (26 basal cell carcinomas and 3 squamous cell carcinomas) and 10 were recurrent/subsequent malignancies (9 basal cell carcinomas and 1 squamous cell carcinoma).

2.2 Epidemiology of non-melanoma skin cancer

Non-melanoma skin cancer (NMSC) includes basal cell carcinoma (BCC) which is the most common cancer in humans and squamous cell carcinoma (SCC). Chronical exposure to ultraviolet radiation has been recognized for a long time to be the main environmental factor in the causation of these two type of neoplasms in light-skinned people. The incidence of NMSC increases with age. Although BCC and SCC are very frequent, there is considerable under-reporting worldwide[1] because of their low case fatality rate and because they are commonly diagnosed and treated in the primary care setting. Information about the incidence of NMSC, that is the occurrence of newly diagnosed cases, has not been systematically reported by all countries[2] and is very often specifically excluded from traditional cancer registries such as SEER (Surveillance, Epidemiology, and End Results).[3] Despite the lack of fully reliable epidemiological data, information from studies performed in Australia, Europe and the United States suggests marked geographical differences in the incidence of these cancers among caucasians worldwide.[4,5,6,7,8] The incidence rates for whites in the US are intermediate between the highest rates of Australia and the lowest rates for the UK, Canada and the Netherlands. Furthermore, the incidence of both BCC and SCC has considerably risen in developed countries during the eighties, and there is no evidence that the epidemic has peaked in more recent years. Therefore, for the purpose of the current report, there is a need for data as contemporaneous as possible to the clinical trial and originated in a geographical area as similar as possible to the area covered by the clinical trial.

Data on the natural history of these two cancers evidence a high frequency of multiple tumors. A second or later BCC in a different anatomical site (subsequent BCC) or in the same anatomical site (recurrent BCC) occurs in one third of the cases.[9] For SCC, subsequent and

recurrent lesions occur in 16% of the cases.[10] This has to be borne in mind when interpreting epidemiological data on BCC and SCC.

3. Objectives

To report the results of the epidemiological analysis conducted with the aim of assessing whether there is an association between the exposure to Miacalcin® NS and the occurrence of incident NMSC by:

a) comparing the occurrence of BCC and SCC among study participants with that in a standard reference general population by means of an indirect morbidity standardization.

b) estimating the incidence rates by person-time of BCC and SCC in the different treatment arms.

c) evaluating potential effects of cumulative dose and duration of exposure to assess different hypothesis on drug-related effects.

4. Methods

4.1 Data set

The analysis corresponds to the clinical trial database at the time of the "last patient last visit" of the study, on April 20 1998.

4.2 Case definition

An **incident case** was defined as a patient with no prior history of a BCC or a SCC who had been diagnosed, respectively, a BCC or a SCC during the study period.

Considering that more than one NMSC were diagnosed in some patients either during the study or previously, a **malignancy** was defined as a BCC or a SCC diagnosed in a patient during the study, independently of whether it was an incident, a recurrent (second tumor in the same anatomical site) or a subsequent (second tumor in a different anatomical site) BCC or SCC, respectively.

All NMSCs occurred in caucasian U.S. residents. The distribution of the NMSC malignancies by type of cancer, presence of a lesion at entry in the study, and history of skin cancer is shown on table 1. The age, type of treatment and duration of treatment at time of removal are displayed for all incident cases on table 2 (and for recurrent/subsequent malignancies on table 3).

4.3 Person-time calculation

Person-time considers the number of subjects at risk for a particular outcome and the risk period, that is, time to either the date of occurrence of the outcome or the end of the study. For the date of the outcome occurrence, date of removal of the skin cancer rather than date of

diagnosis was used because this was a more accurate date for most of the patients. Person-years of follow-up were calculated for the 1255 participants according to the analysis outcome (incident cases or malignancies), date of removal of the BCC or SCC and to their time on study as follows:

Analysis of incident cases:

- patients who were diagnosed an incident BCC (or SCC) during the study: time from entry in the study to removal of BCC (or SCC, respectively);
- remaining patients: time from entry in the study to last dose of Miacalcin.

Analysis of malignancies:

- time from entry in the study to last dose of Miacalcin.

4.3. Analysis

4.3.1 Indirect Standardization

The indirect standardization[11] method was used to compare the study BCC and SCC occurrence with that in a reference population. In indirect standardization, age-specific annual incidence rates from a standard population are applied to the age-specific person-years of follow-up of the study population. This allows to estimate the expected number of BCC and SCC cases in the study population if patients were diagnosed at the same (age-specific) rate as women in the standard population.

The Standard Morbidity Ratio (SMR), namely the ratio of the observed number of BCC cases in the study population over the number of cases expected after standardization, was then calculated for the whole study population, for treated patients, and for patients on placebo. The SMR for SCC was also calculated for the whole study population and for treated patients (all SCC cases were in treatment arms). Additionally, SMRs were estimated for BCC and SCC malignancies in treated patients. A SMR greater than one would indicate that the skin cancer morbidity experience in study subjects is greater than the skin cancer morbidity which would have been expected if study subjects were diagnosed with skin cancer at the same age-specific rates as people in the standard population. Ninety five percent Confidence Intervals (95% CI) for these SMRs were calculated assuming a Poisson distribution.[12] A 95% CI of a parameter is the interval that would include the value of the parameter with a probability of 0.95. It is a measure of the precision with which a population parameter can be determined from a study: the narrower the CI, the greater the precision. It is directly related to the amount of information available.

The reference population chosen for the indirect standardization of BCC incidence was the female population of Rochester, Minnesota (1976-84).[9] This population was chosen because results of this study are the closest for a generalization to the white US population during the same period. More recent published data representative of the US white population on the incidence rates of BCC by age and sex were not available at the time of this analysis.

The reference population chosen for the indirect standardization of SCC incidence was the population of Rochester studied by the same research group in a more recent period.[4]

A further analysis was performed on all BCC and all SCC malignancies. The population used for indirect standardization of all BCCs and SCCs was the female non-hispanic white population of Albuquerque, served by Lovelace Health Plan, a major Health Maintenance Organization of New Mexico.[13] The information on this population corresponds to the period 1989-91. This analysis takes into account the possibility of a misdiagnosis between incident, recurrent and subsequent malignancies and also allows a second analysis of BCCs with a more contemporaneous reference population.

4.3.2 Incidence rates

Incidence rates of BCC and SCC for each treatment arm and the respective relative risks (RR) and 95% CI were calculated. In this analysis, RR is the risk of developing primary BCC among women treated with Miacalcin compared with the risk among women on placebo. Since there were no SCC diagnosed on patients on placebo, the reference group chosen in the calculation of the RR was the group on 100 IU of Miacalcin.

4.3.3 Analysis by dose and duration of exposure

Both to identify if there were dose groups at higher risk and to assess whether Miacalcin presented a dose-effect response on the occurrence of BCC and SCC, categorization of the exposure to Miacalcin by cumulative dose taken was computed for each patient by multiplying the duration of treatment in days by 1, 2 or 4 for patients treated with 100 IU, 200 IU or 400 IU, respectively. The distribution of cases according to this parameter was analyzed and relative risks were used to compare the risk of BCC and SCC in the three higher dose quartiles to the lower dose quartile.

Similarly, individuals were distributed in quartiles of years of exposure to assess the effect of the duration of treatment on BCC and SCC incidence. Relative risks were used to compare the risk of BCC and SCC in the three longer exposure quartiles to the quartile with a shorter exposure.

The statistical package used for this analysis was SAS version 6.1.[14]

5. Results

Between February 1991 and July 1993, a total of 1255 postmenopausal patients with established osteoporosis were enrolled in the study. These women were randomly assigned to treatment arms as follows: 316 in the Miacalcin® NS 100 IU group, 316 in the Miacalcin® NS 200 IU group, 312 in the Miacalcin® NS 400 IU group and 311 in the placebo group.

The 1255 participants were followed, on average 3.4 years, and generated approximately a total of 4200 person-years of follow-up. The person-years distribution by treatment arm and type of cancer is presented in table 4.

5.1 Incident Basal Cell Carcinoma

A total of 26 cases of primary BCC were diagnosed (23 in the treatment arms and 3 in the placebo arm). Among these, four patients had a preexisting lesion at the site of the BCC at the time of enrollment, but were considered incident cases since diagnosis was made during the study.

The indirect standardization of BCC cases is presented in table 5 . The number of expected cases in the treatment groups was 13.11. This resulted in an SMR of 1.75 (95%CI: 1.11 - 2.63). The same method applied to the placebo group yielded the following results: 3.01 expected cases (3 observed cases); SMR 1.00 (95% CI: 0.21 - 2.91). When considering the whole study population, the expected number of cases was 17.43 (26 observed), and the SMR was 1.49 (95%CI: 0.97 - 2.19).

The incidence rates of BCC per 100,000 person-years for each treatment arm were estimated and the respective RRs were calculated (table 6). The overall RR of being diagnosed a BCC for women treated with Miacalcin compared to placebo was 2.5 (95 % CI: 1.2 - 5.1). Relative risks in the three arms compared to placebo were 3.4 (95 % CI: 1.4 - 8.0); 1.9 (95 % CI: 0.7 - 5.1); and 2.3 (95 % CI: 0.9 - 5.9) for Miacalcin 100 IU, 200 IU and 400 IU regimens, respectively.

To further explore a potential causal association of Miacalcin and BCC, patients on Miacalcin were distributed in quartiles by cumulative dose intake as shown on table 7. The RRs of having a BCC decreased as the cumulative dose range of the quartile increased: RR was 0.15 and 0.12 in the second and third cumulative dose groups, respectively, compared to the lowest cumulative dose quartile.

The duration of exposure analysis is displayed on table 8. Over half of the patients had been on treatment less than 2 years, so that the incidence rate of BCC was highest in the quartile with the lowest duration of treatment. The RR in the second quartile was 0.19 (95%CI: 0.08 - 0.47), the RR was lower in the two quartiles with the longer duration of treatment.

5.2 Incident Squamous Cell Carcinoma

Three incident cases of squamous cell carcinoma (SCC) of the skin were diagnosed during the trial. All three were in the treatment arms. Two additional in situ SCCs (Bowen's disease) diagnosed, have been excluded from the analysis because this condition is not consistently registered in incidence studies. Both patients were in the 200 IU treatment arm.

With indirect standardization, the expected number of SCCs among patients treated with Miacalcin (table 9), was 8.92. This resulted in an SMR of 0.34 (95%CI: 0.07 - 0.98). The same analysis performed on the whole study population yielded an SMR of 0.25 (95% CI: 0.05 - 0.74) corresponding to a total expected number of SCC of 11.88.

The incidence rates of SCC per 100,000 person-years by treatment arms are shown on table 10. Since no cases of SCC were diagnosed in the placebo group, the group with the lesser exposure (100 IU) was taken as a reference.

The incidence rates per 100,000 person-years and RRs of SCC by quartiles of cumulative dose of Miacalcin are presented on table 11. The highest incidence rate corresponds to the lowest cumulative dose quartile.

The highest incidence rate of SCC corresponds to the quartile with the lowest duration of treatment, as shown on table 12.

On tables 11 and 12, most of the information is in the highest cumulative dose or duration of treatment quartile which include most person-years of follow-up, therefore the estimators are more precise in the highest quartiles.

5.3 Malignancies

Recurrent or subsequent malignancies (9 BCCs and 1 SCC) were diagnosed and removed during the study period in ten patients, namely 3 women who had already presented an incident NMSC during the study and 7 who had a former history of NMSC. The distribution of these patients by age and treatment arm is shown on table 3.

The average annual rates of BCC (either incident, recurrent or subsequent) between 1989 and 1991 in the female non-hispanic white population of Albuquerque by age group are shown on table 13. According to these rates, 52 BCC malignancies were expected in the Miacalcin treatment groups (32 BCC malignancies observed). This resulted in an SMR of 0.60 (95%CI: 0.41 - 0.85).

The same type of analysis with SCC malignancies is presented on table 14. There were 7.7 SCC events expected and 4 events observed. The SMR was 0.51 (95%CI: 0.14 - 1.31).

6. Discussion

A higher proportion of BCC and SCC in the treatment arms compared to the placebo arm was detected in the Miacalcin®NS study N°320. No articles have been found in the medical scientific journals regarding the biological plausibility of salmon calcitonin as a promoter or initiator for non-melanoma skin cancer.

In the analysis of incident BCC by indirect standardization, data from 1976-84 were used. Incidence studies show that NMSC has increased in developed countries in the last decades. Moreover, SCC, a cancer with the same risk factors that BCC, was studied in the same reference female population and an increase in adjusted annual incidence rates from 22.5 cases per 100,000 in the period 1976-84[10] to 99.7 in 1992[4] was observed. This greater than fourfold increase in SCC incidence suggests that BCC incidence may have also increased at similar levels. These data suggest that the incidence of BCC in the reference population used is considerably lower than the incidence in the same population one decade later and therefore the number of expected cases is very likely underestimated in this analysis.

The estimation of the overall incidence rate of BCC for the Miacalcin treatment arms showed that Miacalcin treated patients had 2.5 times higher risk of BCC when compared to the placebo group. The cumulative dose analysis showed that the risk was higher in patients on the 100 IU Miacalcin arm compared to patients in the 200 IU or 400 IU Miacalcin arms. The inverse association observed suggests a lack of a cumulative dose-effect of Miacalcin. Similarly, the duration of exposure analysis showed that most patients with an incident BCC had been diagnosed within the first two years. These two analyses show that Miacalcin does not behave like a carcinogen for BCC. The mechanisms of carcinogenesis indicate that cancer develops through a series of essential steps involving genetic changes (initiation) and epigenetic changes (promotion). A *promoter* is a substance that causes the initiated cell to progress through the carcinogenic process. The action of promoters requires their presence at high levels for a long time.[15] Given that promoters require high levels and a chronic period of exposure in order to produce cancer, this clustering of cases in the low cumulative-dose- and exposure-duration groups strongly suggests that Miacalcin is not causally related to BCC.

The analysis of SCC incidence by indirect standardization was performed with data from the female population of Rochester, Minnesota in 1992. This population was almost all white (96%), and according to the authors of the study was similar in terms of socioeconomic parameters and sunlight exposure to whites in the US as a whole. This study was nearly contemporaneous to the Miacalcin study. The number of expected cases of SCC based on the indirect standardization was higher than the number of observed cases of SCC suggesting that the morbidity experience of SCC in the Miacalcin Study was not above the expected.

From the statistical point of view, due to the distribution of person-time for both the cumulative dose and the duration of exposure analyses by quartiles most of the information is in the highest quartiles and the estimators of the lower quartiles is less precise.

The fact that the overall risk of being diagnosed a NMSC while in the active treatment was highest during the first two years of the study and progressively decreased thereafer, is

suggestive of a detection bias[16] due to a tighter medical control of participants at the beginning of the study compared to the previous period. This effect due to a change in medical control was lost over the study.

The occurrence of either recurrent or subsequent BCC and SCC is very common. It has been estimated that one third of the patients with a NMSC develop one new NMSC after 3 years of the first malignancy. Previous history of NMSC was not available for the whole study population therefore there is not sufficient information to assess the effect of prior history as a risk factor for a new NMSC in our study population.

In the Miacalcin study 10 out of the 39 NMSCs diagnosed were recurrent or subsequent. The non-hispanic white population of Albuquerque was chosen to assess the occurrence of NMSC malignancies in the Miacalcin study because this was the unit of analysis used in that study, and the results were nearly contemporaneous to the Miacalcin study. The morbidity experience of BCC and SCC malignancies in the Miacalcin study was not higher than in the reference population of Albuquerque.

7. Conclusions

The epidemiological analysis showed that the overall number of BCC cases diagnosed in the Miacalcin NS study N° 320 treatment arms is higher than what would have been expected in a reference population of Minnesota studied from 1976-84. This result has to be evaluated in the context of the incidence trends of NMSC, namely a sustained increase in the last years. Although the Minnesota population was, as of this date, the best available reference for the purpose of this analysis, it might have resulted in an underestimation of the expected number of cases. The analysis of the cases by level of exposure to the treatment clearly suggests that Miacalcin NS does not behave like a carcinogen for BCC.

Using the information from a reference population of Minnesota in 1992, the overall number of SCC cases in the Miacalcin NS study N° 320 is lower than expected.

A secondary analysis of all the BCC and SCC malignancies that occurred during the study and comparing them to the occurrence in a reference population of New Mexico, the number of expected cases of both BCC and SCC was higher than the observed malignancies in the Miacalcin study.

Concluding, an increased number of BCC cases has been diagnosed in the Miacalcin NS treatment arms versus placebo. However, the trends in NMSC in external population suggest that the risk might have been overestimated. Results of the analysis by dose and duration of treatment suggest the effect of a potential detection bias rather than a BCC initiating or promoting role of Miacalcin.

8. Tables

Table 1. Study 320: Non-melanoma skin cancer: type of malignancy and prior history

Type of cancer	Number of malignancies	History of skin cancer	Lesion present at entry in the study
incident BCC	21	No	No
	1	Yes, melanoma	No
	4	No	Yes
recurrent/subsequent BCC	9	Yes	No
incident SCC	3	Yes, BCC	No
recurrent/subsequent SCC	1	Yes	No
Total number of malignancies	39		

Table 2. Study 320: Incident cases of non-melanoma skin cancer: Age, type of cancer, treatment arm and duration from entry in the study to cancer removal

Case ID Number	Type of cancer	Age (years)	Treatment arm	Time on study at removal (months)
01050	BCC	65	Placebo	13.1
02004	BCC	64	Placebo	0.8
02033	BCC	70	Placebo	1.0
03061	BCC	67	Miacalcin 400 IU	5.1
08013	BCC	68	Miacalcin 200 IU	22.6
11010	BCC	71	Miacalcin 200 IU	39.1
14010	BCC	67	Miacalcin 200 IU	34.9
14021	BCC	68	Miacalcin 400 IU	28.0
16001	BCC	65	Miacalcin 100 IU	60.3
16029	BCC	57	Miacalcin 400 IU	37.0
17002	BCC	75	Miacalcin 100 IU	4.2
18014	BCC	78	Miacalcin 200 IU	16.8
18022	BCC	81	Miacalcin 100 IU	2.9
26020	BCC	63	Miacalcin 100 IU	34.9
26025	BCC	65	Miacalcin 200 IU	22.7
27010	BCC	77	Miacalcin 200 IU	4.7
27022	BCC	63	Miacalcin 400 IU	2.5
29008*	BCC	73	Miacalcin 100 IU	8.9
30043	BCC	69	Miacalcin 100 IU	41.0
30051	BCC	76	Miacalcin 100 IU	33.0
30059	BCC	76	Miacalcin 100 IU	53.7
31028	BCC	79	Miacalcin 400 IU	2.9
31030	BCC	74	Miacalcin 400 IU	9.2
33002	BCC	58	Miacalcin 100 IU	26.0
33017	BCC	65	Miacalcin 400 IU	28.4
36018	BCC	66	Miacalcin 100 IU	12.0

Table 2. (cont.) Study 320: Incident cases of non-melanoma skin cancer: Age, type of cancer, treatment arm and duration from entry in the study to cancer removal

Case ID Number	Type of cancer	Age (years)	Treatment arm	Time on study at removal (months)
01063*	SCC	76	Miacalcin 100 IU	35.7
16010	SCC	77	Miacalcin 200 IU	54.0
33032*	SCC	63	Miacalcin 400 IU	14.2

BCC: basal cell carcinoma

SCC: squamous cell carcinoma

* patient also presented a recurrent/subsequent BCC

Table 3. **Study 320: Recurrent/subsequent malignancies (non-melanoma skin cancer): Age, type of cancer, treatment arm and duration from entry in the study to cancer removal**

Case ID Number	Type of cancer	Age (years)	Treatment arm	Time on study at removal (months)
01002	BCC	70	Miacalcin 100 IU	19.3
01063*	BCC	76	Miacalcin 100 IU	35.7
13018	BCC	74	Miacalcin 200 IU	10.0
17015	BCC	67	Miacalcin 400 IU	1.3
20039	BCC	70	Miacalcin 100 IU	11.1
26026	BCC	74	Miacalcin 400 IU	8.9
29008*	BCC	73	Miacalcin 100 IU	35.0
30030	BCC	74	Miacalcin 200 IU	28.2
33032*	BCC	63	Miacalcin 400 IU	3.6
30029	SCC	83	Miacalcin 200 IU	0.2

BCC: basal cell carcinoma

SCC: squamous cell carcinoma

* patient also presented an incident NMSC during the study

Table 4. Study 320: Distribution of person-years at risk for an incident BCC, for an incident SCC, and for any NMSC malignancy by treatment arm

Treatment arm	Person-years at risk for incident BCC	Person-years at risk for incident SCC	Person-years at risk for any malignancy*
Placebo	1033.46	1047.15	1047.15
Total treated	3171.50	3242.84	3251.08
Miacalcin NS 100 IU	1018.42	1049.11	1050.11
Miacalcin NS 200 IU	1093.92	1110.18	1113.65
Miacalcin NS 400 IU	1059.16	1083.55	1087.32
Total	4204.96	4289.99	4298.23

* incident, recurrent or subsequent BCC or SCC

Table 5. **Study 320: Expected number of skin incident BCC cases according toindirect standardization with the population of Rochester, Minnesota (1976-84).**

Miacalcin treated patients

Age group	BCC incidence rates per 100,000 female population	Person-years	Expected nº of BCC cases	Observed nº of BCC cases in the treatment arms
35-44	61.3	4.99	0.00	0
45-54	165.8	123.01	0.20	0
55-64	279.6	859.49	2.40	4
65-74	430.8	1603.84	6.91	12
75-84	598.7	544.28	3.26	7
85+	927.8	35.89	0.33	0
Total	--	3171.50	13.11	23

Standard Morbidity Ratio = 1.75 (95% CI: 1.11-2.63)

Placebo

Standard Morbidity Ratio =1.00 (95%CI: 0.21 - 2.91)

Whole study population

Standard Morbidity Ratio =1.49 (95%CI: 0.97 - 2.19)

Table 6. Study 320: Incidence rates of BCC per 100,000 person-years and RR by treatment arm

Treatment arm	Cases	Person-years	Incidence rate	RR	95% CI
Placebo	3	1033.46	290.29	1	--
Total treated	23	3171.50	725.21	2.5	1.2 - 5.1
Miacalcin 100 IU	10	1018.42	981.91	3.4	1.4 - 8.0
Miacalcin 200 IU	6	1093.92	548.49	1.9	0.7 - 5.1
Miacalcin 400 IU	7	1059.16	660.90	2.3	0.9 - 5.9

RR: relative risk
CI: Confidence Interval
IU: international units

Table 7. **Study 320: Distribution of individuals, incidence rates of BCC per 100,000 person-years and RRs with 95% CI by quartiles of cumulative dose intake of Miacalcin.**

Cumulative dose range (IU x 10^{-2})	Nº of persons in the quartile	Person-years	Cases of BCC	Incidence rate per 100,000 person-years	RR	95% CI
< 1119	233	269.93	12	4445.6	1	--
1120 -1876	234	892.42	6	672.3	0.15	0.06 - 0.41
1881 - 3682	235	944.33	5	529.5	0.12	0.04 - 0.34
3684 -7604	234	1064.82	0	0.0	--	--

CI: Confidence Interval

IU: International units

RR: relative risk

Table 8. **Study 320: Distribution of individuals, incidence rates of BCC per 100,000 person-years and RRs with 95% CI by quartiles of duration of treatment with Miacalcin.**

Duration of treatment (years)	Nº of persons in the quartile	Person-years	Cases of BCC	Incidence rate per 100,000 person-years	RR	95% CI
< 1.92	234	206.46	13	6296.6	1	--
1.93 - 4.02	233	674.74	8	1185.6	0.19	0.08 - 0.47
4.03 - 4.98	238	1125.68	1	88.8	0.01	0.00 - 0.11
4.99 - 5.61	231	1164.61	1	85.9	0.01	0.00 - 0.11

CI: Confidence Interval

RR: relative risk

Table 9. **Study 320: Expected number of skin incident SCC cases according to indirect standardization with the population of Rochester, Minnesota (1992).**

Miacalcin treated patients

Age group	SCC incidence rates per 100,000 female population	Person-years	Expected nº of SCC cases	Observed nº of SCC cases
35-44	51.2	4.99	0.00	0
45-54	135.4	123.01	0.17	0
55-64	185.3	869.01	1.61	1
65-74	222.4	1646.20	3.66	0
75-84	531.6	563.74	2.99	2
85+	1344.9	35.89	0.48	0
Total	--	3242.84	8.92	3
Standard Morbidity Ratio = 0.34 (95% CI: 0.07-0.98)				

