CATÓLICA
FACULDADE DE MEDICINA DENTÁRIA
VISEU

Mestrado Integrado em Medicina Dentária

Antisclerostin Effect on Osseointegration and Bone Remodeling – A Systematic Review

Dissertação apresentada à Universidade Católica Portuguesa para obtenção do grau de Mestre em Medicina Dentária

Bárbara Alexandra do Amaral Couto

Viseu, 2021

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Viseu, 2021

Epígrafe

"Não recuses nenhum dos teus limites,
Só eles dizem a grandeza do que tens"

- Daniel Faria, "O Livro do Joaquim", 2007

Acknowledgments

(*In Portuguese*)

No decorrer do desenvolvimento da presente Dissertação foram vencidos muitos obstáculos vencidos e muitas horas foram dedicadas para conseguir ao final. Sem o apoio das seguintes pessoas isso não teria sido possível.

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Resumo

Objetivo: O objetivo desta revisão sistemática foi verificar se a administração local ou sistémica de antiesclerostina melhora a osseointegração de implantes dentários ou ortopédicos e estimula a remodelação óssea.

Materiais e Métodos: Uma pesquisa extensiva foi conduzida através das bases de dados MEDLINE (PubMed®), PubMed Central® e Web of Science®, e revistas específicas revistas por pares para identificar relatos de casos, séries de casos, estudos randomizados controlados, ensaios clínicos e estudos em animais comparando a administração local ou sistémica de antiesclerostina com a sua não utilização, no grupo controlo, para determinar o efeito na osseointegração e remodelação óssea. Foram incluídos artigos em inglês e sem restrição de período. A questão de investigação foi determinada de acordo com a estratégia PICO.

Resultados: Vinte artigos foram incluídos para leitura integral. Um dos vinte artigos foi excluído e 19 artigos foram incluídos no estudo, dos quais 16 foram estudos animais e 3 foram estudos randomizados controlados. Três dos 16 estudos animais reportaram dois estudos diferentes, ficando com 19 estudos animais e 3 estudos randomizados controlados para análise. Estes estudos foram divididos em dois grupos, um para avaliar as propriedades de osseointegração e o outro para verificar o potencial de formação óssea.

Conclusão: A antiesclerostina parece ser uma opção de tratamento promissora para acelerar a osseointegração de implantes dentários e/ou melhorar a neoformação óssea quando estão presentes patologias que podem levar à perda de estrutura óssea.

Palavras-chave: Antiesclerostina, Anticorpo Esclerostina, Romosozumab, Osseointegração, Remodelação Óssea, Formação Óssea

Abstract

Purpose: The objective of this systematic review was to verify whether the local or systemic administration of antisclerostin improves the osseointegration of dental or orthopedics implants and stimulates bone remodeling.

Materials and Methods: An extensive electronic search was conducted through MEDLINE (PubMed®), PubMed Central® and Web of Science® databases, and specific Journals peer-reviewed to identify case report, case series, randomized controlled trial, clinical trial, and animal studies comparing either the systemic or local administration of antisclerostin with no use, in control group to determine the effect in osseointegration and bone remodeling. Articles in English and with no restriction of period were included. The focused question was determined according to PICO strategy.

Results: Twenty articles were included for full review. One out of the twenty was excluded and 19 articles were included in the study, of which 16 were animal studies and 3 were randomized control trials (RCTs). Three of the 16 animal studies reported two different studies, remaining with 19 animal studies and 3 RCTs to analysis. Those studies were divided into two groups, one to evaluate the osseointegration proprieties and the other to verify the bone remodeling potential.

Conclusion: The antisclerostin appears to be a promising treatment option to accelerate the osseointegration of dental implants and/or improve the bone neoformation when are present pathologies that could lead to loss of bone structure.

Keywords: Antisclerostin, Sclerostin Antibody, Romosozumab, Osseointegration, Bone Remodeling, Bone Formation