Placebo

no cases

Whole study population

Standard Morbidity Ratio =0.25 (95% CI: 0.05-0.74)

Table 10. Study 320: Incidence rates of SCC per 100,000 person-years and RR by treatment arm

Treatment arm	Cases	Person-years at risk	Incidence rate	RR	95% CI
Placebo	0	1047.15	--	--	--
Total treated	3	3242.84	92.51	--	--
Miacalcin 100 IU	1	1049.11	95.32	1	--
Miacalcin 200 IU	1	1110.18	90.08	0.94	0.12 - 7.32
Miacalcin 400 IU	1	1083.55	92.29	0.97	0.12 - 7.50

RR: relative risk
CI: Confidence Interval
IU: international units

Miacalcin 100 IU treatment arm was taken as the reference group because there were no cases in the placebo group

Table 11. **Study 320: Distribution of individuals, incidence rates of SCC per 100,000 person-years and RRs with 95% CI by quartiles of cumulative dose intake of Miacalcin.**

Cumulative dose range (IU x 10^{-2})	Nº of persons in the quartile	Person-years	Cases of SCC	Incidence rate per 100,000 person-years	RR	95% CI
< 1159	235	285.01	1	350.8	1	--
1168 - 1930	236	931.38	1	107.4	0.31	0.04 - 2.37
1940 - 3694	236	953.58	1	104.9	0.30	0.04 - 2.32
3696 - 7604	236	1072.82	0	0.0	--	--

CI: Confidence Interval

IU: International units

RR: relative risk

Table 12. **Study 320: Distribution of individuals, incidence rates of SCC per 100,000 person-years and RRs with 95% CI by quartiles of duration of treatment with Miacalcin.**

Duration of treatment (years)	Nº of persons in the quartile	Person-years	Cases of SCC	Incidence rate per 100,000 person-years	RR	95% CI
< 1.97	236	221.81	1	450.8	1	--
1.98 - 4.01	235	704.60	1	141.9	0.31	0,04 - 2.44
4.02- 4.99	239	1141.47	1	87.6	0.19	0.03 - 1.51
5.00 - 5.61	233	1174.97	0	0.0	--	--

CI: Confidence Interval

RR: relative risk

Table 13. **Study 320: Expected number of skin BCC malignancies according to indirect standardization with the non-hispanic white female population of Albuquerque, New Mexico (1989-91).**

Miacalcin treated patients

Age group	BCC annual rates per 100,000	Person-years	Expected nº of BCCs	Observed nº of BCCs
40-49	439	44.2	0.19	0
50-59	778	371.9	2.89	2
60-69	1,524	1,443.1	21.99	13
70-79	1,959	1,210.0	23.70	16
80+	2,670	181.9	4.86	1
Total	--	3,251.1	53.64	32

Standard Morbidity Ratio = 0.60 (95% CI: 0.41 - 0.85)

Table 14. **Study 320: Expected number of skin SCC malignancies according to indirect standardization with the non-hispanic white female population of Albuquerque, New Mexico (1989-91).**

Miacalcin treated patients

Age group	SCC annual rates per 100,000	Person-years	Expected nº of SCCs	Observed nº of SCCs
40-49	42	44.2	0.02	0
50-59	22	371.9	0.08	0
60-69	237	1,443.1	3.42	1
70-79	260	1,210.0	3.14	2
80+	679	181.9	1.23	1
Total	--	3,251.1	7.90	4
Standard Morbidity Ratio =0.51 (95%CI: 0.14 - 1.31)				

Addendum

Epidemiological Assessment of Non-Melanoma Skin Cancer Cases in the Clinical Trial Nº 320 (Miacalcin® Salmon Calcitonin)

Clinical Safety and Epidemiology

Global Epidemiology

Author(s): Montserrat Miret MD, MPH

Lia P. Gutiérrez, BSN, MPH

Release date: September 22 1998

Since the Epidemiology report was completed based on the (last patient last visit) of the study on April 20, 1998, the following additional information was identified:

Pt. No. 09005 (200 IU) - Squamous Cell Carcinoma

Pt. No. 19033 (200 IU) - Squamous Cell Carcinoma

Pt. No. 33032 (400 IU) - Basel Cell Carcinoma (2nd incident)

This additional information does not change the main conclusion that was provided in this report.

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Appendix 4 Epidemiological Assessment of Breast Cancer Cases in the Clinical Trial Nº 320 (Miacalcin® Salmon Calcitonin). Gutierrez LP, Miret M (1998)

NOVARTIS

Novartis Farmacéutica
Barcelona, Spain

Clinical Safety and Epidemiology

Global Pharmacoepidemiology

Miacalcic® Nasal Spray 200 IU
(Salmon Calcitonin)

Epidemiological Assessment of Breast Cancer Cases in the Clinical Trial Nº 320

Author(s): Lia P. Gutierrez, BSN, MPH
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Glossary of abbreviations

BMD	-	bone mineral density
BMI	-	body mass index
CI	-	confidence interval
IR	-	incidence rate
LPLV	-	last patient last visit
N =	-	number of patients in a trial or treatment group
PY	-	person-years
RR	-	relative risk
SEER	-	Surveillance, Epidemiology and End Results Program
SMR	-	Standard Morbidity Ratio

1. Summary

The Miacalcic® (salmon calcitonin) Study N° 320 is a multicenter trial conducted in the United States and the United Kingdom with the objective of investigating the efficacy of three doses of Mialcalcic Nasal Spray (NS) versus placebo in the prevention of osteoporotic vertebral fractures. A total of 1255 postmenopausal women was randomized into four treatment groups. At the time of the final analysis, 16 women were diagnosed as having primary breast cancer (14 in the Miacalcic groups and 2 in the placebo group). Additionally three women (2 in the Miacalcic 400 IU group and one in the placebo group) were diagnosed with recurrent breast carcinomas. This document reports the results of the analysis conducted to assess the incident breast cancer morbidity experience in this cohort of postmenopausal patients.

The 1255 women were followed, on average 3.2 years, and generated a total of 4287.13 person-years of follow-up. After application of the indirect standardization method[1], the total expected number of breast cancer cases (16.24) was found to be the same than the observed number of incident cases (16) in the Mialcalcic Study 320, indicating that the breast cancer morbidity experience in study subjects did not differ from the breast cancer morbidity in the standard population[2] of reference. Estimation of the incidence rates (IR) of breast cancer by treatment arm did not reveal a significant association of Mialcalcic and breast cancer. The assessments of the effects of Mialcalcic cumulative dose intake and duration of treatment also supported lack of association between exposure to Mialcalcic and incident breast cancer.

There were three recurrent breast cancer cases diagnosed during the study period. When these cases were included in the analyses (worst case scenario analysis) very similar results were obtained.

2. Background

The Miacalcic NS Study N° 320 was designed as a multicentered, double-blind, placebo-controlled randomized study and was conducted in forty-two centers in the United States and seven centers in the United Kingdom, from February 1991 to April 20, 1998. The study aimed to determine the efficacy and safety of three dose levels of Miacalcic NS in reducing the rates of incident vertebral fractures in postmenopausal women with established osteoporosis. Patients were randomized to receive 100 IU, 200 IU, 400 IU Miacalcic NS or placebo once daily in the morning, for 5 years and were additionally requested to ingest at least 1500 mg calcium and 400 IU Vitamin D daily. At the time of the analysis, 16 of the 1255 patients included, had been diagnosed as having incident breast cancer.

There were no significant differences between treatment groups with respect to age, weight, height, race, lumbar bone mineral density (BMD), body mass index (BMI), history of smoking/alcohol use, personal biographical data or gynecological history (history of gynecological surgery, history of cervical, uterine, and/or ovarian neoplasms, use and duration of oral contraception, time since menopause and number of full-term pregnancies). The majority of patients were Caucasian (97%) and more than 5 years postmenopausal (98%). The patients' ages at entry ranged from 44 to 94 years (mean 68 years).

3. Objectives

This document reports the results of the analysis conducted with the aims of assessing whether there is an association between the exposure to Miacalcic NS and the occurrence of incident breast cancer by:

a) estimating the incidence rate in the different treatment arms;

b) comparing the breast cancer occurrence among study participants with that in a standard reference general population;

c) evaluating potential effects of treatment arm dose, cumulative dose and duration of exposure.

4. Methods

4.1. Data set

The analysis corresponds to the clinical trial database at the time of the "last patient last visit" (LPLV) of the study, on April 20, 1998.

4.2. Person-time calculation

Person-years of follow-up were calculated for the 1255 participants according to their breast cancer diagnosis and to their time on study as follows:

- patients who developed breast cancer (incident cases) during the study: time from trial initiation to breast cancer diagnosis;
- patients who completed the study (were followed for 5 years): time from trial initiation to the end of the study;
- patients who discontinued medication prematurely: time from trial initiation to last follow-up visit on drug;
- subsequently, patients who were diagnosed with "recurrent breast carcinomas" were included in a second analysis in which they were treated as incident cases and their person-time calculation based on time from trial initiation to diagnosis of the recurrence.

4.3. Analysis

4.3.1. Indirect Standardization Method

The indirect standardization[1] method was used to compare the study breast cancer occurrence with that in the white female population of the USA from the Surveillance, Epidemiology and End Results Program (SEER)[2] shown in Table 1. In indirect standardization, age-specific annual incidence rates from a standard population (i.e., white female USA population, since 97% of the study population were Caucasian females mainly from the USA) are applied to the age-specific person-years of follow-up of the study population. This allows to estimate the

expected number of breast cancer cases in the study population if patients were diagnosed at the same (age-specific) rate as women in the standard population.

The Standard Morbidity Ratio (SMR), namely the ratio of the observed number of cases in the study population over the number of cases expected after standardization, was then calculated for the whole study population, and subsequently for the treated as well as the untreated patients. A SMR greater than one would indicate that the breast cancer morbidity experience in study subjects is greater than the breast cancer morbidity that would have been expected if study subjects were diagnosed with breast cancer at the same age-specific rates as people in the standard population. Ninety-five percent Confidence Intervals (95% CI) for these SMRs were calculated assuming a Poisson distribution.[3] A 95% CI of a parameter is the interval that would include the value of the parameter with a probability of 0.95. It is a measure of the precision with which a population parameter can be determined from a study: the narrower the CI, the greater the precision. It is directly related to the amount of information available.

4.3.2. Incidence rate

Incidence rates (IR) of breast cancer for each treatment arm and the respective relative risks (RR) and 95% CI were calculated. In this analysis, RR is the risk of developing primary breast cancer among women treated with Mialcalcic compared with the risk among women on placebo.

4.3.3. Analysis by dose and duration of exposure

Both to identify if there were dose groups at higher risks and to assess whether Mialcalcic presented a dose-effect response on the occurrence of breast cancer, categorization of the exposure to Mialcalcic by cumulative dose taken was computed for each individual by multiplying the duration of treatment in days by 100, 200 or 400 for patients treated with 100 IU, 200 IU or 400 IU, respectively. The distribution of cases according to this parameter was analyzed and relative risks were used to compare the risk of breast cancer across quartiles.

Similarly, individuals were distributed in quartiles of years of exposure to assess the effect of the duration of treatment on breast cancer incidence. Relative risks were used to compare the risk of breast cancer across quartiles.

4.3.4. Analysis including recurrent breast cancer cases

Three women were diagnosed with recurrent breast carcinomas. A worst case scenario analysis was performed on all breast cancer cases (incident and recurrent) assuming the possibility of a misdiagnosis – namely that these cases had been incident instead of recurrent– or a potential role of Mialcalcic in accelerating recurrence of breast cancer.

The statistical package used for this analysis was SAS version 6.12[4]

5. Results

Between February 1991 and July 1993, a total of 1255 postmenopausal patients with established osteoporosis was enrolled in the study. These women were randomly assigned to treatment arms as follows: 316 in the Mialcalcic NS 100 IU group, 316 in the Miacalcic NS 200 IU group, 312 in the Mialcalcic NS 400 IU group and 311 in the placebo group.

A total of 16 cases of primary breast cancer was diagnosed and information regarding the cases' age, time on the study and treatment arm is presented in Table 2. The same information for the three (3) cases of recurrent breast carcinoma is presented in Table 2A.

The 1255 participants were followed, on average 3.2 years, and generated a total of 4287.53 person-years of follow-up. The person-years distribution by treatment arm is presented in Table 3. For the purpose of applying the indirect standardization method, age-specific person-years of follow-up were computed for all participants in the trial (Table 4). The total expected number of breast cancer cases (16.24) was found to be the same than the observed number of cases (16) and the SMR was 0.99 (95% CI: 0.57 - 1.60). The same standardization method was used for the Mialcalcic treated and for the placebo patients separately (see Tables 5 and 6). In the treatment groups the observed number of cases (14) was slightly higher than the expected number of cases (12.29), the SMR for this group of patients was 1.14 (95% CI: 0.62-1.91). In the placebo group the observed number of cases (2) was slightly lower than the expected number of cases (3.95) and the SMR was 0.51 (95% CI: 0.06 - 1.84).

The incidence rates of breast cancer per 100 000 person-years for each treatment arm were estimated and the respective RR were calculated (Table 7). The overall RR of developing cancer for women treated with Mialcalcic compared to placebo was 2.3 (95 % CI: 0.51 - 9.96). Relative risks in the three arms compared to placebo were 3.0 (95 % CI: 0.61 -14.88); 1.4 (95 % CI: 0.24 - 8.47); and 2.4 (95 % CI: 0.47 - 12.46) for Mialcalcic 100 IU, 200 IU and 400 IU regimens, respectively.

Patients on Mialcalcic were distributed in quartiles by cumulative dose intake as shown on Table 8. The highest incidence rates per 100 000 person-years appeared in the lowest cumulative dose quartiles. Relative risks (incidence rate in the quartile / incidence rate in the lowest cumulative dose quartile) in the highest cumulative dose quartiles were lower than 1.

Table 9 presents the results of the duration of treatment analysis. Distribution of patients by time quartiles reflected the large number of patients who discontinued medication prematurely. Results indicated that the groups of patients treated for longer periods progressively presented lower incidence rates of breast cancer. Consequently RR in the longer duration of exposure quartiles (greater than 4 years) were close to zero.

6. Discussion

In the analysis by indirect standardization using as reference the USA white female population, the overall number of observed breast cancer cases in the study population was not different from the number of expected cases, as reflected by the SMR of 0.99 and the 95% CI including unity. The subgroup analysis for the Mialcalcic and placebo treated groups, showed a slightly higher number of observed cases for the Mialcalcic treated groups (SMR= 1.14; 95% CI: 0.62 - 1.91) and a lower number of observed cases for the placebo group (SMR= 0.51; 95% CI: 0.06 - 1.84). The wide 95% CI reflect the small amount of information on which these estimates are based, therefore they can be considered somewhat unstable from the statistical point of view.

The estimation of the overall incidence rate of breast cancer for the Mialcalcic treatment arms showed that Mialcalcic treated patients had 2.3 times higher risk of breast cancer when compared to the placebo group. However, as in the prior analysis due to sparse data, this result is unstable and compatible with no difference between the placebo and the treatment arms.

Two analyses, by cumulative dose and by duration of exposure, were performed in order to further explore a potential causal association of Mialcalcic treatment and breast cancer. Such an association would be suggested if RRs increased with higher doses and longer duration of exposure. However this does not occur in the Mialcalcic study. These results, although somewhat limited as above by sparse data do not suggest a causal effect of Mialcalcic on the occurrence of breast cancer.

No substantial changes were observed when the analysis including recurrent breast cancer cases was run (see Tables 7 and 7A). Although the RR for the treated patients slightly decreased (1.7), 95% CI were still quite large and included unity. Again, the results of both analyses reflect the statistical unstability of data due to the small number of cases. Neither the indirect standardization analysis and calculation of SMRs, nor the cumulative dose or the duration of treatment analyses (data not presented in this report) disclosed any relevant difference with respect to the first analysis.

7. Conclusions

The results of this epidemiological analysis show that the overall number of breast cancer cases diagnosed in the Mialcalcic NS study N° 320 is not different from what would have been expected in a reference general population (white females U.S.A.). Results for the Mialcalcic treatment groups showed that their breast cancer experience is not significantly different from the experience in the same general population. In the evaluation of the analysis the statistical unstability of results needs to be considered due to low numbers. Analyses by treatment arm dose, cumulative dose and duration of exposure do not support a causal role of Mialcalcic in the occurrence of breast cancer.

8. Tables

Table 1. U.S.A. Average annual incidence of breast cancer per 100 000 white females by age group. SEER* 1983-1987

Age group (years)	Incidence rate
45-49	186.5
50-54	221.0
55-59	272.1
60-64	334.6
65-69	392.2
70-74	417.8
75-79	443.8
80-84	442.1
85 +	410.8

* Surveillance, epidemiology & end results program (SEER)[2]

Table 2. Incident cases of breast cancer in Mialcalcic Study Nº 320: Age, treatment arm and duration on study

Case ID Number	Age (years)	Treatment arm	Time on study at diagnosis (months)
01013	49	Mialcalcic 100 IU	48.0
04016	55	Mialcalcic 100 IU	15.5
07024	72	Mialcalcic 400 IU	15.9
09013	82	Mialcalcic 100 IU	10.0
12025	75	Mialcalcic 400 IU	5.7
17010	72	Mialcalcic 100 IU	26.3
21023	70	Mialcalcic 200 IU	26.9
25005	75	Mialcalcic 200 IU	24.8
30009	61	Mialcalcic 100 IU	11.6
30027	84	Mialcalcic 100 IU	39.5
30053	69	Mialcalcic 400 IU	58.6
35025	56	Mialcalcic 200 IU	25.2
35030	59	Placebo	57.5
36015	69	Mialcalcic 400 IU	18.7
39019	67	Placebo	52.4
42002	64	Mialcalcic 400 IU	52.8

Table 2A. Recurrent cases of breast cancer in Mialcalcic Study Nº 320: Age, treatment arm and duration on study

Case ID Number	Age (years)	Treatment arm	Time on study at diagnosis (months)
16029	57	Mialcalcic 400 IU	43.2
31032	82	Placebo	20.2
47030	62	Mialcalcic 400 IU	49.1

Table 3. Distribution of person-years by treatment arm in the Mialcalcic NS study Nº 320

Treatment arm	Person-years
Placebo	1047.36
Total treated	3239.77
Mialcalcic NS 100 IU	1046.21
Mialcalcic NS 200 IU	1110.53
Mialcalcic NS 400 IU	1083.03
Total	4287.13

Table 4. Expected number of breast cancer cases in Study 320 Mialcalcic patients according to indirect standardization with the white female population of the U.S.A.

Age group	Breast Ca annual incidence rates per 100 000 population[1]	Person-yrs	Expected nº of breast cancer cases	Observed nº of breast cancer cases
45-49	186.5	48.36	0.09	1
50-54	221.0	101.79	0.22	0
55-59	272.1	403.27	1.10	3
60-64	334.6	784.27	2.62	2
65-69	392.2	1188.73	4.66	3
70-74	417.8	955.88	3.99	3
75-79	443.8	533.85	2.37	2
80-84	442.1	219.14	0.97	2
85+	410.8	51.87	0.21	0
Total	--	4287.13	16.24	16
Standard Morbidity Ratio = 0.99 (95% CI: 0.57-1.60)				

[1] USA white female population (SEER)

Table 5. Expected number of breast cancer cases in Mialcalcic treated patients according to indirect standardization with the white female population of the U.S.A.

Age group	Breast Ca annual incidence rates per 100 000 population[1]	treatment groups person-yrs	Expected nº of breast cancer cases	Observed nº of breast cancer cases
45-49	186.5	43.25	0.08	1
50-54	221.0	83.79	0.19	0
55-59	272.1	287.38	0.78	2
60-64	334.6	584.02	1.95	2
65-69	392.2	855.00	3.35	2
70-74	417.8	787.46	3.29	3
75-79	443.8	418.86	1.86	2
80-84	442.1	144.11	0.64	2
85+	410.8	35.89	0.15	0
Total	--	3239.77	12.29	14
Standard Morbidity Ratio= 1.14 (95% CI: 0.62-1.91)				

[1] USA white female population (SEER)

Table 6. Expected number of breast cancer cases in study placebo patients according to indirect standardization with the white female population of the U.S.A.

Age group	Breast Ca annual incidence rates per 100 000 population[1]	Person-yrs	Expected nº of breast cancer cases	Observed nº of breast cancer cases
45-49	186.5	5.11	0.01	0
50-54	221.0	17.99	0.04	0
55-59	272.1	115.88	0.32	1
60-64	334.6	200.25	0.67	0
65-69	392.2	333.72	1.31	1
70-74	417.8	168.42	0.70	0
75-79	443.8	114.98	0.51	0
80-84	442.1	75.03	0.33	0
85+	410.8	15.98	0.07	0
Total	--	1047.36	3.95	2
Standard Morbidity Ratio= 0.51 (95% CI: 0.06-1.84)				

[1] USA white female population (SEER)

Table 7. Incidence rates of breast cancer per 100 000 person-years and RR by treatment arm in Study Nº320.

Treatment arm	Cases	Person-years	Incidence rate	RR	95% CI
Placebo	2	1047.36	190.96	1	--
Total treated	14	3239.77	432.13	2.3	0.51 - 9.96
Mialcalcic 100 IU	6	1046.21	573.50	3.0	0.61 - 14.88
Mialcalcic 200 IU	3	1110.53	270.14	1.4	0.24 - 8.47
Mialcalcic 400 IU	5	1083.03	461.67	2.4	0.47 - 12.46

RR: relative risk
CI: Confidence Interval
IU: international units

Table 7A. Incidence rates of breast cancer per 100 000 person-years and RR by treatment arm in Study Nº320 (Recurrent cases included)

Treatment arm	Cases	Person-years	Incidence rate	RR	95% CI
Placebo	3	1047.02	286.53	1	--
Total treated	16	3239.24	493.94	1.7	0.50 - 5.92
Mialcalcic 100 IU	6	1046.21	573.50	2.0	0.50 - 8.00
Mialcalcic 200 IU	3	1110.53	270.14	0.9	0.19 - 4.67
Mialcalcic 400 IU	7	1082.50	646.65	2.3	0.58 - 8.73

RR: relative risk
CI: Confidence Interval
IU: international units

Table 8. **Distribution of individuals, incidence rates of breast cancer per 100 000 person-years and RRs with 95% CI by quartiles of cumulative dose intake of Mialcalcic.**

Cumulative dose range (IU)	Nº of persons in the quartile	Person-years	Cases of breast cancer	Incidence rate per 100,000 person-years	RR	95% CI
< 116,800	235	283.86	5	1761.4	1	--
117,200 -193,000	237	931.52	6	644.1	0.37	0.11 - 1.20
195,200 - 369,200	236	952.20	1	105.0	0.06	0.02 - 0.51
369,400 -760,400	236	1072.20	2	186.5	0.11	0.34 - 0.55

CI: Confidence Interval

IU: International units

RR: relative risk

Table 9. **Distribution of individuals, incidence rates of breast cancer per 100 000 person-years and RRs with 95% CI by quartiles of duration of treatment with Mialcalcic.**

Duration of treatment (years)	Nº of persons in the quartile	Person-years	Cases of breast cancer	Incidence rate per 100 000 person-years	RR	95% CI
< 1.98	236	221.05	6	2714.3	1	--
1.98 - 4.08	236	705.11	6	850.9	0.31	0.10 - 0.97
4.09 - 4.98	232	1103.84	2	181.2	0.07	0.01 - 0.33
4.99 - 5.61	240	1209.76	0	0	0.00	--

CI: Confidence Interval

IU: International units

RR: relative risk

9. References

1 Rothman KJ. Modern epidemiology. Little, Brown and Company, Boston 1986.

2 International Agency for Research on Cancer (IARC). Cancer Incidence in Five Continents. Volume VI. IARC Scientific Publications N° 120. Lyon 1992.

3 Breslow NE, Day NE. Statistical methods in cancer research. Volume II - The design and analysis of cohort studies. IARC Scientific Publications, Lyon, France, 1987; 69-70.

4 SAS System for Personal Computers. Release 6.08. Cary, NC: SAS Institute, Inc., 1992.

Appendix 5

Appendix 5 Meta-analysis tests for heterogeneity

Table 1.1a (Page 1 of 2)
Test of heterogeneity of odds ratios across studies

Malignancy	Program	Method	Q	P-value	df	I-squared
Any malignancy	Nasal calcitonin	Peto	11.4	0.5765	13	0.0
	Nasal calcitonin	Peto_CC	12.1	0.7934	17	0.0
	Nasal calcitonin	Peto_TA	11.5	0.8272	17	0.0
	Nasal calcitonin	MH_CC	8.6	0.9512	17	0.0
	Nasal calcitonin	MH_TA	8.5	0.9539	17	0.0
	Nasal + Oral calcitonin	Peto	20.4	0.2045	16	21.4
	Nasal + Oral calcitonin	Peto_CC	20.9	0.4046	20	4.2
	Nasal + Oral calcitonin	Peto_TA	20.4	0.4326	20	2.0
	Nasal + Oral calcitonin	MH_CC	16.7	0.6749	20	0.0
	Nasal + Oral calcitonin	MH_TA	16.8	0.6642	20	0.0
	200IU dosing level	Peto	11.6	0.2339	9	22.7
Any malignancy excluding Basal cell carcinoma	Nasal calcitonin	Peto	10.4	0.6599	13	0.0
	Nasal calcitonin	Peto_CC	10.9	0.8606	17	0.0
	Nasal calcitonin	Peto_TA	10.5	0.8830	17	0.0
	Nasal calcitonin	MH_CC	7.3	0.9797	17	0.0
	Nasal calcitonin	MH_TA	7.5	0.9765	17	0.0
	Nasal + Oral calcitonin	Peto	18.5	0.2973	16	13.4
	Nasal + Oral calcitonin	Peto_CC	18.9	0.5305	20	0.0
	Nasal + Oral calcitonin	Peto_TA	18.5	0.5556	20	0.0
	Nasal + Oral calcitonin	MH_CC	14.6	0.7978	20	0.0
	Nasal + Oral calcitonin	MH_TA	14.9	0.7800	20	0.0
Basal cell carcinoma	Nasal calcitonin	Peto	4.2	0.3738	4	5.8
	Nasal calcitonin	Peto_CC	7.8	0.9698	17	0.0
	Nasal calcitonin	Peto_TA	5.1	0.9975	17	0.0
	Nasal calcitonin	MH_CC	6.9	0.9845	17	0.0

Q = Cochran's Q statistic; df = number of studies included in the meta-analysis - 1
I-squared = 100% * (Q-df)/Q. Negative values of I-squared are set to zero.
MH=Mantel-Haenszel; CC=constant correction; TA=treatment arm correction

Table 1.1a (Page 2 of 2)
Test of heterogeneity of odds ratios across studies

Malignancy	Program	Method	Q	P-value	df	I-squared
Basal cell carcinoma	Nasal calcitonin	MH_TA	5.0	0.9976	17	0.0
	Nasal + Oral calcitonin	Peto	6.0	0.5342	7	0.0
	Nasal + Oral calcitonin	Peto_CC	10.2	0.9650	20	0.0
	Nasal + Oral calcitonin	Peto_TA	7.1	0.9965	20	0.0
	Nasal + Oral calcitonin	MH_CC	9.0	0.9834	20	0.0
	Nasal + Oral calcitonin	MH_TA	6.4	0.9982	20	0.0

Q = Cochran's Q statistic; df = number of studies included in the meta-analysis - 1
I-squared = 100% * (Q-df)/Q. Negative values of I-squared are set to zero.
MH=Mantel-Haenszel; CC=constant correction; TA=treatment arm correction

Appendix 6

Appendix 6 Forest plots of meta-analysis results for Miacalcin malignancy risk

NOVARTIS

Drug Regulatory Affairs

Miacalcin® (calcitonin-salmon)

FDA Joint Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee Meeting on the Benefit/Risk of Salmon Calcitonin for the Treatment of Postmenopausal Osteoporosis

Appendix 6: Forest plots of meta-analysis results

Author(s): Peter Mesenbrink

Document type: Briefing book appendix

Document status: Final

Release date: 28-Jan-2013

CSMC021– Safety Analysis 2012

Figure 4.1a (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.27(0.16– 9.95)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.18– 2.32)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.77(0.57– 5.51)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.62(1.00– 2.61)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 45.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 522	4.0/ 156.0 (2.56)	0.0/ 52.0 (0.00)	3.87(0.40– 37.81)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	122.0/2304.0 (5.30)	30.0/1021.0 (2.94)	1.54(1.06– 2.23)

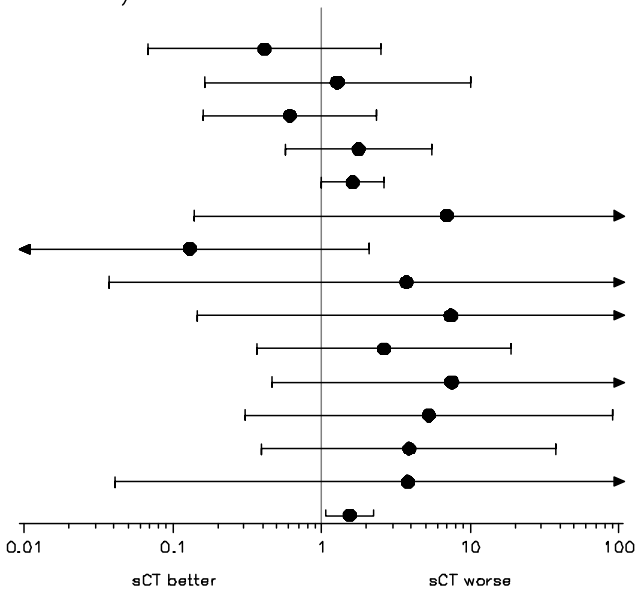

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Figure 4.1b (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto with constant correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.27(0.16– 9.95)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.77(0.57– 5.51)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.62(1.00– 2.61)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.47(<.01– 30.10)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.47(<.01– 30.20)
SMCO 522	4.0/ 156.0 (2.56)	0.0/ 52.0 (0.00)	3.87(0.40– 37.81)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	124.0/2716.0 (4.57)	32.0/1313.0 (2.44)	1.50(1.04– 2.16)

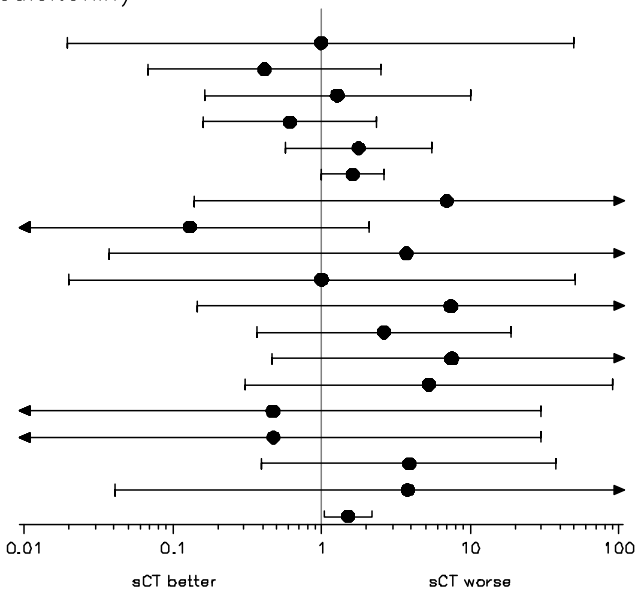

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Figure 4.1c (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto with treatment arm correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.27(0.16– 9.95)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.77(0.57– 5.51)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.62(1.00– 2.61)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 74.06)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 74.02)
SMCO 522	4.0/ 156.0 (2.56)	0.0/ 52.0 (0.00)	3.87(0.40– 37.81)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	124.4/2716.6 (4.58)	31.6/1312.4 (2.41)	1.52(1.06– 2.19)

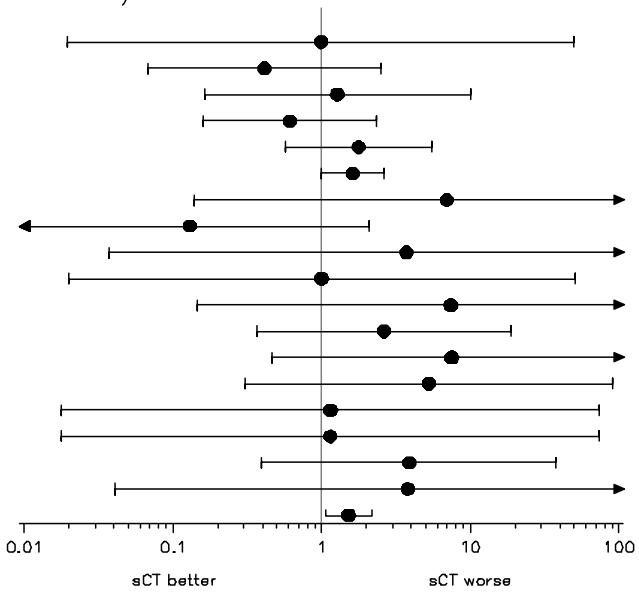

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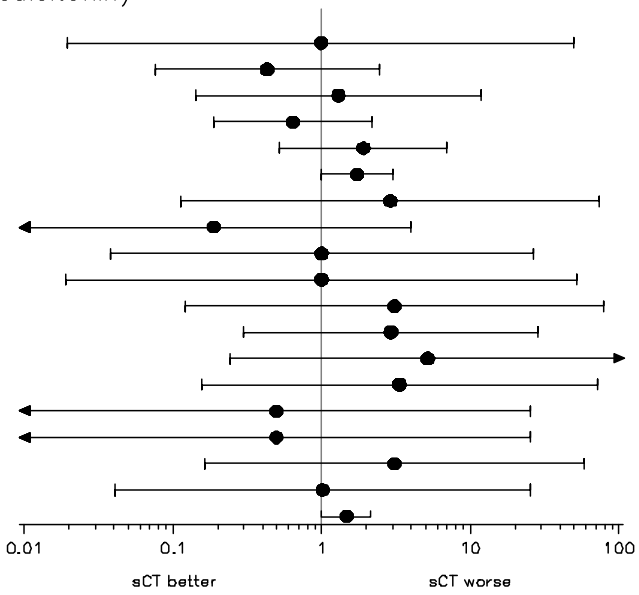
Figure 4.1d (Page 1 of 1)
Incidences and odds ratio for any malignancy by MH with constant correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.29(0.14– 11.78)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.91(0.52– 7.01)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.73(>.99– 3.01)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	2.5/ 46.0 (5.43)	0.19(<.01– 4.01)
SMCO 005	1.5/ 33.0 (4.55)	0.5/ 11.0 (4.55)	1.00(0.04– 26.47)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.5/ 72.0 (3.47)	0.5/ 47.0 (1.06)	3.35(0.16– 71.28)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.50(<.01– 25.19)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.50(<.01– 25.57)
SMCO 522	4.5/ 157.0 (2.87)	0.5/ 53.0 (0.94)	3.10(0.18– 58.52)
SMCO 524	1.5/ 101.0 (1.49)	0.5/ 34.0 (1.47)	1.01(0.04– 25.39)
Total	128.0/2724.0 (4.70)	36.0/1321.0 (2.73)	1.47(>.99– 2.15)



MH: Mantel–Haenszel method

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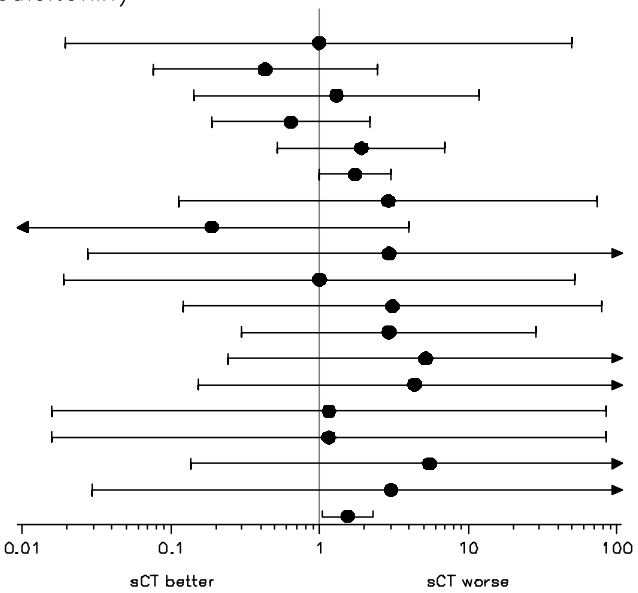
Figure 4.1e (Page 1 of 1)
Incidences and odds ratio for any malignancy by MH with treatment arm correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.29(0.14– 11.78)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.91(0.52– 7.01)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.73(>.99– 3.01)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	2.5/ 46.0 (5.43)	0.19(<.01– 4.01)
SMCO 005	1.8/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	4.8/ 157.5 (3.05)	0.3/ 52.5 (0.57)	5.47(0.13– 221.6)
SMCO 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	129.4/2726.3 (4.75)	34.7/1318.7 (2.63)	1.54(1.04– 2.27)



MH: Mantel–Haenszel method

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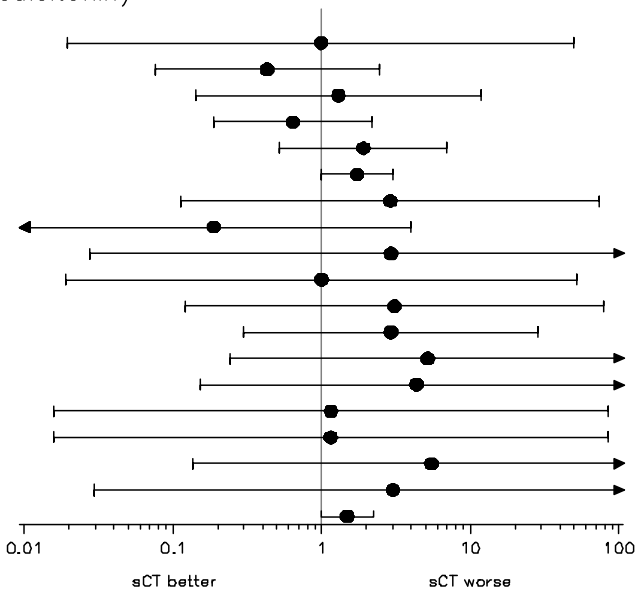
Figure 4.1f (Page 1 of 1)
Incidences and odds ratio for any malignancy by random effect model
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.29(0.14– 11.78)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.91(0.52– 7.01)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.73(>.99– 3.01)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	2.5/ 46.0 (5.43)	0.19(<.01– 4.01)
SMCO 005	1.8/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	4.8/ 157.5 (3.05)	0.3/ 52.5 (0.57)	5.47(0.13– 221.6)
SMCO 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	129.4/2726.3 (4.75)	34.7/1318.7 (2.63)	1.49(>.99– 2.22)



Odds ratio for each study obtained by Mantel–Haenszel with treatment arm correction
Random effect model applied to the pooled odds ratio

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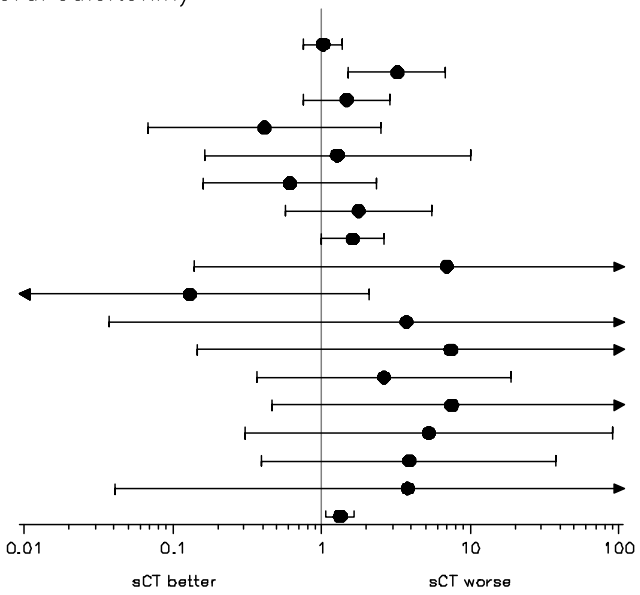
Figure 4.2a (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto
(Nasal and Oral calcitonin)

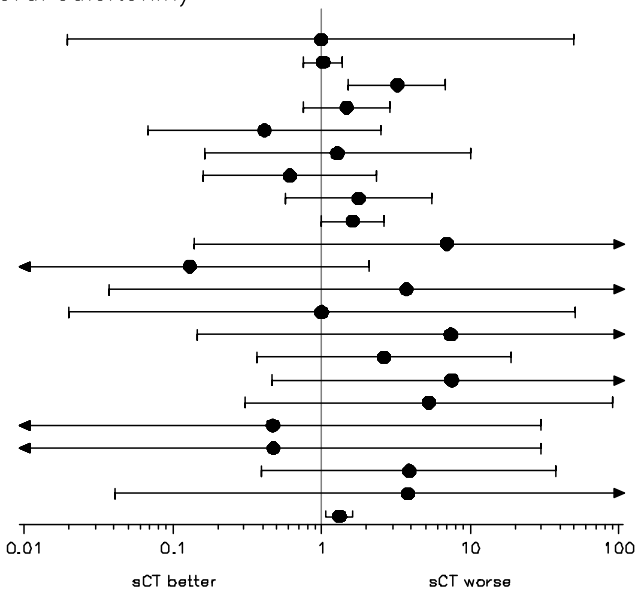
Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
A2303	89.0/2334.0 (3.81)	87.0/2331.0 (3.73)	1.02(0.76– 1.38)
C2301	22.0/ 585.0 (3.76)	6.0/ 584.0 (1.03)	3.22(1.52– 6.81)
C2302	21.0/ 520.0 (4.04)	14.0/ 508.0 (2.76)	1.48(0.75– 2.90)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.27(0.16– 9.95)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.77(0.57– 5.51)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.62(1.00– 2.61)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 522	4.0/ 156.0 (2.56)	0.0/ 52.0 (0.00)	3.87(0.40– 37.81)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	254.0/5743.0 (4.42)	137.0/4444.0 (3.08)	1.33(1.07– 1.64)



CSMC021– Safety Analysis 2012

Figure 4.2b (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto with constant correction
(Nasal and Oral calcitonin)

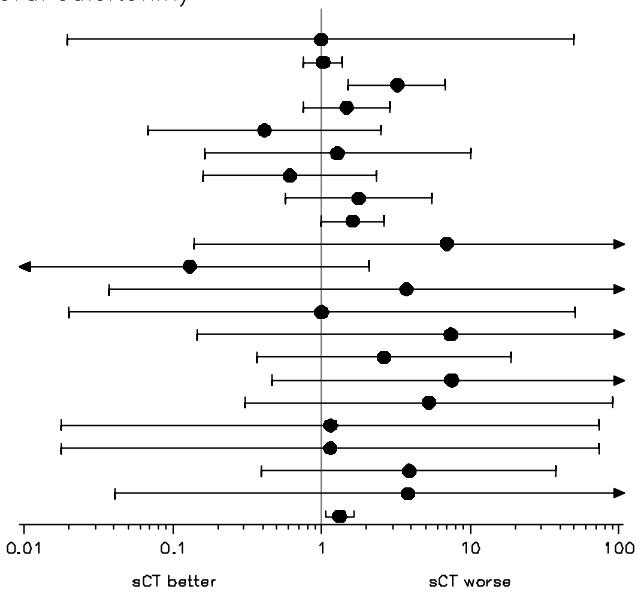
Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
A2303	89.0/2334.0 (3.81)	87.0/2331.0 (3.73)	1.02(0.76– 1.38)
C2301	22.0/ 585.0 (3.76)	6.0/ 584.0 (1.03)	3.22(1.52– 6.81)
C2302	21.0/ 520.0 (4.04)	14.0/ 508.0 (2.76)	1.48(0.75– 2.90)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.27(0.16– 9.95)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.77(0.57– 5.51)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.62(1.00– 2.61)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 5D3	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 5D4	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 5D6	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.47(<.01– 30.10)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.47(<.01– 30.20)
SMCO 522	4.0/ 156.0 (2.56)	0.0/ 52.0 (0.00)	3.87(0.40– 37.81)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	256.0/6155.0 (4.16)	139.0/4736.0 (2.93)	1.32(1.07– 1.63)



CSMC021– Safety Analysis 2012

Figure 4.2c (Page 1 of 1)
Incidences and odds ratio for any malignancy by Peto with treatment arm correction
(Nasal and Oral calcitonin)

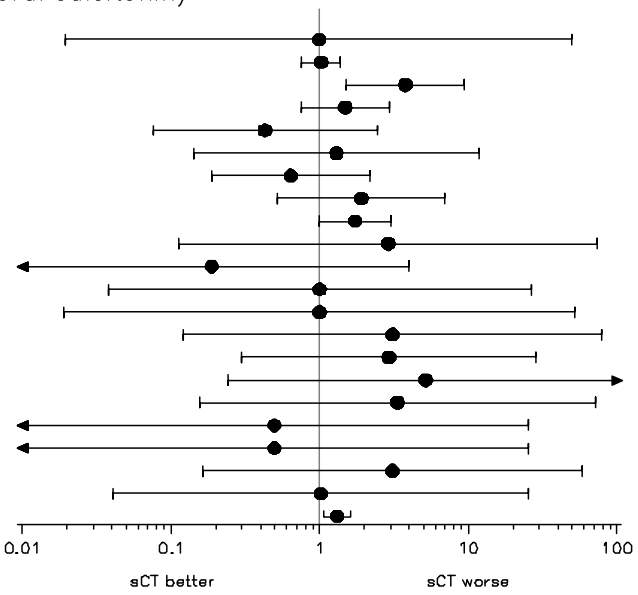
Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
A2303	89.0/2334.0 (3.81)	87.0/2331.0 (3.73)	1.02(0.76– 1.38)
C2301	22.0/ 585.0 (3.76)	6.0/ 584.0 (1.03)	3.22(1.52– 6.81)
C2302	21.0/ 520.0 (4.04)	14.0/ 508.0 (2.76)	1.48(0.75– 2.90)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.27(0.16– 9.95)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.77(0.57– 5.51)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.62(1.00– 2.61)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 74.06)
SMCO 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 74.02)
SMCO 522	4.0/ 156.0 (2.56)	0.0/ 52.0 (0.00)	3.87(0.40– 37.81)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	256.4/6155.6 (4.17)	138.6/4735.4 (2.93)	1.32(1.07– 1.64)



CSMC021– Safety Analysis 2012

Figure 4.2d (Page 1 of 1)
Incidences and odds ratio for any malignancy by MH constant correction
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
A2303	89.0/2334.0 (3.81)	87.0/2331.0 (3.73)	1.02(0.76– 1.38)
C2301	22.0/ 585.0 (3.76)	6.0/ 584.0 (1.03)	3.76(1.52– 9.35)
C2302	21.0/ 520.0 (4.04)	14.0/ 508.0 (2.76)	1.48(0.75– 2.95)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.29(0.14– 11.78)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.91(0.52– 7.01)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.73(>.99– 3.01)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	2.5/ 46.0 (5.43)	0.19(<.01– 4.01)
SMCO 005	1.5/ 33.0 (4.55)	0.5/ 11.0 (4.55)	1.00(0.04– 26.47)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.5/ 72.0 (3.47)	0.5/ 47.0 (1.06)	3.35(0.16– 71.28)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.50(<.01– 25.19)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.50(<.01– 25.57)
SMCO 522	4.5/ 157.0 (2.87)	0.5/ 53.0 (0.94)	3.10(0.16– 58.52)
SMCO 524	1.5/ 101.0 (1.49)	0.5/ 34.0 (1.47)	1.01(0.04– 25.39)
Total	260.0/6163.0 (4.22)	143.0/4744.0 (3.01)	1.31(1.06– 1.62)



MH: Mantel–Haenszel method

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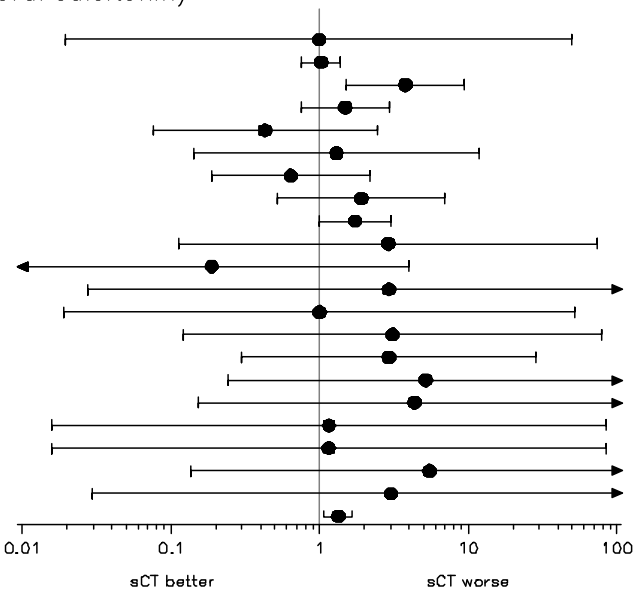
Final Version

CSMC021– Safety Analysis 2012

Figure 4.2e (Page 1 of 1)
Incidences and odds ratio for any malignancy by MH treatment arm correction
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
A2303	89.0/2334.0 (3.81)	87.0/2331.0 (3.73)	1.02(0.76– 1.38)
C2301	22.0/ 585.0 (3.76)	6.0/ 584.0 (1.03)	3.76(1.52– 9.35)
C2302	21.0/ 520.0 (4.04)	14.0/ 508.0 (2.76)	1.48(0.75– 2.95)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.29(0.14– 11.78)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.91(0.52– 7.01)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.73(>.99– 3.01)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	2.5/ 46.0 (5.43)	0.19(<.01– 4.01)
SMCO 005	1.8/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	4.8/ 157.5 (3.05)	0.3/ 52.5 (0.57)	5.47(0.13– 221.6)
SMCO 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	261.4/6165.3 (4.24)	141.7/4741.7 (2.99)	1.33(1.07– 1.65)



MH: Mantel–Haenszel method

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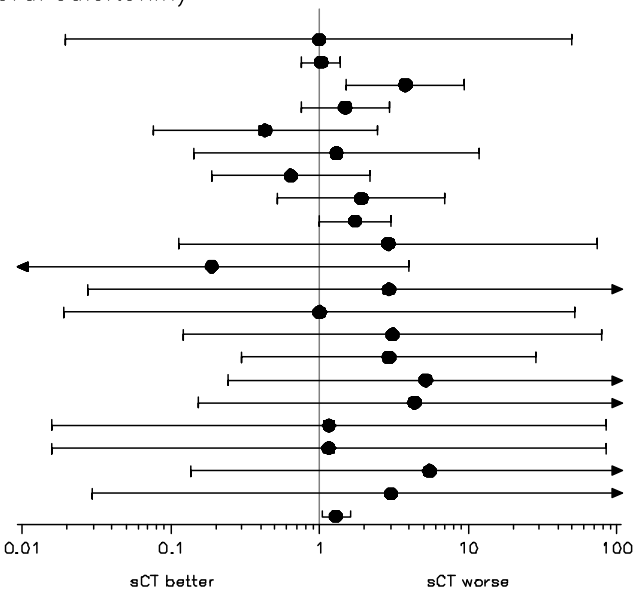
Final Version

CSMC021– Safety Analysis 2012

Figure 4.2f (Page 1 of 1)

Incidences and odds ratio for any malignancy by random effect model
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
A2303	89.0/2334.0 (3.81)	87.0/2331.0 (3.73)	1.02(0.76– 1.38)
C2301	22.0/ 585.0 (3.76)	6.0/ 584.0 (1.03)	3.76(1.52– 9.35)
C2302	21.0/ 520.0 (4.04)	14.0/ 508.0 (2.76)	1.48(0.75– 2.95)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	4.0/ 211.0 (1.90)	1.0/ 68.0 (1.47)	1.29(0.14– 11.78)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	11.0/ 201.0 (5.47)	3.0/ 102.0 (2.94)	1.91(0.52– 7.01)
CT 320	81.0/ 944.0 (8.58)	16.0/ 311.0 (5.14)	1.73(>.99– 3.01)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	2.5/ 46.0 (5.43)	0.19(<.01– 4.01)
SMCO 005	1.5/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	4.8/ 157.5 (3.05)	0.3/ 52.5 (0.57)	5.47(0.13– 221.6)
SMCO 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	261.4/6165.3 (4.24)	141.7/4741.7 (2.99)	1.28(1.03– 1.60)



Odds ratio for each study obtained by Mantel–Haenszel with treatment arm correction
Random effect model applied to the pooled odds ratio

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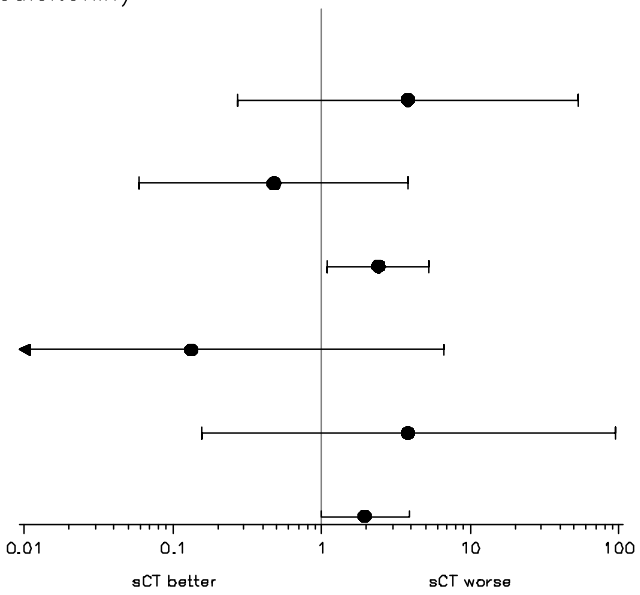
CSMC021– Safety Analysis 2012

Figure 4.3a (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto
(Nasal calcitonin)

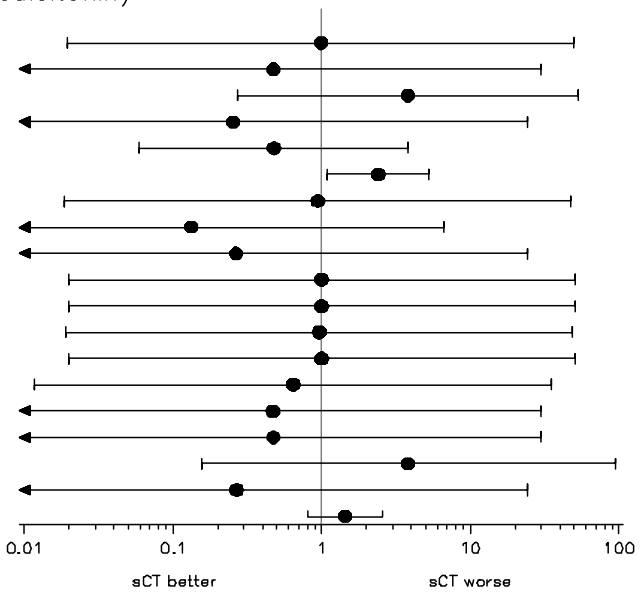
Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 310	3.0/ 211.0 (1.42)	0.0/ 68.0 (0.00)	3.79(0.27– 53.36)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.48(0.06– 3.84)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	2.41(1.09– 5.30)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMC0 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
Total	38.0/1558.0 (2.44)	6.0/ 578.0 (1.04)	1.95(0.99– 3.86)



CSMC021– Safety Analysis 2012

Figure 4.3b (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto with constant correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
CT 211	0.5/ 32.0 (1.56)	0.5/ 16.0 (3.13)	0.47(<.01– 30.20)
CT 310	3.0/ 211.0 (1.42)	0.0/ 68.0 (0.00)	3.79(0.27– 53.36)
CT 311	0.5/ 245.0 (0.20)	0.5/ 80.0 (0.63)	0.25(<.01– 24.09)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.48(0.05– 3.84)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	2.41(1.09– 5.30)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 47.43)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	0.5/ 33.0 (1.52)	0.5/ 11.0 (4.55)	0.26(<.01– 24.36)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 50.40)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.39)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 50.40)
SMCO 514	0.5/ 72.0 (0.69)	0.5/ 47.0 (1.06)	0.64(0.01– 35.51)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.47(<.01– 30.10)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.47(<.01– 30.20)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	0.5/ 101.0 (0.50)	0.5/ 34.0 (1.47)	0.27(<.01– 24.49)
Total	44.5/2725.0 (1.63)	12.5/1322.0 (0.95)	1.44(0.80– 2.59)



CSMC021– Safety Analysis 2012

Figure 4.3c (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto with treatment arm correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
CT 211	0.7/ 32.3 (2.17)	0.3/ 15.7 (1.91)	1.13(0.02– 73.76)
CT 310	3.0/ 211.0 (1.42)	0.0/ 68.0 (0.00)	3.79(0.27– 53.36)
CT 311	0.8/ 245.5 (0.33)	0.2/ 79.5 (0.25)	1.27(0.01– 121.6)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.48(0.05– 3.84)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	2.41(1.09– 5.30)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 47.43)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	0.8/ 33.5 (2.39)	0.2/ 10.5 (1.90)	1.24(0.01– 122.8)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 50.40)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.39)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 50.40)
SMCO 514	0.6/ 72.2 (0.83)	0.4/ 46.8 (0.85)	0.97(0.02– 53.74)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 74.06)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 74.02)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	0.8/ 101.5 (0.79)	0.2/ 33.5 (0.60)	1.29(0.01– 121.0)
Total	46.1/2727.6 (1.69)	10.9/1319.4 (0.83)	1.66(0.92– 2.99)

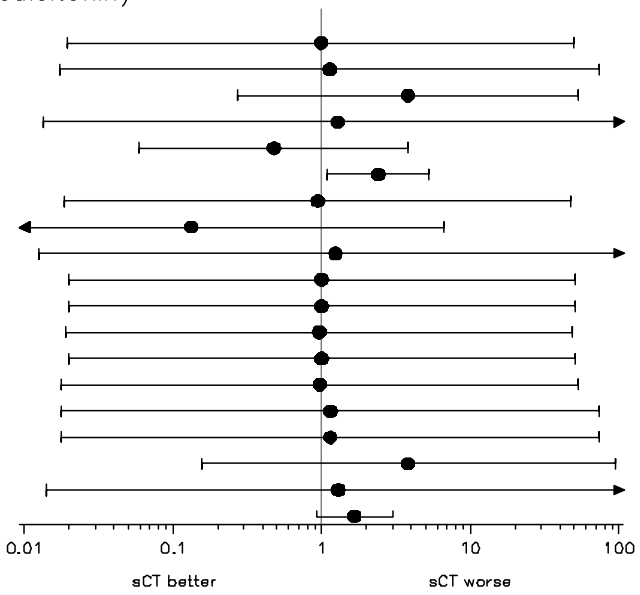


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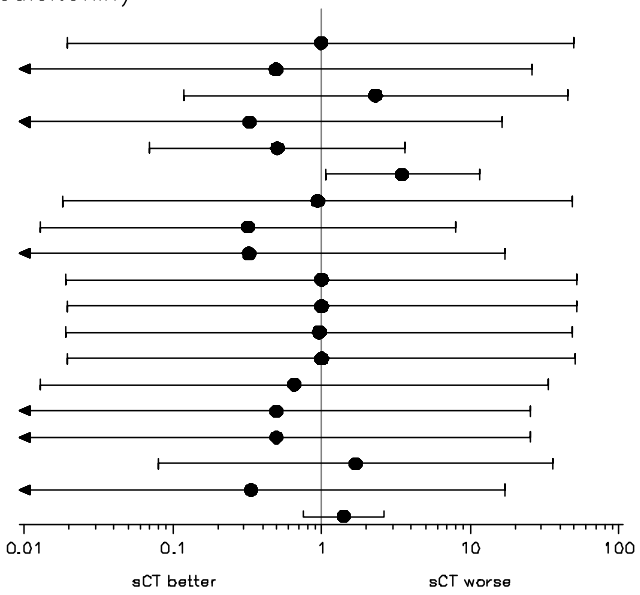
Figure 4.3d (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by MH with constant correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	0.5/ 32.0 (1.56)	0.5/ 16.0 (3.13)	0.49(<.01– 25.99)
CT 310	3.5/ 212.0 (1.65)	0.5/ 69.0 (0.72)	2.30(0.12– 45.08)
CT 311	0.5/ 245.0 (0.20)	0.5/ 80.0 (0.63)	0.33(<.01– 16.52)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.50(0.07– 3.62)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	3.49(1.06– 11.48)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 48.79)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	0.5/ 33.0 (1.52)	0.5/ 11.0 (4.55)	0.32(<.01– 17.31)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 52.09)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.68)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 51.22)
SMCO 514	0.5/ 72.0 (0.69)	0.5/ 47.0 (1.06)	0.65(0.01– 33.35)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.50(<.01– 25.19)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.50(<.01– 25.57)
SMCO 522	2.5/ 157.0 (1.59)	0.5/ 53.0 (0.94)	1.70(0.08– 35.96)
SMCO 524	0.5/ 101.0 (0.50)	0.5/ 34.0 (1.47)	0.33(<.01– 17.13)
Total	46.0/2728.0 (1.69)	14.0/1325.0 (1.06)	1.41(0.75– 2.63)



MH: Mantel–Haenszel method

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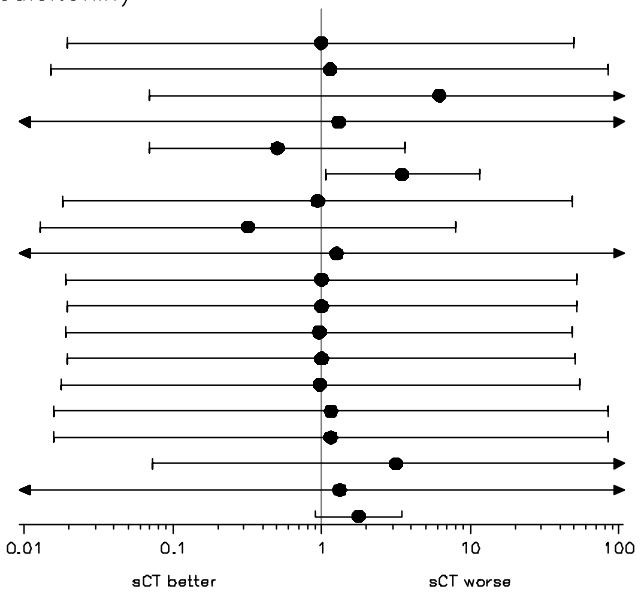
Figure 4.3e (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by MH with treatment arm correction
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	0.7/ 32.3 (2.17)	0.3/ 15.7 (1.91)	1.14(0.02– 85.51)
CT 310	3.8/ 212.5 (1.79)	0.2/ 68.5 (0.29)	6.22(0.07– 562.4)
CT 311	0.8/ 245.5 (0.33)	0.2/ 79.5 (0.25)	1.30(<.01– 175.2)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.50(0.07– 3.62)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	3.49(1.06– 11.48)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 48.79)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	0.8/ 33.5 (2.39)	0.2/ 10.5 (1.90)	1.26(<.01– 177.8)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 52.09)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.68)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 51.22)
SMCO 514	0.6/ 72.2 (0.83)	0.4/ 46.8 (0.85)	0.97(0.02– 54.02)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMCO 524	0.8/ 101.5 (0.79)	0.2/ 33.5 (0.60)	1.32(<.01– 180.4)
Total	48.2/2731.6 (1.76)	11.9/1321.4 (0.90)	1.77(0.91– 3.45)



MH: Mantel–Haenszel method

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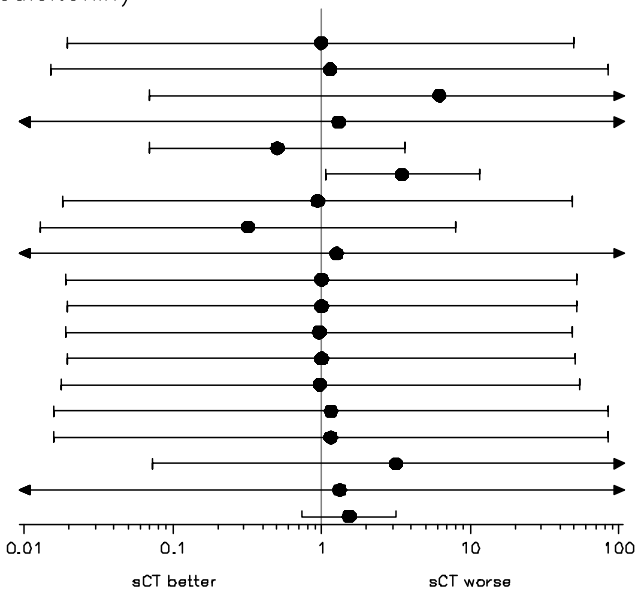
Figure 4.3f (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by random effect model
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	0.7/ 32.3 (2.17)	0.3/ 15.7 (1.91)	1.14(0.02– 85.51)
CT 310	3.8/ 212.5 (1.79)	0.2/ 68.5 (0.29)	6.22(0.07– 562.4)
CT 311	0.8/ 245.5 (0.33)	0.2/ 79.5 (0.25)	1.30(<.01– 175.2)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.50(0.07– 3.62)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	3.49(1.06– 11.48)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 48.79)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	0.8/ 33.5 (2.39)	0.2/ 10.5 (1.90)	1.26(<.01– 177.8)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 52.09)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.68)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 51.22)
SMCO 514	0.6/ 72.2 (0.83)	0.4/ 46.8 (0.85)	0.97(0.02– 54.02)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMCO 524	0.8/ 101.5 (0.79)	0.2/ 33.5 (0.60)	1.32(<.01– 180.4)
Total	48.2/2731.6 (1.76)	11.9/1321.4 (0.90)	1.53(0.74– 3.15)



Odds ratio for each study obtained by Mantel–Haenszel with treatment arm correction
Random effect model applied to the pooled odds ratio

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Figure 4.4a (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
A2303	16.0/2334.0 (0.69)	8.0/2331.0 (0.34)	1.95(0.88– 4.35)
C2301	3.0/ 585.0 (0.51)	0.0/ 584.0 (0.00)	7.40(0.77– 71.30)
C2302	2.0/ 520.0 (0.38)	2.0/ 508.0 (0.39)	0.98(0.14– 6.96)
CT 310	3.0/ 211.0 (1.42)	0.0/ 68.0 (0.00)	3.79(0.27– 53.36)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.48(0.06– 3.84)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	2.41(1.09– 5.30)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
Total	59.0/4997.0 (1.18)	16.0/4001.0 (0.40)	1.99(1.22– 3.25)

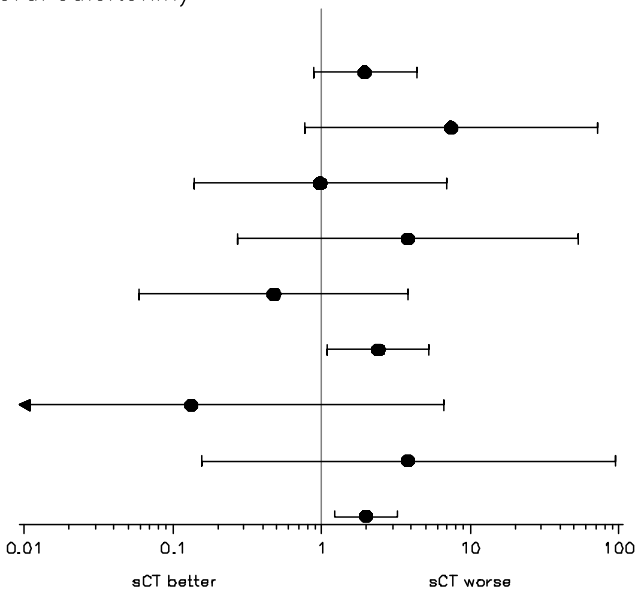

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Figure 4.4b (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto with constant correction
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
A2303	16.0/2334.0 (0.69)	8.0/2331.0 (0.34)	1.95(0.88– 4.35)
C2301	3.0/ 585.0 (0.51)	0.0/ 584.0 (0.00)	7.40(0.77– 71.30)
C2302	2.0/ 520.0 (0.38)	2.0/ 508.0 (0.39)	0.98(0.14– 6.96)
CT 211	0.5/ 32.0 (1.56)	0.5/ 16.0 (3.13)	0.47(<.01– 30.20)
CT 310	3.0/ 211.0 (1.42)	0.0/ 68.0 (0.00)	3.79(0.27– 53.36)
CT 311	0.5/ 245.0 (0.20)	0.5/ 80.0 (0.63)	0.25(<.01– 24.09)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.48(0.06– 3.84)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	2.41(1.09– 5.30)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 47.43)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	0.5/ 33.0 (1.52)	0.5/ 11.0 (4.55)	0.26(<.01– 24.36)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 50.40)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.39)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 50.40)
SMCO 514	0.5/ 72.0 (0.69)	0.5/ 47.0 (1.06)	0.64(0.01– 35.51)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.47(<.01– 30.10)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.47(<.01– 30.20)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	0.5/ 101.0 (0.50)	0.5/ 34.0 (1.47)	0.27(<.01– 24.49)
Total	65.5/6164.0 (1.06)	22.5/4745.0 (0.47)	1.66(1.06– 2.60)

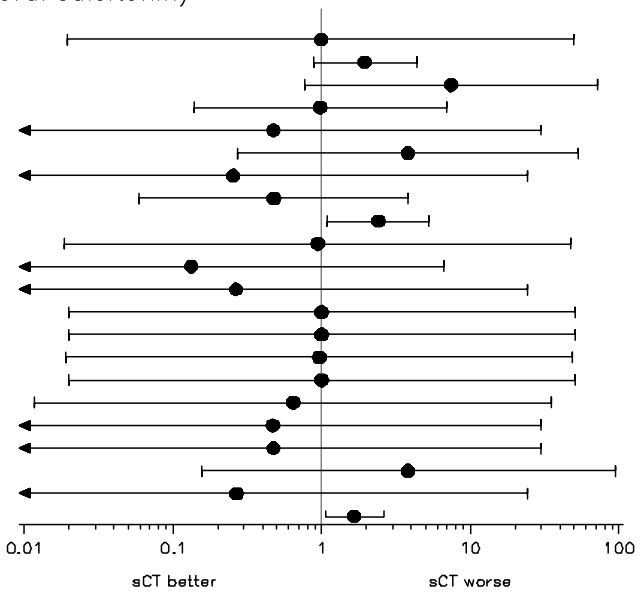

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Figure 4.4c (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by Peto with treatment arm correction
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
A2303	16.0/2334.0 (0.69)	8.0/2331.0 (0.34)	1.95(0.88– 4.35)
C2301	3.0/ 585.0 (0.51)	0.0/ 584.0 (0.00)	7.40(0.77– 71.30)
C2302	2.0/ 520.0 (0.38)	2.0/ 508.0 (0.39)	0.98(0.14– 6.96)
CT 211	0.7/ 32.3 (2.17)	0.3/ 15.7 (1.91)	1.13(0.02– 73.76)
CT 310	3.0/ 211.0 (1.42)	0.0/ 68.0 (0.00)	3.79(0.27– 53.36)
CT 311	0.8/ 245.5 (0.33)	0.2/ 79.5 (0.25)	1.27(0.01– 121.6)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.48(0.06– 3.84)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	2.41(1.09– 5.30)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 47.43)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	0.8/ 33.5 (2.39)	0.2/ 10.5 (1.90)	1.24(0.01– 122.8)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 50.40)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.39)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 50.40)
SMCO 514	0.6/ 72.2 (0.83)	0.4/ 46.8 (0.85)	0.97(0.02– 53.74)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 74.06)
SMCO 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 74.02)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	0.8/ 101.5 (0.79)	0.2/ 33.5 (0.60)	1.29(0.01– 121.0)
Total	67.1/6166.6 (1.09)	20.9/4742.4 (0.44)	1.80(1.15– 2.83)

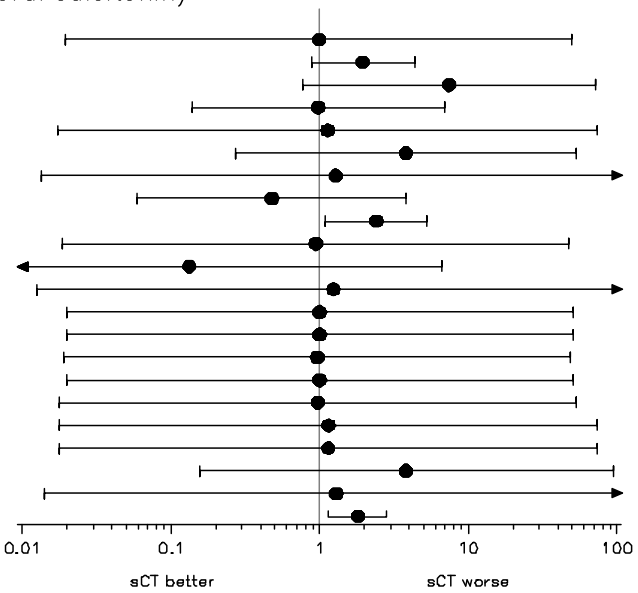

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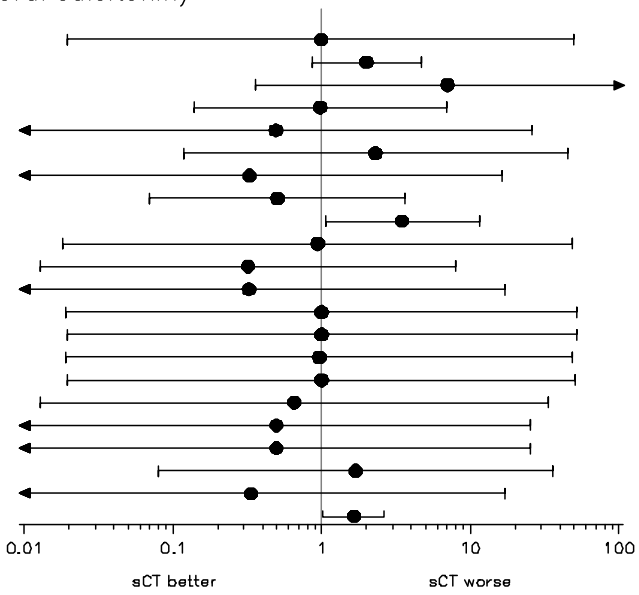
Figure 4.4d (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by MH constant correction
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
AZ303	16.0/2334.0 (0.69)	8.0/2331.0 (0.34)	2.00(0.86– 4.69)
C2301	3.5/ 586.0 (0.60)	0.5/ 585.0 (0.09)	7.02(0.36– 136.3)
C2302	2.0/ 520.0 (0.38)	2.0/ 508.0 (0.39)	0.98(0.14– 6.96)
CT 211	0.5/ 32.0 (1.56)	0.5/ 16.0 (3.13)	0.49(<.01– 25.99)
CT 310	3.5/ 212.0 (1.65)	0.5/ 69.0 (0.72)	2.30(0.12– 45.08)
CT 311	0.5/ 245.0 (0.20)	0.5/ 80.0 (0.63)	0.33(<.01– 16.52)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.50(0.07– 3.62)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	3.49(1.06– 11.48)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 48.79)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	0.5/ 33.0 (1.52)	0.5/ 11.0 (4.55)	0.32(<.01– 17.31)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 52.09)
SMCO 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.68)
SMCO 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 51.22)
SMCO 514	0.5/ 72.0 (0.69)	0.5/ 47.0 (1.06)	0.65(0.01– 33.35)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.50(<.01– 25.19)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.50(<.01– 25.57)
SMCO 522	2.5/ 157.0 (1.59)	0.5/ 53.0 (0.94)	1.70(0.08– 35.96)
SMCO 524	0.5/ 101.0 (0.50)	0.5/ 34.0 (1.47)	0.33(<.01– 17.13)
Total	67.5/6168.0 (1.09)	24.5/4749.0 (0.52)	1.64(1.02– 2.65)



MH: Mantel–Haenszel method

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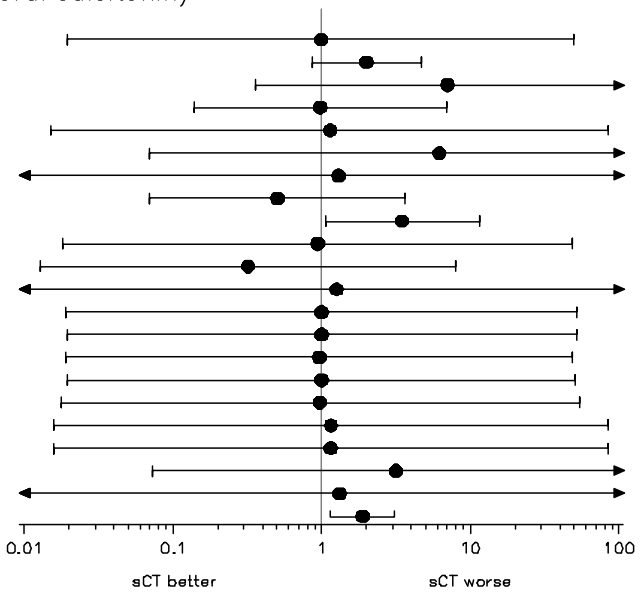
Final Version

CSMC021– Safety Analysis 2012

Figure 4.4e (Page 1 of 1)
Incidences and odds ratio for Basal Cell Carcinoma by MH treatment arm correction
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
A2303	16.0/2334.0 (0.69)	8.0/2331.0 (0.34)	2.00(0.86– 4.69)
C2301	3.5/ 586.0 (0.60)	0.5/ 585.0 (0.09)	7.02(0.36– 136.3)
C2302	2.0/ 520.0 (0.38)	2.0/ 508.0 (0.39)	0.98(0.14– 6.96)
CT 211	0.7/ 32.3 (2.17)	0.3/ 15.7 (1.91)	1.14(0.02– 85.51)
CT 310	3.8/ 212.5 (1.79)	0.2/ 68.5 (0.29)	6.22(0.07– 562.4)
CT 311	0.8/ 245.5 (0.33)	0.2/ 79.5 (0.25)	1.30(<.01– 175.2)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.50(0.07– 3.62)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	3.49(1.06– 11.48)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 48.79)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMC0 005	0.8/ 33.5 (2.39)	0.2/ 10.5 (1.90)	1.26(<.01– 177.8)
SMC0 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMC0 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 52.09)
SMC0 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.68)
SMC0 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 51.22)
SMC0 514	0.6/ 72.2 (0.83)	0.4/ 46.8 (0.85)	0.97(0.02– 54.02)
SMC0 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMC0 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMC0 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMC0 524	0.8/ 101.5 (0.79)	0.2/ 33.5 (0.60)	1.32(<.01– 180.4)
Total	69.7/6171.6 (1.13)	22.4/4745.4 (0.47)	1.88(1.15– 3.09)



MH: Mantel–Haenszel method

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Final Version

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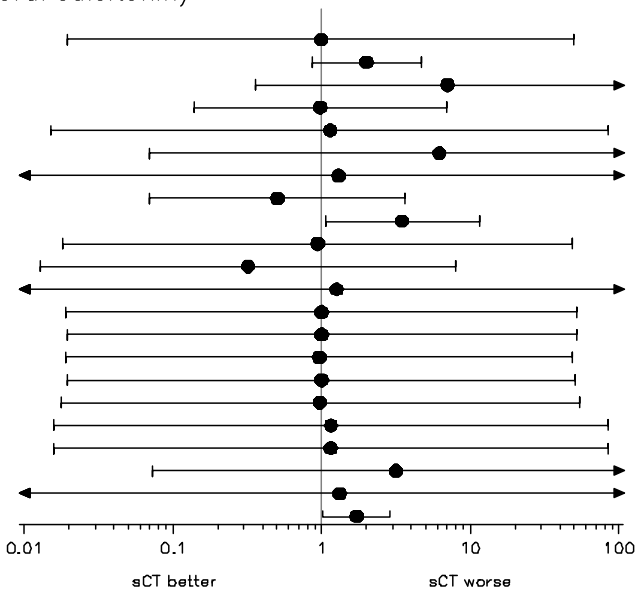
Figure 4.4f (Page 1 of 1)

Incidences and odds ratio for Basal Cell Carcinoma by random effect model
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
AZ303	16.0/2334.0 (0.69)	8.0/2331.0 (0.34)	2.00(0.86– 4.69)
C2301	3.5/ 586.0 (0.60)	0.5/ 585.0 (0.09)	7.02(0.36– 136.3)
C2302	2.0/ 520.0 (0.38)	2.0/ 508.0 (0.39)	0.98(0.14– 6.96)
CT 211	0.7/ 32.3 (2.17)	0.3/ 15.7 (1.91)	1.14(0.02– 85.51)
CT 310	3.8/ 212.5 (1.79)	0.2/ 68.5 (0.29)	6.22(0.07– 562.4)
CT 311	0.8/ 245.5 (0.33)	0.2/ 79.5 (0.25)	1.30(<.01– 175.2)
CT 312	2.0/ 201.0 (1.00)	2.0/ 102.0 (1.96)	0.50(0.07– 3.62)
CT 320	31.0/ 944.0 (3.28)	3.0/ 311.0 (0.96)	3.49(1.06– 11.48)
MIA 16	0.5/ 33.0 (1.52)	0.5/ 31.0 (1.61)	0.94(0.02– 48.79)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMC0 005	0.8/ 33.5 (2.39)	0.2/ 10.5 (1.90)	1.26(<.01– 177.8)
SMC0 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMC0 504	0.5/ 30.0 (1.67)	0.5/ 30.0 (1.67)	1.00(0.02– 52.09)
SMC0 506	0.5/ 148.0 (0.34)	0.5/ 142.0 (0.35)	0.96(0.02– 48.68)
SMC0 511	0.5/ 61.0 (0.82)	0.5/ 61.0 (0.82)	1.00(0.02– 51.22)
SMC0 514	0.6/ 72.2 (0.83)	0.4/ 46.8 (0.85)	0.97(0.02– 54.02)
SMC0 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMC0 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMC0 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMC0 524	0.8/ 101.5 (0.79)	0.2/ 33.5 (0.60)	1.32(<.01– 180.4)
Total	69.7/6171.6 (1.13)	22.4/4745.4 (0.47)	1.72(1.02– 2.90)



Odds ratio for each study obtained by Mantel–Haenszel with treatment arm correction
Random effect model applied to the pooled odds ratio

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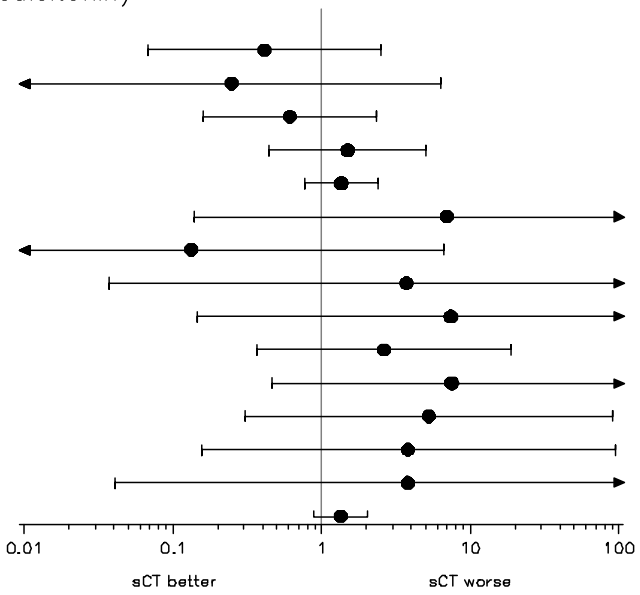
CSMC021– Safety Analysis 2012

Figure 4.6a (Page 1 of 1)
Incidences and odds ratio for any malignancy excluding BCC by Peto
(Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 45.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	88.0/2304.0 (3.82)	26.0/1021.0 (2.55)	1.34(0.88– 2.04)



CSMC021– Safety Analysis 2012

Figure 4.6b (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by Peto with constant correction (Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.47(<.01– 30.10)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.47(<.01– 30.20)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	90.0/2716.0 (3.31)	28.0/1313.0 (2.13)	1.30(0.86– 1.96)

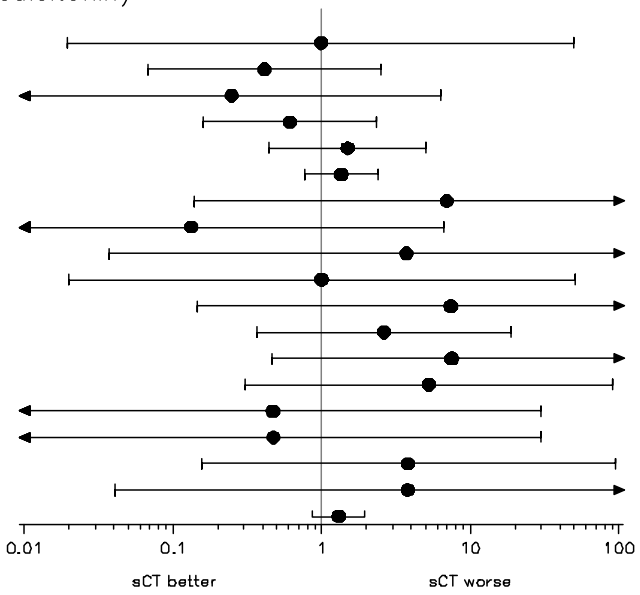


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Figure 4.6c (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by Peto with treatment arm correction (Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 74.06)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 74.02)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	90.4/2716.6 (3.33)	27.6/1312.4 (2.10)	1.32(0.87– 2.00)

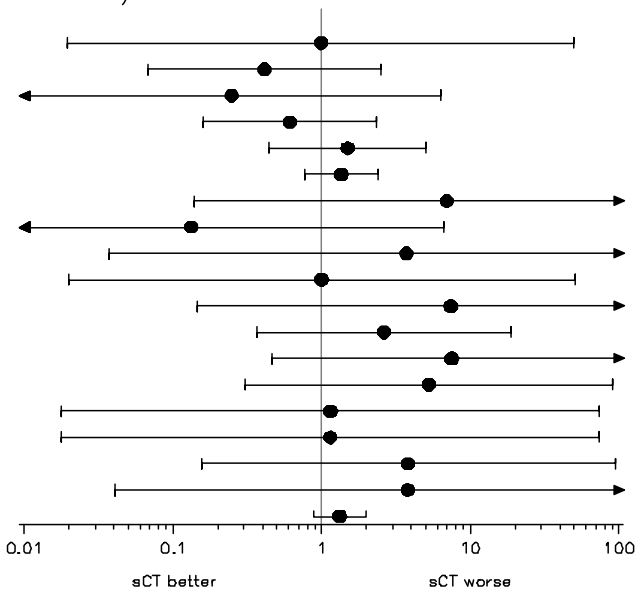

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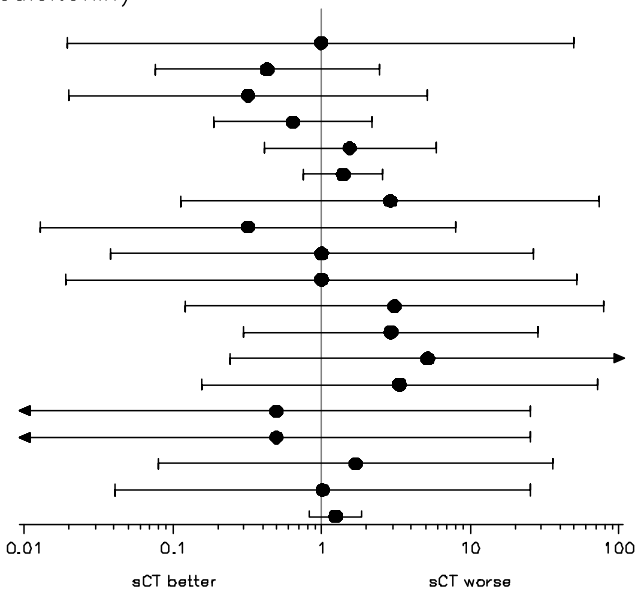
Figure 4.6d (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by MH with constant correction (Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.32(0.02– 5.17)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.55(0.41– 5.84)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.39(0.75– 2.58)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	1.5/ 33.0 (4.55)	0.5/ 11.0 (4.55)	1.00(0.04– 26.47)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.5/ 72.0 (3.47)	0.5/ 47.0 (1.06)	3.35(0.16– 71.28)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.50(<.01– 25.19)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.50(<.01– 25.57)
SMCO 522	2.5/ 157.0 (1.59)	0.5/ 53.0 (0.94)	1.70(0.08– 35.96)
SMCO 524	1.5/ 101.0 (1.49)	0.5/ 34.0 (1.47)	1.01(0.04– 25.39)
Total	94.0/2724.0 (3.45)	32.0/1321.0 (2.42)	1.24(0.82– 1.87)



MH: Mantel–Haenszel method

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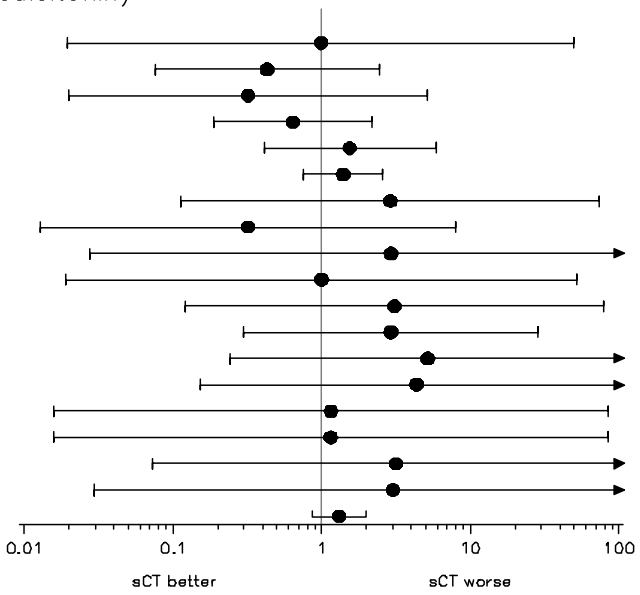
Figure 4.6e (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by MH with treatment arm correction (Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.32(0.02– 5.17)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.55(0.41– 5.84)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.39(0.75– 2.58)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	1.8/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMCO 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	95.4/2726.3 (3.50)	30.7/1318.7 (2.33)	1.31(0.86– 1.99)



MH: Mantel–Haenszel method

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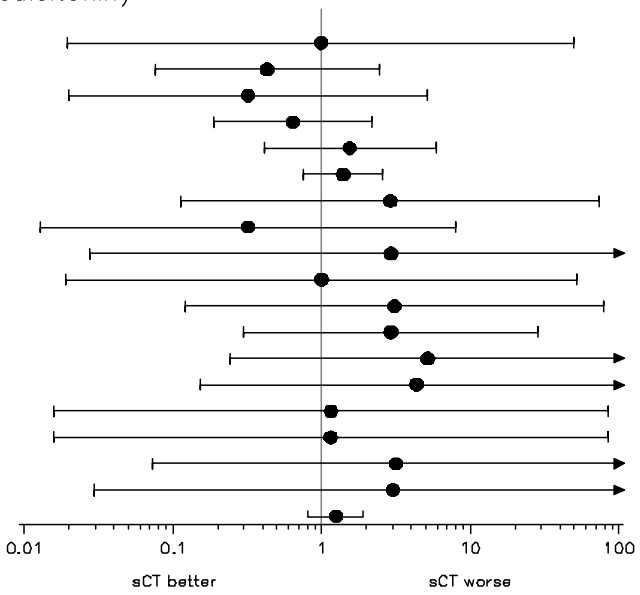
Figure 4.6f (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by random effect model (Nasal calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.32(0.02– 5.17)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.55(0.41– 5.84)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.39(0.75– 2.58)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	1.8/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 66.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMCO 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	95.4/2726.3 (3.50)	30.7/1318.7 (2.33)	1.25(0.81– 1.92)



Odds ratio for each study obtained by Mantel–Haenszel with treatment arm correction
Random effect model applied to the pooled odds ratio

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Figure 4.7a (Page 1 of 1)
Incidences and odds ratio for any malignancy excluding BCC by Peto
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
A2303	73.0/2334.0 (3.13)	79.0/2331.0 (3.39)	0.92(0.67– 1.27)
C2301	19.0/ 585.0 (3.25)	6.0/ 584.0 (1.03)	2.89(1.31– 6.37)
C2302	19.0/ 520.0 (3.65)	12.0/ 508.0 (2.36)	1.55(0.78– 3.18)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 45.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	199.0/5743.0 (3.47)	123.0/4444.0 (2.77)	1.20(0.95– 1.51)

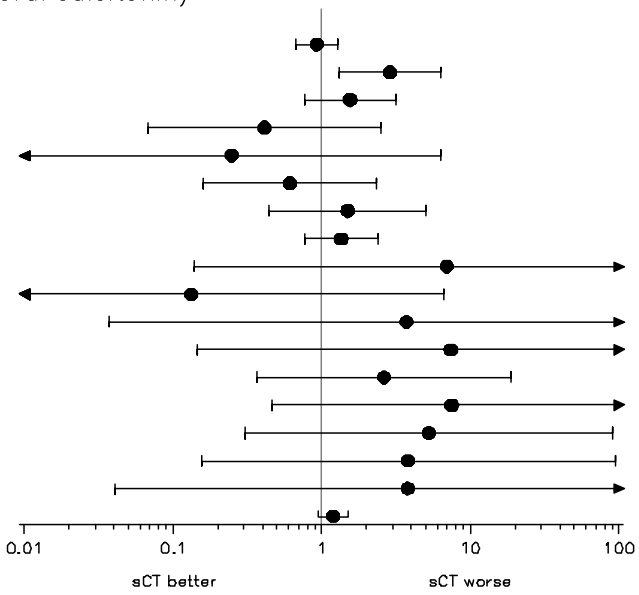

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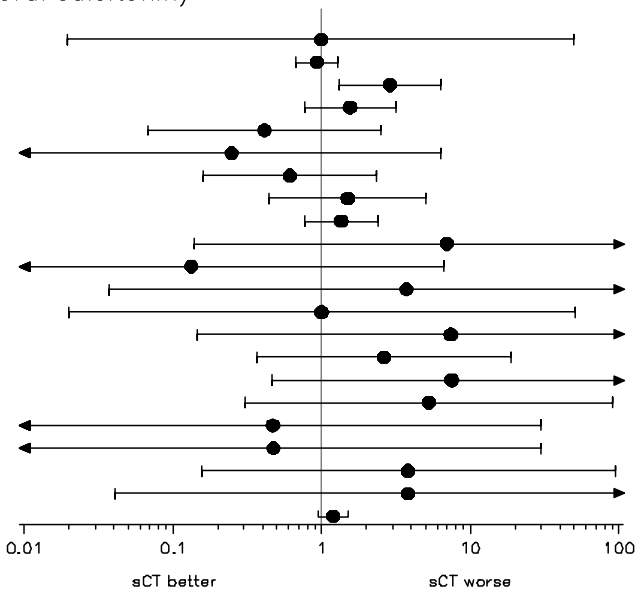
Figure 4.7b (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by Peto with constant correction (Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
A2303	73.0/2334.0 (3.13)	79.0/2331.0 (3.39)	0.92(0.67– 1.27)
C2301	19.0/ 585.0 (3.25)	6.0/ 584.0 (1.03)	2.89(1.31– 6.37)
C2302	19.0/ 520.0 (3.65)	12.0/ 508.0 (2.36)	1.55(0.76– 3.18)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.47(<.01– 30.10)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.47(<.01– 30.20)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	201.0/6155.0 (3.27)	125.0/4736.0 (2.64)	1.19(0.95– 1.50)



CSMC021– Safety Analysis 2012

Figure 4.7c (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by Peto with treatment arm correction (Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 49.73)
A2303	73.0/2334.0 (3.13)	79.0/2331.0 (3.39)	0.92(0.67– 1.27)
C2301	19.0/ 585.0 (3.25)	6.0/ 584.0 (1.03)	2.89(1.31– 6.37)
C2302	19.0/ 520.0 (3.65)	12.0/ 508.0 (2.36)	1.55(0.76– 3.18)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.41(0.07– 2.51)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.25(<.01– 6.29)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.61(0.16– 2.32)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.50(0.44– 5.06)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.36(0.77– 2.40)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
QUEST	0.0/ 46.0 (0.00)	1.0/ 45.0 (2.22)	0.13(<.01– 6.67)
SMCO 005	1.0/ 32.0 (3.13)	0.0/ 10.0 (0.00)	3.72(0.04– 370.3)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 50.40)
SMCO 504	1.0/ 29.0 (3.45)	0.0/ 29.0 (0.00)	7.39(0.15– 372.4)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.63(0.37– 18.91)
SMCO 511	2.0/ 60.0 (3.33)	0.0/ 60.0 (0.00)	7.52(0.46– 121.6)
SMCO 514	2.0/ 71.0 (2.82)	0.0/ 46.0 (0.00)	5.27(0.31– 91.09)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 74.06)
SMCO 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 74.02)
SMCO 522	2.0/ 156.0 (1.28)	0.0/ 52.0 (0.00)	3.82(0.15– 94.46)
SMCO 524	1.0/ 100.0 (1.00)	0.0/ 33.0 (0.00)	3.78(0.04– 353.5)
Total	201.4/6155.6 (3.27)	124.6/4735.4 (2.63)	1.20(0.95– 1.50)

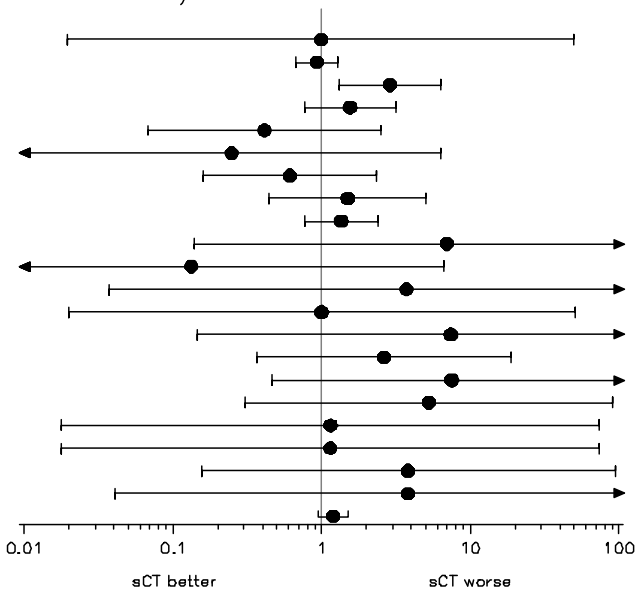


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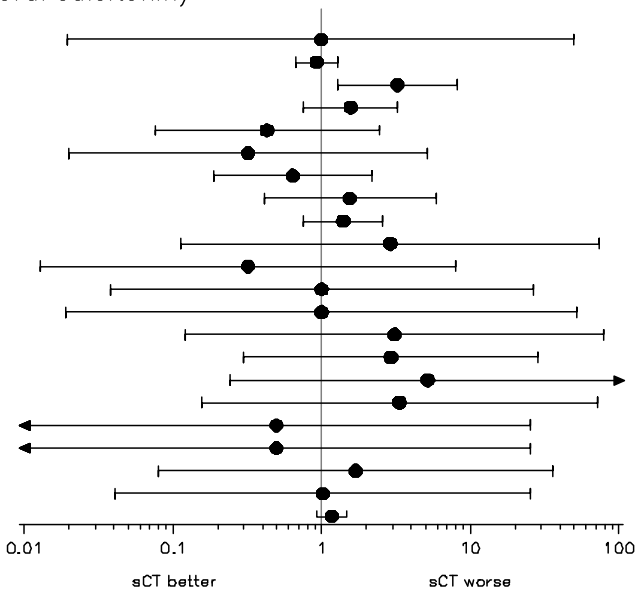
Figure 4.7d (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by MH constant correction
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
A2303	73.0/2334.0 (3.13)	79.0/2331.0 (3.39)	0.92(0.67– 1.27)
C2301	19.0/ 585.0 (3.25)	6.0/ 584.0 (1.03)	3.23(1.28– 8.16)
C2302	19.0/ 520.0 (3.65)	12.0/ 508.0 (2.36)	1.57(0.75– 3.26)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.32(0.02– 5.17)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.55(0.41– 5.84)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.39(0.75– 2.58)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	1.5/ 33.0 (4.55)	0.5/ 11.0 (4.55)	1.00(0.04– 26.47)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.5/ 72.0 (3.47)	0.5/ 47.0 (1.06)	3.35(0.16– 71.28)
SMCO 517	0.5/ 169.0 (0.30)	0.5/ 84.0 (0.60)	0.50(<.01– 25.19)
SMCO 520	0.5/ 66.0 (0.76)	0.5/ 33.0 (1.52)	0.50(<.01– 25.57)
SMCO 522	2.5/ 157.0 (1.59)	0.5/ 53.0 (0.94)	1.70(0.08– 35.96)
SMCO 524	1.5/ 101.0 (1.49)	0.5/ 34.0 (1.47)	1.01(0.04– 25.39)
Total	205.0/6163.0 (3.33)	129.0/4744.0 (2.72)	1.17(0.93– 1.48)



MH: Mantel–Haenszel method

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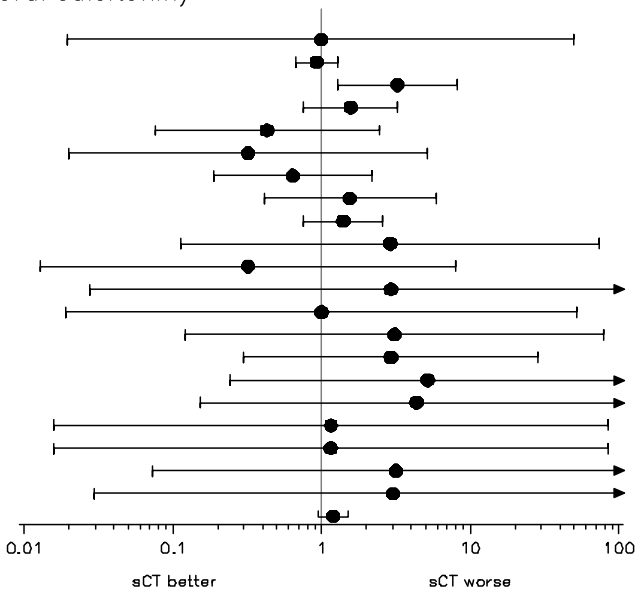
Figure 4.7e (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by MH treatment arm correction (Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
A2303	73.0/2334.0 (3.13)	79.0/2331.0 (3.39)	0.92(0.67– 1.27)
C2301	19.0/ 585.0 (3.25)	6.0/ 584.0 (1.03)	3.23(1.28– 8.16)
C2302	19.0/ 520.0 (3.65)	12.0/ 508.0 (2.36)	1.57(0.75– 3.26)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.32(0.02– 5.17)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.55(0.41– 5.84)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.39(0.75– 2.58)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMCO 005	1.5/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMCO 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMCO 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMCO 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMCO 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMCO 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMCO 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMCO 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMCO 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMCO 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	206.4/6165.3 (3.35)	127.7/4741.7 (2.69)	1.19(0.95– 1.50)



MH: Mantel–Haenszel method

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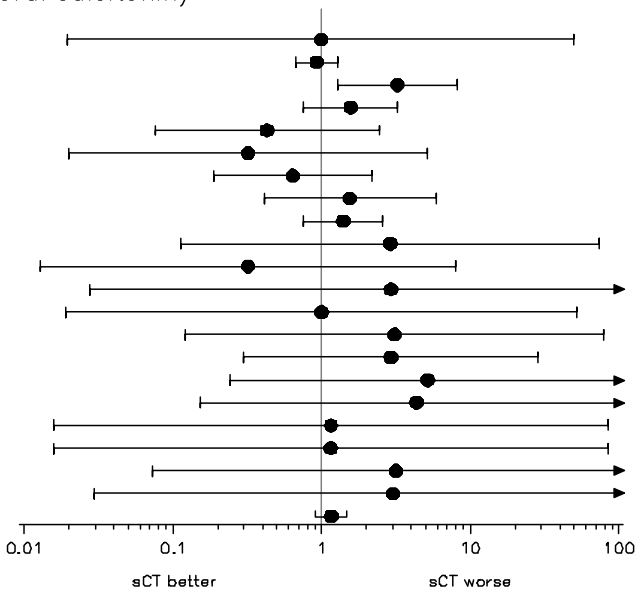
Figure 4.7f (Page 1 of 1)

Incidences and odds ratio for any malignancy excluding BCC by random effect model
(Nasal and Oral calcitonin)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
2402	0.5/ 150.0 (0.33)	0.5/ 148.0 (0.34)	0.99(0.02– 50.05)
A2303	73.0/2334.0 (3.13)	79.0/2331.0 (3.39)	0.92(0.67– 1.27)
C2301	19.0/ 585.0 (3.25)	6.0/ 584.0 (1.03)	3.23(1.28– 8.16)
C2302	19.0/ 520.0 (3.65)	12.0/ 508.0 (2.36)	1.57(0.75– 3.26)
CT 211	3.0/ 31.0 (9.68)	3.0/ 15.0 (20.0)	0.43(0.08– 2.44)
CT 310	1.0/ 211.0 (0.47)	1.0/ 68.0 (1.47)	0.32(0.02– 5.17)
CT 311	8.0/ 244.0 (3.28)	4.0/ 79.0 (5.06)	0.64(0.19– 2.17)
CT 312	9.0/ 201.0 (4.48)	3.0/ 102.0 (2.94)	1.55(0.41– 5.84)
CT 320	54.0/ 944.0 (5.72)	13.0/ 311.0 (4.18)	1.39(0.75– 2.58)
MIA 16	1.5/ 33.0 (4.55)	0.5/ 31.0 (1.61)	2.90(0.11– 74.10)
QUEST	0.5/ 47.0 (1.06)	1.5/ 46.0 (3.26)	0.32(0.01– 8.04)
SMC0 005	1.5/ 33.5 (5.37)	0.2/ 10.5 (1.90)	2.92(0.03– 312.9)
SMC0 503	0.5/ 27.0 (1.85)	0.5/ 27.0 (1.85)	1.00(0.02– 52.29)
SMC0 504	1.5/ 30.0 (5.00)	0.5/ 30.0 (1.67)	3.11(0.12– 79.43)
SMC0 506	3.0/ 147.0 (2.04)	1.0/ 141.0 (0.71)	2.92(0.30– 28.38)
SMC0 511	2.5/ 61.0 (4.10)	0.5/ 61.0 (0.82)	5.17(0.24– 110.0)
SMC0 514	2.6/ 72.2 (3.60)	0.4/ 46.8 (0.85)	4.33(0.15– 123.4)
SMC0 517	0.7/ 169.3 (0.41)	0.3/ 83.7 (0.36)	1.15(0.02– 83.80)
SMC0 520	0.7/ 65.3 (1.06)	0.3/ 32.7 (0.92)	1.15(0.02– 84.74)
SMC0 522	2.8/ 157.5 (1.78)	0.3/ 52.5 (0.57)	3.15(0.07– 137.8)
SMC0 524	1.8/ 101.5 (1.77)	0.2/ 33.5 (0.60)	3.01(0.03– 310.1)
Total	206.4/6165.3 (3.35)	127.7/4741.7 (2.69)	1.16(0.91– 1.46)



Odds ratio for each study obtained by Mantel–Haenszel with treatment arm correction
Random effect model applied to the pooled odds ratio

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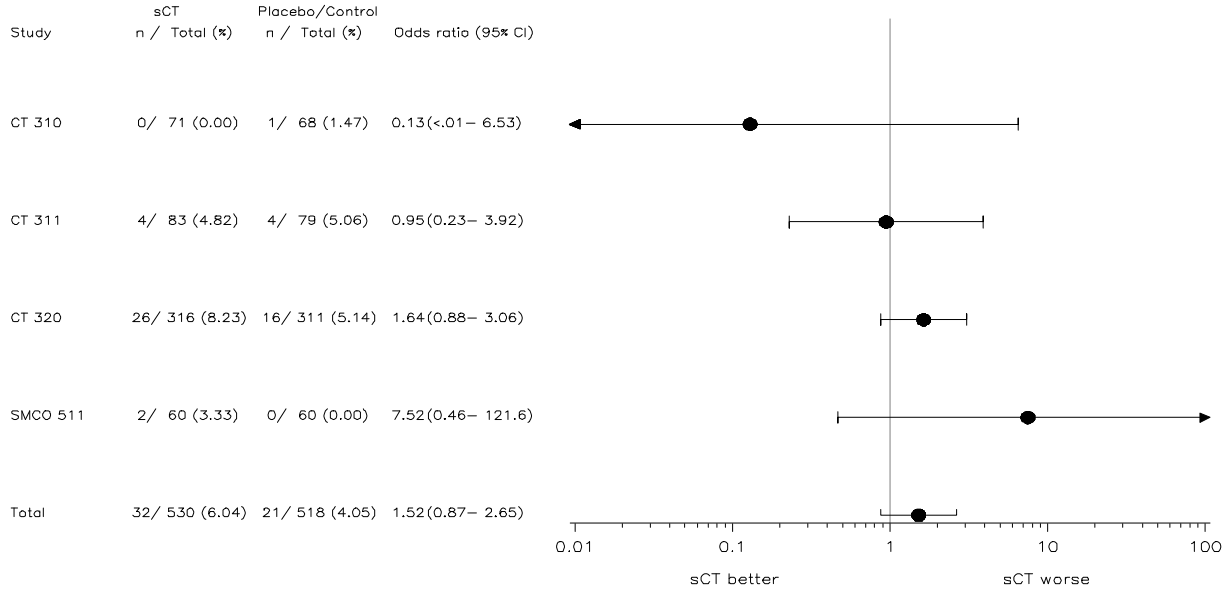
CSMC021– Safety Analysis 2012

Figure 3.3a (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal spray dosing level 100IU vs Placebo



Odds ratio (sCT vs Placebo/Control) obtained by Peto method.
Arrows represent estimates outside of axis range.
Odds ratio estimate in Total row only includes studies with at least one event in either treatment group.

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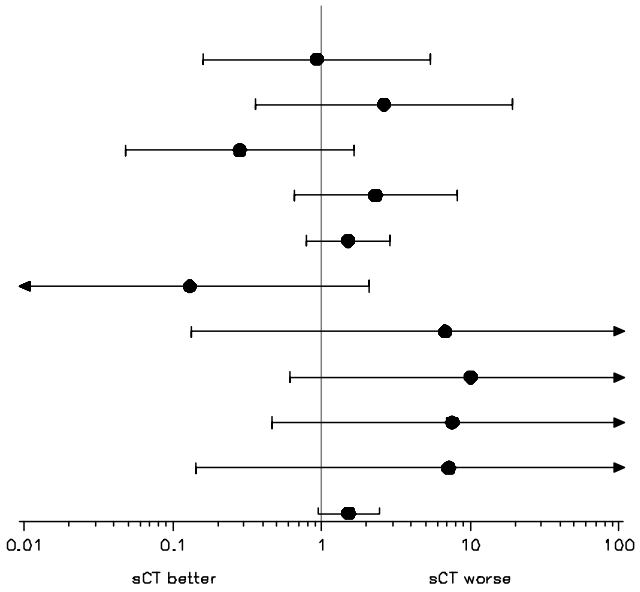
CSMC021– Safety Analysis 2012

Figure 4.5a (Page 1 of 1)
Incidences and odds ratio for any malignancy (Nasal spray dosing level 200IU vs Placebo)

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 211	3.0/ 16.0 (18.8)	3.0/ 15.0 (20.0)	0.93(0.16– 5.35)
CT 310	3.0/ 72.0 (4.17)	1.0/ 68.0 (1.47)	2.62(0.36– 19.04)
CT 311	1.0/ 82.0 (1.22)	4.0/ 79.0 (5.06)	0.28(0.05– 1.66)
CT 312	7.0/ 102.0 (6.86)	3.0/ 102.0 (2.94)	2.31(0.65– 8.21)
CT 320	24.0/ 316.0 (7.59)	16.0/ 311.0 (5.14)	1.51(0.79– 2.86)
QUEST	0.0/ 46.0 (0.00)	2.0/ 45.0 (4.44)	0.13(<.01– 2.10)
SMCO 005	1.0/ 11.0 (9.09)	0.0/ 10.0 (0.00)	6.75(0.13– 341.5)
SMCO 514	2.0/ 36.0 (5.56)	0.0/ 46.0 (0.00)	10.04(0.60– 166.7)
SMCO 522	2.0/ 52.0 (3.85)	0.0/ 52.0 (0.00)	7.54(0.46– 122.1)
SMCO 524	1.0/ 34.0 (2.94)	0.0/ 33.0 (0.00)	7.17(0.14– 361.7)
Total	44.0/ 767.0 (5.74)	29.0/ 761.0 (3.81)	1.52(0.95– 2.44)



Odds ratio obtained by Peto method.
Only includes studies with at least one event in either treatment group.

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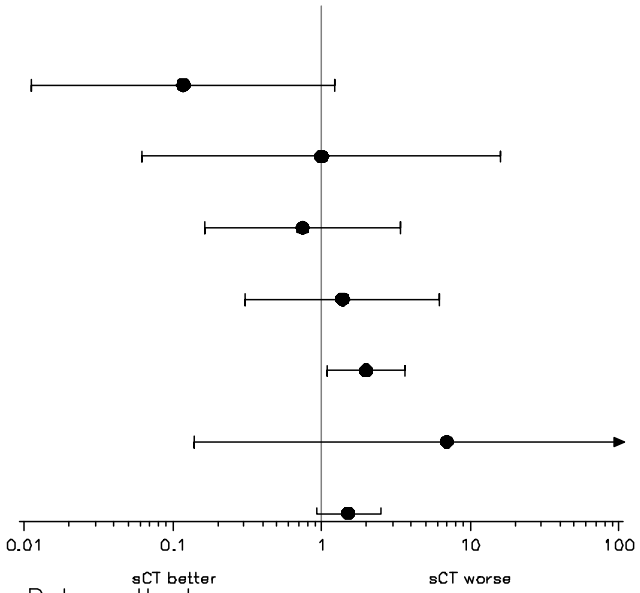
CSMC021– Safety Analysis 2012

Figure 3.3c1 (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal spray dosing level 400IU vs Placebo

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
CT 211	0.0/ 15.0 (0.00)	3.0/ 15.0 (20.0)	0.12(0.01– 1.22)
CT 310	1.0/ 68.0 (1.47)	1.0/ 68.0 (1.47)	1.00(0.06– 16.15)
CT 311	3.0/ 79.0 (3.80)	4.0/ 79.0 (5.06)	0.74(0.16– 3.37)
CT 312	4.0/ 99.0 (4.04)	3.0/ 102.0 (2.94)	1.38(0.31– 6.23)
CT 320	31.0/ 312.0 (9.94)	16.0/ 311.0 (5.14)	1.99(1.10– 3.60)
MIA 16	1.0/ 32.0 (3.13)	0.0/ 30.0 (0.00)	6.94(0.14– 350.5)
Total	40.0/ 605.0 (6.61)	27.0/ 605.0 (4.46)	1.51(0.92– 2.48)



Odds ratio (sCT vs Placebo/Control) obtained by Peto method.
Arrows represent estimates outside of axis range.
Odds ratio estimate in Total row only includes studies with at least one event in either treatment group.

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Appendix 7

Appendix 7 Prolia (Denosumab) Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROLIA safely and effectively. See full prescribing information for PROLIA.

Prolia® (denosumab)
Injection, for subcutaneous use
Initial U.S. Approval: 2010

----------RECENT MAJOR CHANGES----------

• Indications and Usage (1.2)	09/2012
• Dosage and Administration (2.2)	09/2012
• Contraindications (4.2, 4.3)	05/2012
• Warnings and Precautions (5.6)	09/2012

----------INDICATIONS AND USAGE----------

Prolia is a RANK ligand (RANKL) inhibitor indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture (1.1)
- Treatment to increase bone mass in men with osteoporosis at high risk for fracture (1.2)
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer (1.3)
- Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer (1.4)

----------DOSAGE AND ADMINISTRATION----------

- Prolia should be administered by a healthcare professional (2.1)
- Administer 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.1)
- Instruct patients to take calcium 1000 mg daily and at least 400 IU vitamin D daily (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

- Single-use prefilled syringe containing 60 mg in a 1 mL solution (3)
- Single-use vial containing 60 mg in a 1 mL solution (3)

----------CONTRAINDICATIONS----------

- Hypocalcemia (4.1, 5.2)
- Pregnancy (4.2, 8.1)
- Known hypersensitivity to Prolia (4.3, 6.2)

----------WARNINGS AND PRECAUTIONS----------

- Same Active Ingredient: Patients receiving Prolia should not receive XGEVA® (5.1)
- Hypocalcemia: Must be corrected before initiating Prolia. May worsen, especially in patients with renal impairment. Adequately supplement patients with calcium and vitamin D (5.2)
- Serious infections including skin infections: May occur, including those leading to hospitalization. Advise patients to seek prompt medical attention if they develop signs or symptoms of infection, including cellulitis (5.3)
- Dermatologic reactions: Dermatitis, rashes, and eczema have been reported. Consider discontinuing Prolia if severe symptoms develop (5.4)
- Osteonecrosis of the jaw: Has been reported with Prolia. Monitor for symptoms (5.5)
- Atypical femoral fractures: Have been reported. Evaluate patients with thigh or groin pain to rule out a femoral fracture (5.6)
- Suppression of bone turnover: Significant suppression has been demonstrated. Monitor for consequences of bone oversuppression (5.7)

----------ADVERSE REACTIONS----------

- Postmenopausal osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials (6.1)
- Male Osteoporosis: Most common adverse reactions (> 5% and more common than placebo) were: back pain, arthralgia, and nasopharyngitis (6.1)
- Bone loss due to hormone ablation for cancer: Most common adverse reactions (≥ 10% and more common than placebo) were: arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Pediatric patients: Safety and efficacy not established (8.4)
- Renal impairment: No dose adjustment is necessary in patients with renal impairment. Patients with creatinine clearance < 30 mL/min or receiving dialysis are at risk for hypocalcemia. Supplement with calcium and vitamin D, and consider monitoring serum calcium (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture

Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures *[see Clinical Studies (14.1)]*.

1.2 Treatment to Increase Bone Mass in Men with Osteoporosis

Prolia is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy *[see Clinical Studies (14.2)]*.

1.3 Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

Prolia is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures *[see Clinical Studies (14.3)]*.

1.4 Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

Prolia is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Prolia should be administered by a healthcare professional.

The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily *[see Warnings and Precautions (5.2)]*.

If a dose of Prolia is missed, administer the injection as soon as the patient is available. Thereafter, schedule injections every 6 months from the date of the last injection.

2.2 Preparation and Administration

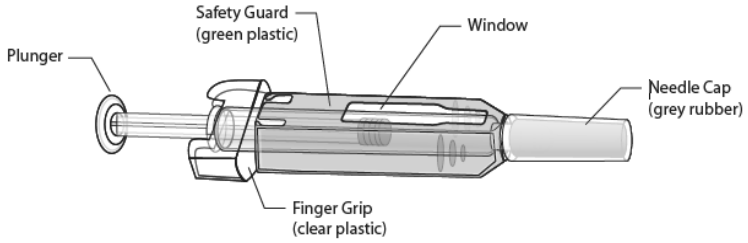
Visually inspect Prolia for particulate matter and discoloration prior to administration whenever solution and container permit. Prolia is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter.

Latex Allergy: People sensitive to latex should not handle the grey needle cap on the single-use prefilled syringe, which contains dry natural rubber (a derivative of latex).

Prior to administration, Prolia may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Prolia in any other way *[see How Supplied/Storage and Handling (16)]*.

Instructions for Prefilled Syringe with Needle Safety Guard
IMPORTANT: In order to minimize accidental needlesticks, the Prolia single-use prefilled syringe will have a green safety guard; manually activate the safety guard after the injection is given.

DO NOT slide the green safety guard forward over the needle before administering the injection; it will lock in place and prevent injection.

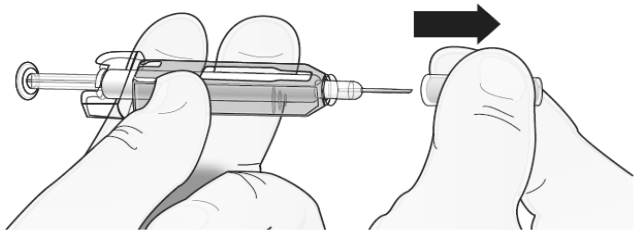


Activate the green safety guard (slide over the needle) after the injection.

The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex); people sensitive to latex should not handle the cap.

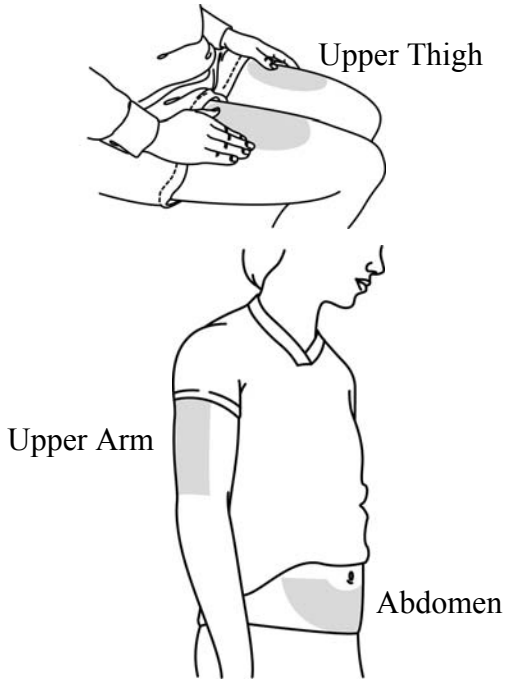
Step 1: Remove Grey Needle Cap

Remove needle cap.

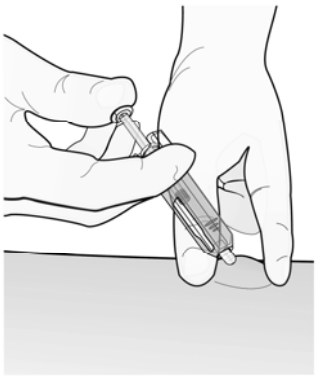


Step 2: Administer Subcutaneous Injection

Choose an injection site. The recommended injection sites for Prolia include: the upper arm OR the upper thigh OR the abdomen.



Insert needle and inject all the liquid subcutaneously. Do not administer into muscle or blood vessel.



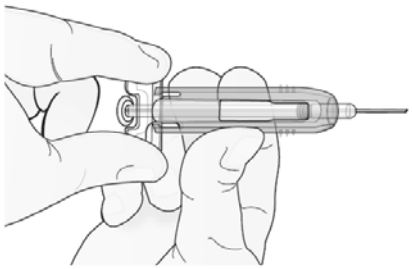
DO NOT put grey needle cap back on needle.

Step 3: Immediately Slide Green Safety Guard Over Needle

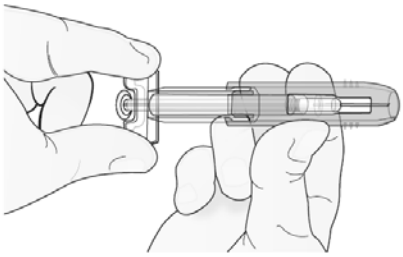
With the *needle pointing away from you…*

Hold the prefilled syringe by the clear plastic finger grip with one hand. Then, with the other hand, grasp the green safety guard by its base and gently slide it towards the needle until the green safety guard locks securely in place and/or you hear a "click." **DO NOT** grip the green safety guard too firmly – it will move easily if you hold and slide it gently.

Hold clear finger grip.



Gently slide green safety guard over needle and lock securely in place. Do not grip green safety guard too firmly when sliding over needle.



Immediately dispose of the syringe and needle cap in the nearest sharps container. **DO NOT** put the needle cap back on the used syringe.

Instructions for Single-use Vial
For administration of Prolia from the single-use vial, use a 27-gauge needle to withdraw and inject the 1 mL dose. Do not re-enter the vial. Discard vial and any liquid remaining in the vial.

3 DOSAGE FORMS AND STRENGTHS

- 1 mL of a 60 mg/mL solution in a single-use prefilled syringe
- 1 mL of a 60 mg/mL solution in a single-use vial

4 CONTRAINDICATIONS

4.1 Hypocalcemia

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia *[see Warnings and Precautions (5.2)]*.

4.2 Pregnancy

Prolia may cause fetal harm when administered to a pregnant woman. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. Prolia is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

4.3 Hypersensitivity

Prolia is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included facial swelling and urticaria *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Prolia contains the same active ingredient (denosumab) found in Xgeva. Patients receiving Prolia should not receive Xgeva.

5.2 Hypocalcemia and Mineral Metabolism

Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended.

Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

Adequately supplement all patients with calcium and vitamin D *[see Dosage and Administration (2.1), Contraindications (4.1), Adverse Reactions (6.1), and Patient Counseling Information (17.2)]*.

5.3 Serious Infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group *[see Adverse Reactions (6.1)]*. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Endocarditis was also reported more frequently in Prolia-treated patients. The incidence of opportunistic infections was similar between placebo and Prolia groups, and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. Consider the benefit-risk profile in such patients before treating with Prolia. In patients who develop serious infections while on Prolia, prescribers should assess the need for continued Prolia therapy.

5.4 Dermatologic Adverse Reactions

In a large clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the Prolia group compared to the placebo group. Most of these events were not specific to the injection site *[see Adverse Reactions (6.1)]*. Consider discontinuing Prolia if severe symptoms develop.

5.5 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. ONJ has been reported in patients receiving

denosumab *[see Adverse Reactions (6.1)]*. A routine oral exam should be performed by the prescriber prior to initiation of Prolia treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with Prolia in patients with risk factors for ONJ such as invasive dental procedures (e.g. tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (e.g. chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g. periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures). Good oral hygiene practices should be maintained during treatment with Prolia.

For patients requiring invasive dental procedures, clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit-risk assessment.

Patients who are suspected of having or who develop ONJ while on Prolia should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia therapy should be considered based on individual benefit-risk assessment.

5.6 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia *[see Adverse Reactions (6.1)]*. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Prolia therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.7 Suppression of Bone Turnover

In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry *[see Clinical Pharmacology (12.2) and Clinical Studies (14.1)]*. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and also elsewhere in the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.2)]*
- Serious Infections *[see Warnings and Precautions (5.3)]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions (5.4)]*

- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.5)]*
- Atypical Subtrochanteric and Diaphyseal Femoral Fractures *[see Warnings and Precautions (5.6)]*

The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.

The most common adverse reactions reported with Prolia in men with osteoporosis are back pain, arthralgia, and nasopharyngitis.

The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials.

The most common adverse reactions leading to discontinuation of Prolia in patients with postmenopausal osteoporosis are back pain and constipation.

The Prolia Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please see www.proliasafety.com or call 1-800-772-6436 for more information about this program.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Treatment of Postmenopausal Women with Osteoporosis

The safety of Prolia in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3886 women were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 2.3% (n = 90) in the placebo group and 1.8% (n = 70) in the Prolia group. The incidence of nonfatal serious adverse events was 24.2% in the placebo group and 25.0% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 2% of postmenopausal women with osteoporosis and more frequently in the Prolia-treated women than in the placebo-treated women are shown in the table below.

Table 1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More Frequently than in Placebo-treated Patients

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	129 (3.3)	107 (2.8)
CARDIAC DISORDERS		
Angina pectoris	101 (2.6)	87 (2.2)
Atrial fibrillation	79 (2.0)	77 (2.0)
EAR AND LABYRINTH DISORDERS		
Vertigo	195 (5.0)	187 (4.8)
GASTROINTESTINAL DISORDERS		
Abdominal pain upper	129 (3.3)	111 (2.9)
Flatulence	84 (2.2)	53 (1.4)
Gastroesophageal reflux disease	80 (2.1)	66 (1.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema peripheral	189 (4.9)	155 (4.0)
Asthenia	90 (2.3)	73 (1.9)
INFECTIONS AND INFESTATIONS		
Cystitis	228 (5.9)	225 (5.8)
Upper respiratory tract infection	190 (4.9)	167 (4.3)
Pneumonia	152 (3.9)	150 (3.9)
Pharyngitis	91 (2.3)	78 (2.0)
Herpes zoster	79 (2.0)	72 (1.9)
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolemia	280 (7.2)	236 (6.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1347 (34.7)	1340 (34.6)
Pain in extremity	453 (11.7)	430 (11.1)
Musculoskeletal pain	297 (7.6)	291 (7.5)
Bone pain	142 (3.7)	117 (3.0)
Myalgia	114 (2.9)	94 (2.4)
Spinal osteoarthritis	82 (2.1)	64 (1.7)

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 3886) n (%)	Placebo (N = 3876) n (%)
NERVOUS SYSTEM DISORDERS		
Sciatica	178 (4.6)	149 (3.8)
PSYCHIATRIC DISORDERS		
Insomnia	126 (3.2)	122 (3.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	96 (2.5)	79 (2.0)
Pruritus	87 (2.2)	82 (2.1)

Hypocalcemia
Decreases in serum calcium levels to less than 8.5 mg/dL at any visit were reported in 0.4% women in the placebo group and 1.7% women in the Prolia group. The nadir in serum calcium level occurs at approximately day 10 after Prolia dosing in subjects with normal renal function.

In clinical studies, subjects with impaired renal function were more likely to have greater reductions in serum calcium levels compared to subjects with normal renal function. In a study of 55 subjects with varying degrees of renal function, serum calcium levels < 7.5 mg/dL or symptomatic hypocalcemia were observed in 5 subjects. These included no subjects in the normal renal function group, 10% of subjects in the creatinine clearance 50 to 80 mL/min group, 29% of subjects in the creatinine clearance < 30 mL/min group, and 29% of subjects in the hemodialysis group. These subjects did not receive calcium and vitamin D supplementation. In a study of 4550 postmenopausal women with osteoporosis, the mean change from baseline in serum calcium level 10 days after Prolia dosing was -5.5% in subjects with creatinine clearance < 30 mL/min vs. -3.1% in subjects with creatinine clearance ≥ 30 mL/min.

Serious Infections
Receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as Prolia may increase the risk of infection.

In the clinical study of 7808 postmenopausal women with osteoporosis, the incidence of infections resulting in death was 0.2% in both placebo and Prolia treatment groups. However, the incidence of nonfatal serious infections was 3.3% in the placebo and 4.0% in the Prolia groups. Hospitalizations due to serious infections in the abdomen (0.7% placebo vs. 0.9% Prolia), urinary tract (0.5% placebo vs. 0.7% Prolia), and ear (0.0% placebo vs. 0.1% Prolia) were reported. Endocarditis was reported in no placebo patients and 3 patients receiving Prolia.

Skin infections, including erysipelas and cellulitis, leading to hospitalization were reported more frequently in patients treated with Prolia (< 0.1% placebo vs. 0.4% Prolia).

The incidence of opportunistic infections was similar to that reported with placebo.

Dermatologic Reactions
A significantly higher number of patients treated with Prolia developed epidermal and dermal adverse events (such as dermatitis, eczema, and rashes), with these events reported in 8.2% of the placebo and

10.8% of the Prolia groups ($p < 0.0001$). Most of these events were not specific to the injection site *[see Warnings and Precautions (5.4)]*.

Osteonecrosis of the Jaw
ONJ has been reported in the osteoporosis clinical trial program in patients treated with Prolia *[see Warnings and Precautions (5.5)]*.

Atypical Subtrochanteric and Diaphyseal Fractures
In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with Prolia. The duration of Prolia exposure to time of atypical femoral fracture diagnosis was as early as 2½ years *[see Warnings and Precautions (5.6)]*.

Pancreatitis
Pancreatitis was reported in 4 patients (0.1%) in the placebo and 8 patients (0.2%) in the Prolia groups. Of these reports, 1 patient in the placebo group and all 8 patients in the Prolia group had serious events, including one death in the Prolia group. Several patients had a prior history of pancreatitis. The time from product administration to event occurrence was variable.

New Malignancies
The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia groups. New malignancies related to the breast (0.7% placebo vs. 0.9% Prolia), reproductive system (0.2% placebo vs. 0.5% Prolia), and gastrointestinal system (0.6% placebo vs. 0.9% Prolia) were reported. A causal relationship to drug exposure has not been established.

Treatment to Increase Bone Mass in Men with Osteoporosis

The safety of Prolia in the treatment of men with osteoporosis was assessed in a 1-year randomized, double-blind, placebo-controlled study. A total of 120 men were exposed to placebo and 120 men were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All men were instructed to take at least 1000 mg of calcium and 800 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 0.8% (n = 1) in the placebo group and 0.8% (n = 1) in the Prolia group. The incidence of nonfatal serious adverse events was 7.5% in the placebo group and 8.3% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 0% and 2.5% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 5% of men with osteoporosis and more frequently with Prolia than in the placebo-treated patients were: back pain (6.7% placebo vs. 8.3% Prolia), arthralgia (5.8% placebo vs. 6.7% Prolia), and nasopharyngitis (5.8% placebo vs. 6.7% Prolia).

Serious Infections
Serious infection was reported in 1 patient (0.8%) in the placebo group and no patients in the Prolia group.

Dermatologic Reactions
Epidermal and dermal adverse events (such as dermatitis, eczema, and rashes) were reported in 4 patients (3.3%) in the placebo group and 5 patients (4.2%) in the Prolia group.

Osteonecrosis of the Jaw
No cases of ONJ were reported.

Pancreatitis
Pancreatitis was reported in 1 patient (0.8%) in the placebo group and 1 patient (0.8%) in the Prolia group.

New Malignancies
New malignancies were reported in no patients in the placebo group and 4 (3.3%) patients (3 prostate cancers, 1 basal cell carcinoma) in the Prolia group.

Treatment of Bone Loss in Patients Receiving Androgen Deprivation Therapy for Prostate Cancer or Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

The safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 1468 men aged 48 to 97 years. A total of 725 men were exposed to placebo and 731 men were exposed to Prolia administered once every 6 months as a single 60 mg subcutaneous dose. All men were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of serious adverse events was 30.6% in the placebo group and 34.6% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 6.1% and 7.0% for the placebo and Prolia groups, respectively.

The safety of Prolia in the treatment of bone loss in women with nonmetastatic breast cancer receiving aromatase inhibitor (AI) therapy was assessed in a 2-year, randomized, double-blind, placebo-controlled, multinational study of 252 postmenopausal women aged 35 to 84 years. A total of 120 women were exposed to placebo and 129 women were exposed to Prolia administered once every 6 months as a single 60 mg subcutaneous dose. All women were instructed to take at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of serious adverse events was 9.2% in the placebo group and 14.7% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 4.2% and 0.8% for the placebo and Prolia groups, respectively.

Adverse reactions reported in ≥ 10% of Prolia-treated patients receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer, and more frequently than in the placebo-treated patients were: arthralgia (13.0% placebo vs. 14.3% Prolia) and back pain (10.5% placebo vs. 11.5% Prolia). Pain in extremity (7.7% placebo vs. 9.9% Prolia) and musculoskeletal pain (3.8% placebo vs. 6.0% Prolia) have also been reported in clinical trials. Additionally in Prolia-treated men with nonmetastatic prostate cancer receiving ADT, a greater incidence of cataracts was observed (1.2% placebo vs. 4.7% Prolia). Hypocalcemia (serum calcium < 8.4 mg/dL) was reported only in Prolia-treated patients (2.4% vs. 0%) at the month 1 visit.

6.2 Postmarketing Experience

Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post approval use of Prolia:

- Drug-related hypersensitivity reactions: rash, urticaria, facial swelling and erythema
- Hypocalcemia: severe symptomatic hypocalcemia

6.3 Immunogenicity

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% (55 out of 8113) of patients treated with Prolia for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based in vitro biological assay. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with binding antibody development.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with Prolia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary
Prolia may cause fetal harm when administered to a pregnant woman based on findings in animals. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. Prolia is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Women who become pregnant during Prolia treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

Clinical Considerations
The effects of Prolia on the fetus are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies, such as denosumab, are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. If the patient becomes pregnant during Prolia therapy, treatment should be discontinued and the patient should consult their physician.

Animal Data
The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene removal (a "knockout mouse"). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal,

mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia and tooth malalignment; and decreased neonatal growth. At birth out to 1 month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.2)]*.

8.3 Nursing Mothers

It is not known whether Prolia is excreted into human milk. Measurable concentrations of denosumab were present in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Prolia, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Maternal exposure to Prolia during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. However in cynomolgus monkeys treated with denosumab throughout pregnancy, maternal mammary gland development was normal, with no impaired lactation. Mammary gland histopathology at 6 months of age was normal in female offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.2)]*.

8.4 Pediatric Use

Prolia is not recommended in pediatric patients. The safety and effectiveness of Prolia in pediatric patients have not been established.

Treatment with Prolia may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of Prolia therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 10 and 50 times (10 and 50 mg/kg dose) higher than the recommended human dose of 60 mg administered every 6 months, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.

Cynomolgus monkeys exposed in utero to denosumab exhibited bone abnormalities, an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes, reduced hematopoiesis, tooth malalignment, and decreased neonatal growth. Some bone abnormalities recovered once exposure was ceased following

birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth *[see Use in Specific Populations (8.1)]*.

8.5 Geriatric Use

Of the total number of patients in clinical studies of Prolia, 9943 patients (76%) were ≥ 65 years old, while 3576 (27%) were ≥ 75 years old. Of the patients in the osteoporosis study in men, 133 patients (55%) were ≥ 65 years old, while 39 patients (16%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary in patients with renal impairment.

In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcemia. Consider the benefit-risk profile when administering Prolia to patients with severe renal impairment or receiving dialysis. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis *[see Warnings and Precautions (5.2), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of Prolia.

8.8 Males

Prolia may cause fetal harm *[see Use in Specific Populations (8.1)]*.

The extent to which denosumab is present in seminal fluid is unknown. There is a potential for fetal exposure to denosumab when a man treated with Prolia has unprotected sexual intercourse with a pregnant partner. The risk of fetal harm is likely to be low. Advise men being treated with Prolia who have a pregnant partner of this potential risk.

10 OVERDOSAGE

There is no experience with overdosage with Prolia.

11 DESCRIPTION

Prolia (denosumab) is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Prolia is a sterile, preservative-free, clear, colorless to pale yellow solution.

Each 1 mL single-use prefilled syringe of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

Each 1 mL single-use vial of Prolia contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM acetate, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prolia binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Prolia prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

12.2 Pharmacodynamics

In clinical studies, treatment with 60 mg of Prolia resulted in reduction in the bone resorption marker serum type 1 C-telopeptide (CTX) by approximately 85% by 3 days, with maximal reductions occurring by 1 month. CTX levels were below the limit of assay quantitation (0.049 ng/mL) in 39% to 68% of patients 1 to 3 months after dosing of Prolia. At the end of each dosing interval, CTX reductions were partially attenuated from a maximal reduction of ≥ 87% to ≥ 45% (range: 45% to 80%), as serum denosumab levels diminished, reflecting the reversibility of the effects of Prolia on bone remodeling. These effects were sustained with continued treatment. Upon reinitiation, the degree of inhibition of CTX by Prolia was similar to that observed in patients initiating Prolia treatment.

Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers (i.e. osteocalcin and procollagen type 1 N-terminal peptide [PlNP]) were observed starting 1 month after the first dose of Prolia. After discontinuation of Prolia therapy, markers of bone resorption increased to levels 40% to 60% above pretreatment values but returned to baseline levels within 12 months.

12.3 Pharmacokinetics

In a study conducted in healthy male and female volunteers (n = 73, age range: 18 to 64 years) following a single subcutaneously administered Prolia dose of 60 mg after fasting (at least for 12 hours), the mean maximum denosumab concentration (C_{max}) was 6.75 mcg/mL (standard deviation [SD] = 1.89 mcg/mL). The median time to maximum denosumab concentration (T_{max}) was 10 days (range: 3 to 21 days). After C_{max}, serum denosumab concentrations declined over a period of 4 to 5 months with a mean half-life of 25.4 days (SD = 8.5 days; n = 46). The mean area-under-the-concentration-time curve up to 16 weeks ($AUC_{0\text{-}16\ weeks}$) of denosumab was 316 mcg·day/mL (SD = 101 mcg·day/mL).

No accumulation or change in denosumab pharmacokinetics with time was observed upon multiple dosing of 60 mg subcutaneously administered once every 6 months.

Prolia pharmacokinetics were not affected by the formation of binding antibodies.

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no notable differences in pharmacokinetics with age (in postmenopausal women), race, or body weight (36 to 140 kg).

Drug Interactions
No drug-drug interaction studies have been conducted with Prolia.

Specific Populations
Gender: Mean serum denosumab concentration-time profiles observed in a study conducted in healthy men ≥ 50 years were similar to those observed in a study conducted in postmenopausal women using the same dose regimen.

Age: The pharmacokinetics of denosumab were not affected by age across all populations studied whose ages ranged from 28 to 87 years.

Race: The pharmacokinetics of denosumab were not affected by race.

Renal Impairment: In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus, dose adjustment for renal impairment is not necessary.

Hepatic Impairment: No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

Mutagenicity
The genotoxic potential of denosumab has not been evaluated.

Impairment of Fertility
Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 13- to 50-fold higher than the recommended human dose of 60 mg subcutaneously administered once every 6 months, based on body weight (mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Denosumab is an inhibitor of osteoclastic bone resorption via inhibition of RANKL.

In ovariectomized monkeys, once-monthly treatment with denosumab suppressed bone turnover and increased bone mineral density (BMD) and strength of cancellous and cortical bone at doses 50-fold higher than the recommended human dose of 60 mg administered once every 6 months, based on body weight (mg/kg). Bone tissue was normal with no evidence of mineralization defects, accumulation of osteoid, or woven bone.

Because the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered ("knockout") mice or use of other biological inhibitors of the RANK/RANKL

pathway, namely OPG-Fc, provided additional information on the pharmacodynamic properties of denosumab. RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued.

14 CLINICAL STUDIES

14.1 Postmenopausal Women with Osteoporosis

The efficacy and safety of Prolia in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial. Enrolled women had a baseline BMD T-score between -2.5 and -4.0 at either the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7808 enrolled women were aged 60 to 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD T-score was -2.8, and 23% of women had a vertebral fracture at baseline. Women were randomized to receive subcutaneous injections of either placebo (N = 3906) or Prolia 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically-diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine radiographs (T4-L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.

Effect on Vertebral Fractures

Prolia significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$), as shown in Table 2. The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the Prolia-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3.

Table 2. The Effect of Prolia on the Incidence of New Vertebral Fractures in Postmenopausal Women

	Proportion of Women With Fracture (%)[+]		Absolute Risk Reduction (%)[*] (95% CI)	Relative Risk Reduction (%)[*] (95% CI)
	Placebo N = 3691 (%)	Prolia N = 3702 (%)		
0-1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)
0-2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)
0-3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)

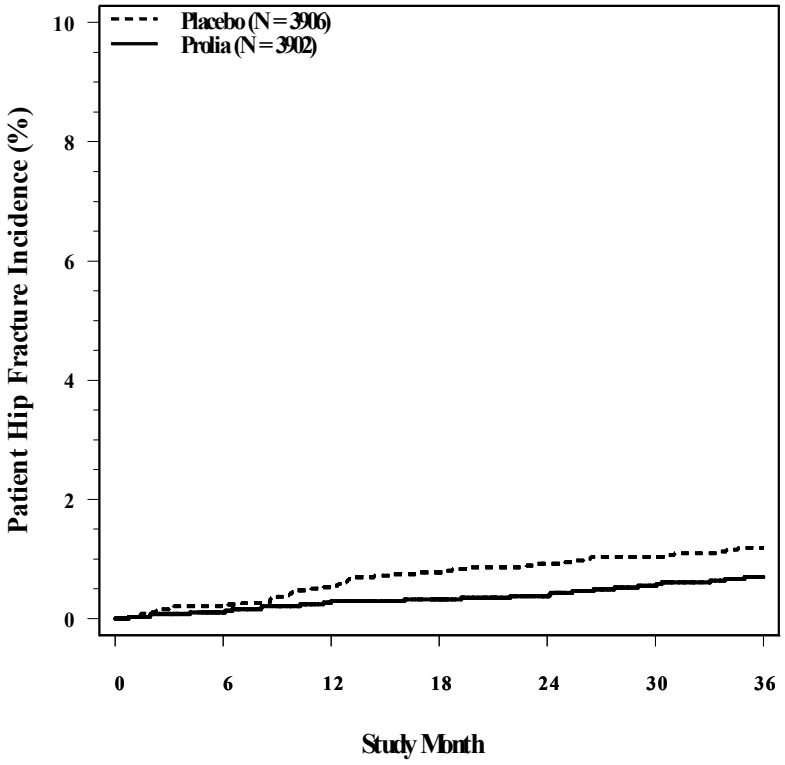
[+] Event rates based on crude rates in each interval.
[*] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group variable.

Prolia was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.

Effect on Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for Prolia-treated women at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years (p = 0.04) (Figure 1).

Figure 1. Cumulative Incidence of Hip Fractures Over 3 Years



N = number of subjects randomized

Effect on Nonvertebral Fractures

Treatment with Prolia resulted in a significant reduction in the incidence of nonvertebral fractures (Table 3).

Table 3. The Effect of Prolia on the Incidence of Nonvertebral Fractures at Year 3

	Proportion of Women With Fracture (%)[+]		Absolute Risk Reduction (%) (95% CI)	Relative Risk Reduction (%) (95% CI)
	Placebo N = 3906 (%)	Prolia N = 3902 (%)		
Nonvertebral fracture[1]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)[*]

[+] Event rates based on Kaplan-Meier estimates at 3 years.
[1] Excluding those of the vertebrae (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, and finger and toe phalanges.
[*] p-value = 0.01.

Effect on Bone Mineral Density (BMD)
Treatment with Prolia significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index (BMI), baseline BMD, and level of bone turnover.

After Prolia discontinuation, BMD returned to approximately baseline levels within 12 months.

Bone Histology and Histomorphometry
A total of 115 transiliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in Prolia group, 62 specimens in placebo group). Of the biopsies obtained, 115 (100%) were adequate for qualitative histology and 7 (6%) were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with Prolia.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with Prolia, 35% had no tetracycline label present at the month 24 biopsy and 38% had no tetracycline label present at the month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo, treatment with Prolia resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

14.2 Treatment to Increase Bone Mass in Men with Osteoporosis

The efficacy and safety of Prolia in the treatment to increase bone mass in men with osteoporosis was demonstrated in a 1-year, randomized, double-blind, placebo-controlled trial. Enrolled men had a baseline BMD T-score between -2.0 and -3.5 at the lumbar spine or femoral neck. Men with a BMD T-score between -1.0 and -3.5 at the lumbar spine or femoral neck were also enrolled if there was a history of prior fragility fracture. Men with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that may affect bone were excluded from this study. The 242 men enrolled in the study ranged in age from 31 to 84 years with a mean age of 65 years. Men were randomized to receive SC injections of either placebo (n = 121) or Prolia 60 mg (n = 121) once every 6 months. All men received at least 1000 mg calcium and at least 800 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to 1 year. Secondary efficacy variables included percent change in total hip, and femoral neck BMD from baseline to 1 year.

Treatment with Prolia significantly increased BMD at 1 year. The treatment differences in BMD at 1 year were 4.8% (+0.9% placebo, +5.7% Prolia; (95% CI: 4.0, 5.6); $p < 0.0001$) at the lumbar spine, 2.0% (+0.3% placebo, +2.4% Prolia) at the total hip, and 2.2% (0.0% placebo, +2.1% Prolia) at femoral neck. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, BMD, testosterone concentrations and level of bone turnover.

Bone Histology and Histomorphometry

A total of 29 transiliac crest bone biopsy specimens were obtained from men with osteoporosis at 12 months (17 specimens in Prolia group, 12 specimens in placebo group). Of the biopsies obtained, 29 (100%) were adequate for qualitative histology and, in Prolia patients, 6 (35%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with Prolia. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with Prolia, 6% had no tetracycline label present at the month 12 biopsy, while 100% of placebo-treated patients had double label present. When compared to placebo, treatment with Prolia resulted in markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

14.3 Treatment of Bone Loss in Men with Prostate Cancer

The efficacy and safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) were demonstrated in a 3-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Men less than 70 years of age had either a BMD T-score at the lumbar spine, total hip, or femoral neck between -1.0 and -4.0, or a history of an osteoporotic fracture. The mean baseline lumbar spine BMD T-score was -0.4, and 22% of men had a vertebral fracture at baseline. The 1468 men enrolled ranged in age from 48 to 97 years (median 76 years). Men were randomized to receive subcutaneous injections of either placebo (n = 734) or Prolia 60 mg (n = 734) once every 6 months for a total of 6 doses. Randomization was stratified by age (< 70 years vs. ≥ 70 years) and duration of ADT at trial entry (≤ 6 months vs. > 6 months). Seventy-nine percent of patients received ADT for more than 6 months at study entry. All men received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)

The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 24. An additional key secondary efficacy variable was the incidence of new vertebral fracture through month 36 diagnosed based on x-ray evaluation by two independent radiologists. Lumbar spine BMD was higher at 2 years in Prolia-treated patients as compared to placebo-treated patients [-1.0% placebo, +5.6% Prolia; treatment difference 6.7% (95% CI: 6.2, 7.1); $p < 0.0001$].

With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% Prolia) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% Prolia) at the total hip, and 4.9% (-1.8% placebo, +3.0% Prolia) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture.

Effect on Vertebral Fractures

Prolia significantly reduced the incidence of new vertebral fractures at 3 years ($p = 0.0125$), as shown in Table 4.

Table 4. The Effect of Prolia on the Incidence of New Vertebral Fractures in Men with Nonmetastatic Prostate Cancer

	Proportion of Men With Fracture (%)[+]		Absolute Risk Reduction (%)[*] (95% CI)	Relative Risk Reduction (%)[*] (95% CI)
	Placebo N = 673 (%)	Prolia N = 679 (%)		
0-1 Year	1.9	0.3	1.6 (0.5, 2.8)	85 (33, 97)
0-2 Years	3.3	1.0	2.2 (0.7, 3.8)	69 (27, 86)
0-3 Years	3.9	1.5	2.4 (0.7, 4.1)	62 (22, 81)

[+] Event rates based on crude rates in each interval.
[*] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group and ADT duration variables.

14.4 Treatment of Bone Loss in Women with Breast Cancer

The efficacy and safety of Prolia in the treatment of bone loss in women receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. The mean baseline lumbar spine BMD T-score was -1.1, and 2.0% of women had a vertebral fracture at baseline. The 252 women enrolled ranged in age from 35 to 84 years (median 59 years). Women were randomized to receive subcutaneous injections of either placebo (n = 125) or Prolia 60 mg (n = 127) once every 6 months for a total of 4 doses. Randomization was stratified by duration of adjuvant AI therapy at trial entry (≤ 6 months vs. > 6 months). Sixty-two percent of patients received adjuvant AI therapy for more than 6 months at study entry. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in Prolia-treated patients as compared to placebo-treated patients [-0.7% placebo, +4.8% Prolia; treatment difference 5.5% (95% CI: 4.8, 6.3); $p < 0.0001$].

With approximately 81% of patients followed for 2 years, treatment differences in BMD at 2 years were 7.6% (-1.4% placebo, +6.2% Prolia) at the lumbar spine, 4.7 % (-1.0% placebo, +3.8% Prolia) at the total hip, and 3.6% (-0.8% placebo, +2.8% Prolia) at the femoral neck.

16 HOW SUPPLIED/STORAGE AND HANDLING

Prolia is supplied in a single-use prefilled syringe with a safety guard or in a single-use vial. The grey needle cap on the single-use prefilled syringe contains dry natural rubber (a derivative of latex).

60 mg/1 mL in a single-use prefilled syringe	1 per carton	NDC 55513-710-01
60 mg/1 mL in a single-use vial	1 per carton	NDC 55513-720-01

Store Prolia in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Prior to administration, Prolia may be allowed to reach room temperature (up to 25°C/77°F) in the original container. Once removed from the refrigerator, Prolia must not be exposed to temperatures above 25°C/77°F and must be used within 14 days. If not used within the 14 days, Prolia should be discarded. Do not use Prolia after the expiry date printed on the label.

Protect Prolia from direct light and heat.

Avoid vigorous shaking of Prolia.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Drug Products with Same Active Ingredient

Advise patients that denosumab is also marketed as Xgeva, and if taking Prolia, they should not receive Xgeva *[see Warnings and Precautions (5.1)]*.

17.2 Hypocalcemia

Adequately supplement patients with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving Prolia *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.

17.3 Serious Infections

Advise patients to seek prompt medical attention if they develop signs or symptoms of infections, including cellulitis *[see Warnings and Precautions (5.3)]*.

17.4 Dermatologic Reactions

Advise patients to seek prompt medical attention if they develop signs or symptoms of dermatological reactions (dermatitis, rashes, and eczema) *[see Warnings and Precautions (5.4)]*.

17.5 Osteonecrosis of the Jaw

Advise patients to maintain good oral hygiene during treatment with Prolia and to inform their dentist prior to dental procedures that they are receiving Prolia. Patients should inform their physician or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.5)]*.

17.6 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Advise patients to report new or unusual thigh, hip, or groin pain *[see Warnings and Precautions (5.6)]*.

17.7 Hypersensitivity

Advise patients to seek prompt medical attention if signs or symptoms of hypersensitivity reactions occur *[see Contraindications (4.3)]*.

17.8 Embryo-Fetal Toxicity

Pregnancy
Advise patients that Prolia is contraindicated in women who are pregnant and may cause fetal harm *[see Contraindications (4.2), Use in Specific Populations (8.1)]*.

Males
Advise patients of a potential for fetal exposure to denosumab when a man treated with Prolia has unprotected sexual intercourse with a pregnant partner *[see Use in Specific Populations (8.8)]*

17.9 Nursing Mothers

Advise patients that because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Prolia, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother *[see Use in Specific Populations (8.3)]*.

17.10 Schedule of Administration

If a dose of Prolia is missed, administer the injection as soon as convenient. Thereafter, schedule injections every 6 months from the date of the last injection.

AMGEN®

Manufactured by:
Amgen Manufacturing Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

This product, its production, and/or its use may be covered by one or more U.S. Patents, including U.S. Patent Nos. 6,740,522; 7,097,834; 7,364,736; and 7,411,050, as well as other patents or patents pending.

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MEDICATION GUIDE

Prolia® (PRÓ-lee-a)

(denosumab)
Injection, for subcutaneous use

Read the Medication Guide that comes with Prolia before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about Prolia.

What is the most important information I should know about Prolia?

If you receive Prolia, you should not receive XGEVA®. Prolia contains the same medicine as Xgeva (denosumab).

Prolia can cause serious side effects including:

1. **Low calcium levels in your blood (hypocalcemia).**
   Prolia may lower the calcium levels in your blood. If you have low blood calcium before you start receiving Prolia, it may get worse during treatment. Your low blood calcium must be treated before you receive Prolia. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:
   - Spasms, twitches, or cramps in your muscles
   - Numbness or tingling in your fingers, toes, or around your mouth

   Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood while you take Prolia. Take calcium and vitamin D as your doctor tells you to.

2. **Serious infections.**
   Serious infections in your skin, lower stomach area (abdomen), bladder, or ear may happen if you take Prolia. Inflammation of the inner lining of the heart (endocarditis) due to an infection also may happen more often in people who take Prolia. You may need to go to the hospital for treatment if you develop an infection.

   Prolia is a medicine that may affect your immune system. People who have weakened immune system or take medicines that affect the immune system may have an increased risk for developing serious infections.

   Call your doctor right away if you have any of the following symptoms of infection:
   - Fever or chills
   - Skin that looks red or swollen and is hot or tender to touch
   - Severe abdominal pain
   - Frequent or urgent need to urinate or burning feeling when you urinate

3. **Skin problems.**
   Skin problems such as inflammation of your skin (dermatitis), rash, and eczema may happen if you take Prolia. Call your doctor if you have any of the following symptoms of skin problems that do not go away or get worse:
   - Redness
   - Itching
   - Small bumps or patches (rash)
   - Your skin is dry or feels like leather
   - Blisters that ooze or become crusty
   - Skin peeling

4. **Severe jaw bone problems (osteonecrosis).**
   Severe jaw bone problems may happen when you take Prolia. Your doctor should examine your mouth before you start Prolia. Your doctor may tell you to see your dentist before you start Prolia. It is important for you to practice good mouth care during treatment with Prolia.

5. **Unusual thigh bone fractures.**
   Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture include new or unusual pain in your hip, groin, or thigh.

Call your doctor right away if you have any of these side effects.

What is Prolia?

Prolia is a prescription medicine used to:

- Treat osteoporosis (thinning and weakening of bone) in women after menopause ("change of life") who:
  - are at high risk for fracture (broken bone)
  - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
- Increase bone mass in men with osteoporosis who are at high risk for fracture
- Treat bone loss in men who are at high risk for fracture receiving certain treatments for prostate cancer that has not spread to other parts of the body
- Treat bone loss in women who are at high risk for fracture receiving certain treatments for breast cancer that has not spread to other parts of the body

It is not known if Prolia is safe and effective in children.

Who should not take Prolia?

Do not take Prolia if you:

- have been told by your doctor that your blood calcium level is too low.
- are pregnant or plan to become pregnant
- are allergic to denosumab or any of the ingredients in Prolia. See the end of this leaflet for a complete list of ingredients in Prolia.

What should I tell my doctor before taking Prolia?

Before taking Prolia, tell your doctor if you:

- Are taking a medicine called Xgeva (denosumab). Xgeva contains the same medicine as Prolia.
- Have low blood calcium
- Cannot take daily calcium and vitamin D
- Had parathyroid or thyroid surgery (glands located in your neck)
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Have kidney problems or are on kidney dialysis
- Plan to have dental surgery or teeth removed.
- Are pregnant or plan to become pregnant. Prolia may harm your unborn baby. Tell your doctor right away if you become pregnant while taking Prolia.
    - **Pregnancy Surveillance Program:** Prolia is not intended for use in pregnant women. If you become pregnant while taking Prolia, talk to your doctor about enrolling in Amgen's Pregnancy Surveillance Program or call 1-800-772-6436 (1-800-77-AMGEN). The purpose of this program is to collect information about women who have become pregnant while taking Prolia.
    - **If you are a man and you receive Prolia:** Small amounts of Prolia may be in semen. If your sexual partner is pregnant, some Prolia from your semen may reach the unborn baby. While the risk is likely to be low, it is important to talk to your doctor if your partner becomes pregnant while you are taking Prolia.
- Are breastfeeding or plan to breastfeed. It is not known if Prolia passes into your breast milk. You and your doctor should decide if you will take Prolia or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of medicines with you to show to your doctor or pharmacist when you get a new medicine.

How will I receive Prolia?

- Prolia is an injection that will be given to you by a healthcare professional. Prolia is injected under your skin (subcutaneous).
- You will receive Prolia 1 time every 6 months.
- You should take calcium and vitamin D as your doctor tells you to while you receive Prolia.
- If you miss a dose of Prolia, you should receive your injection as soon as you can.
- Take good care of your teeth and gums while you receive Prolia. Brush and floss your teeth regularly.
- Tell your dentist that you are receiving Prolia before you have dental work.

What are the possible side effects of Prolia?

Prolia may cause serious side effects.

- See **"What is the most important information I should know about Prolia?"**
- It is not known if the use of Prolia over a long period of time may cause slow healing of broken bones.

The most common side effects of Prolia in women who are being treated for osteoporosis after menopause are:

- back pain
- pain in your arms and legs
- high cholesterol
- muscle pain
- bladder infection

The most common side effects of Prolia in men with osteoporosis are:

- back pain
- joint pain
- common cold (runny nose or sore throat)

The most common side effects of Prolia in patients receiving certain treatments for prostate or breast cancer are:

- joint pain
- back pain
- pain in your arms and legs
- muscle pain

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Prolia. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Prolia if I need to pick it up from a pharmacy?

- Keep Prolia in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton.
- Do not freeze Prolia.
- When you remove Prolia from the refrigerator, Prolia must be kept at room temperature [up to 77°F (25°C)] in the original carton and must be used within 14 days.
- Do not keep Prolia at temperatures above 77°F (25°C). Warm temperatures will affect how Prolia works.
- Do not shake Prolia.
- Keep Prolia in the original carton to protect from light.

Keep Prolia and all medicines out of reach of children.

General information about Prolia.

Do not give Prolia to other people even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Prolia. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Prolia that is written for health professionals.

For more information, go to www.Prolia.com or call Amgen at 1-800-772-6436.

What are the ingredients in Prolia?
Active ingredient: denosumab
Inactive ingredients: sorbitol, acetate, polysorbate 20 (prefilled syringe only), Water for Injection (USP), and sodium hydroxide

AMGEN®

Amgen Manufacturing Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Appendix 8

Appendix 8 Type of malignancies reported in the nSCT and oSCT clinical trial included in the meta-analysis

Type of malignancies reported in the nSCT and oSCT clinical trials included in the meta-analysis

	nSCT trials (n = 2712)	Placebo (n = 1309)	Malignancy	oSCT trials (n = 3,439)	Placebo (n = 3,423)
BCC[a]	38	5	Breast	29	22
Breast	25	5	BCC[a]	27	11
SCC[b]	10	2	Thyroid	16	18
Colon	10	1	Skin	13	8
Lung	9	2	Prostate	12	6
Pancreatic	6	1	Lung	11	11
Ovarian	5	2	Uterine	8	3
Lymphoma	4	1	Rectal	4	3
Melanoma	4	-	Ovarian	4	1
Skin	3	1	Leukemia	4	4
Prostate	2	1	Multiple Myeloma	4	-
Lip / Oral	2	-	Melanoma	3	3
Uterine	2	-	Lymphoma	3	2
Gastric	1	2	SCC[b]	3	1
Leukemia	1	1	Gastric	2	8
Brain	1	1	Bladder	2	2
Bladder	1	-	Colon	2	1
Multiple myeloma	-	2	Renal	1	2
Others[c]	5	3	Pancreatic	-	3
			Others[c]	11	10
Total					

[a] BCC, Basal cell carcinoma

[b] SCC, Squamous cell carcinoma

[c] Cases of uncommon cancers or uncertain type

Appendix 9 Tarsa Malignancy post

ONE YEAR USE OF ORAL RECOMBINANT SALMON CALCITONIN (rsCT) IS NOT ASSOCIATED WITH INCREASED RISK OF CANCER

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ABSTRACT

BACKGROUND: In July 2012 the European Medicines Agency recommended that calcitonin-containing medicines should be used only for short term treatment, due to a possible association with increased risk of (unspecified) cancer. It also recommended that intranasal calcitonin be withdrawn entirely. Although calcitonin has been in global use for at least 30 years, this association has not been previously reported, and historical carcinogenicity studies in rats and mice revealed an increased occurrence of pituitary adenomas (in rats) but no carcinogenicity signal. We recently completed two separate one-year trials of oral recombinant salmon calcitonin.

METHODS: The ORACAL trial was a global (US, EU, Republic of South Africa) trial of oral rsCT compared to intranasal calcitonin and placebo (randomized 4:3:2) in post-menopausal women with frank osteoporosis. TAR01-201 was a US trial of oral rsCT compared to placebo (randomized 2:1) in postmenopausal women with low bone mass and increased risk of fracture. In each trial the treatment duration was approximately 1 year and subjects randomized to oral rsCT received the same dose, 200 µg (1200 IU) per day, a dose of rsCT (200 µg) approximately 6 fold greater than present in nasal sCT formulations (33 µg). Neither trial specifically excluded individuals with cancer, but the presence of uncontrolled acute or chronic medical conditions was exclusionary. Subjects were seen at the clinical site 4 times after randomization in ORACAL and 5 times in 201. At each visit, as well as during regularly scheduled intervening phone calls, adverse events (AEs) were solicited and recorded. The safety databases from the two studies were integrated and AEs in the "Neoplasms benign, malignant and unspecified" system organ class were reviewed for AEs consistent with cancer.

RESULTS: 678 women constitute the safety population. The mean age was approximately 67y, >95% of subjects were White. Adverse events consistent with cancer are displayed in the table. No deaths occurred.

CONCLUSION: No carcinogenicity signal was noted in two trials of this preparation of oral recombinant salmon calcitonin.

BACKGROUND

- Calcitonin, a 32 amino acid peptide hormone, has been used as a therapeutic agent for disorders of excessive bone resorption for more than four decades. Since 1987 salmon calcitonin, manufactured by synthetic chemistry (ssCT) has been available as nasal spray for the treatment of osteoporosis. Calcitonin has had a reputation as an extremely safe drug.
- In 2009, regulatory authorities in the EU began to review the safety of calcitonin due to reports of acceleration of tumor growth of certain prostate cancer cell lines *in vitro* (Shah). On 20 July 2012 the CHMP of the European Medicines Agency (EMA) recommended withdrawal of long term use of calcitonin-containing products and withdrawal of nasal spray calcitonin completely, stating that "Analysis of all available calcitonin trials showed an increased risk of cancer. In long-term clinical trials the risk of developing cancer was 0.7% to 2.4% higher in patients receiving calcitonin-containing medicines compared to those patients receiving placebo, with the higher rates seen in trials with intranasal calcitonin".
- For all other approved indications the CHMP considered that the benefit-risk balance remains positive, but recommended that calcitonin treatment should be given for the shortest possible time.
- However, the CHMP did not actually consider "all available trials"; data from 2 additional one year trials of an investigational oral calcitonin product, conducted in postmenopausal women, are included herein.

ORAL RECOMBINANT SALMON CALCITONIN

- 32 aa peptide, ~ 50% homology to human calcitonin
- Expressed via rDNA transfected *E. coli*
- Structurally indistinguishable from synthetic salmon calcitonin
- Previously described proprietary oral delivery system for peptides (Binkley 2012)
- Efficacy and safety documented in global Phase 3 trial (Binkley 2012)

PLAUSIBILITY

- Previously performed carcinogenicity, mutagenesis and chromosome aberration studies were negative.*
- Human calcitonin was found to accelerate tumor growth in certain prostate cancer cell lines (Shah 1994). However this finding was not replicated in another lab or with other cell lines (Ritchie 1997, Segawa 2001).
- Calcitonin was found to inhibit tumor growth of other tumor cell lines, including breast and renal cell) or to have no effect in certain cell lines (Han 2006, Kinoshita 1985, Mould 2003)
- Calcitonin's mechanism of action via its second messenger, adenylate cyclase, would be expected to inhibit cell growth (Kinoshita 1985)
- Transgenic mice constitutively expressing sCT were not reported to have an excess of tumors (1 year) (Sondergaard 2012)
- No regulatory agency has previously detected this signal, despite decades of global use

* The approved UK Summary of Product Characteristics for salmon calcitonin dated January 27, 2010.

METHODS

- Two clinical trials, each 1 year long, were completed to evaluate oral rsCT in postmenopausal women
- The safety databases from the two trials were integrated
- All events in "Neoplasms, benign and malignant" System Organ Class (MedDRA) were reviewed for newly diagnosed adverse events consistent with malignancy

TRIAL 801

- Global Phase 3 trial of efficacy and safety of oral rsCT compared to placebo and synthetic salmon calcitonin nasal spray
- Double-blind, double dummy
- 565 women with documented osteoporosis at lumbar spine or hip
- 48 weeks of Rx
- Rand 4:3:2 (oral: nasal: placebo)
- Adverse events solicited at periodic visits and phone calls
- Immunogenicity testing for anti-sCT at baseline, week 12, week 48
- No adjudication of cancer events

TRIAL 201

- US trial of oral rsCT compared to placebo in postmenopausal women with osteopenia at lumbar spine or hip (T score ≤ -2.5 at any site excluded)
- FRAX risk at least that of healthy 65 y.o. women
- 129 subjects randomized 2:1 (oral rsCT: placebo)
- 52 weeks of Rx
- Adverse events solicited at periodic visits and phone calls
- No adjudication of events

RESULTS: NEW DIAGNOSES OF CANCER IN TWO TRIALS

	rsCT Tablet		Calcitonin Nasal Spray		Placebo	
	N (pct)	# Events	N (pct)	# Events	N (pct)	# Events
Subjects with at least one Cancer Event	4 (1.1)	7	0 (0.0)	0	4 (2.7)	4
Breast cancer	2 (0.6)	3	0 (0.0)	0	1 (0.7)	1
Thyroid neoplasm	1 (0.3)	1	0 (0.0)	0	1 (0.7)	1
Basal cell carcinoma	0 (0.0)	0	0 (0.0)	0	1 (0.7)	1
Malignant melanoma	1 (0.3)	3	0 (0.0)	0	0 (0.0)	0
Neoplasm skin	0 (0.0)	0	0 (0.0)	0	1 (0.7)	1

RESULTS

- In trial 801 oral rsCT was superior to nasal ssCT and placebo with respect to improvement in lumbar spine BMD (Binkley 2012) and was significantly less immunogenic than nasal ssCT.
- In trial 201 oral rsCT was superior to placebo with respect to improvement in lumbar spine BMD.*

* (Late-Breaking Abstract Presentations - Clinical II; 3:45 PM Oct 15, 2012)

CONCLUSIONS

- There is little biological plausibility to the hypothesis that salmon calcitonin would be expected to be carcinogenic in humans.
- The combined safety data from these two one year clinical trials demonstrate no signal of carcinogenicity.

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