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Table Summary

List of Abbreviations

CTCK: C-terminal cysteine knot-like
DAN: Differential screening-selected gene Aberrative in Neuroblastoma
BMP: Bone Morphogenetic Protein
MSCs: Mesenchymal Stem Cells
BMD: Bone Mineral Density
aScl or Scl-Ab: Sclerostin Antibody
BIC: Bone-to-Implant Contact
BVF or BV/TV: Bone Volume Fraction
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis
PICO: Population, Intervention, Comparison and Outcome
RCTs: Randomized Control Trials
OVX: Ovariectomized
Sham: Sham-ovariectomized
PBS: Phosphate-buffered Saline
ia: Intraarticular
sc: Subcutaneous
iv: Intravenous
DAB: DKK1 Antibody
PE: Polyethylene
ZOL: Zoledronate
cp-Ti: Commercially Pure Titanium
PMMA: Polymethylmethacrylate
EP: Experimental Periodontitis model
PTH: human Parathyroid Hormone
TH: Total Hip
FN: Femoral Neck
DR: Third Distal Radius
LS: Lumbar Spine
AS: Around Entire Screw
MS: Marrow Surrounding
CS: Cortical Surrounding
IT: Implanted Tibia
CT: Contralateral Tibia
BA/TA: Bone Area per Total Area
Ct.Ar: Cortical Area
M.Ar: Medullary/Marrow Area
Tt.Ar: Subperiosteal/Total cross-sectional Area
Tb.Th: Trabecular Thickness
Ct.Th: Cortical Thickness
Tb.N: Trabecular Number
Tb.Sp: Trabecular Separation
SMI: Structural Model Index
MS/BS: Mineralizing Surface
MAR: Mineral Apposition Rate
BFR/BS: Bone Formation Rate
Ec: Endocortical
ES/BS: Eroded Surface
Oc.S/BS: Osteoclast Surface
BMC: Bone Mineral Content
TM: Tibia Metaphysis
UDR: Ultra-Distal Radius
v: Volumetric
PT: Proximal Tibia
LV: 5th Lumbar Vertebra
FD: Femoral Diaphysis
DF: Distal Femur
DXA: Dual energy X-ray absorptiometry
PQCT: Peripheral Quantitative Computed Tomography
DRM: Distal Radius Metaphysis
PTM: Proximal Tibial Metaphysis
WB: Whole Body

CVB: Caudal Vertebral Body

LVB: Lumbar Vertebral Body

UL: Under loaded

NL: Normal loaded

Ps: Periosteal

BSAP: Bone Specific Alkaline Phosphatase

P1NP: Procollagen type 1 N-terminal Propeptide

sCTX: serum C-telopeptide

CTX-1: C-terminal telopeptides of type I collagen

β-CTX: β-isomer of C-terminal telopeptides of type I collagen

TRACP-5b: Tartrate-resistant Acid Phosphatase 5b

INTRODUCTION

1. Introduction

Sclerostin is a glycoprotein encoded in humans by the SOST gene,[1, 2] located on chromosome 17q12-q21,[3] with a C-terminal cysteine knot-like (CTCK) domain and sequence similar to the DAN (Differential screening-selected gene Aberrative in Neuroblastoma), antagonists family of the bone morphogenetic protein (BMP). It is primarily produced and secreted by osteocytes[4, 5] and it is a negative key-regulator of osteoblastic functions,[6] inhibiting its differentiation and bone formation through the inhibition of Wnt signaling pathway after binds with LRP5 and 6 (Wnt co-receptor), inhibiting Wnt binding,[7, 8] decreasing consequently the bone formation.[9, 10]

This canonical Wnt signaling (Wnt/β-catenin pathway) is important on the bone healing,[11-17] promoting pre-osteoblast proliferation, osteoinduction, enhances survival of all cells of the osteoblast lineage, inhibits differentiation of mesenchymal stem cells (MSCs) into chondrocytes and adipocytes, control osteoclast maturation by regulating RANKL levels in osteoblasts receptors,[18] beyond it controls skeletal development as well as bone homeostasis. Alterations in several Wnt pathway members have been shown to cause skeletal abnormalities,[19-22] conversely to low levels of sclerostin or mutations of the SOST gene which can implicate in several genetic skeletal disorders with high bone mineral density (BMD), like in sclerosteosis and van Buchem disease,[1, 2, 6] while the SOST gene over-expression leads to osteopenia.[23]

In this scenario, studies emerged to find a possible control to the situation that favored the augmentation of the sclerostin production, such as by calcitonin.[24] Some of them, that cause a suppression effect on sclerostin are parathyroid hormone,[25, 26] mechanical loading,[27] cytokines (prostaglandin E2),[28] oncostatin M, cardiotrophin-1, and leukemia inhibitory factor.[29] Moreover, a systemic administration of a monoclonal sclerostin antibody (aScl) can significantly help to increase the newly formed bone and its strength,[30-32] also elevates Wnt signaling improving bone-to-implant contact (BIC),[33] helping to increase the bone mass in preclinical studies (ovariectomized rats), and in postmenopausal women,[34, 35] and enhanced the bone performance according to age,[36] what have supporting a beneficial effect of antisclerostin in bone disorders. Already in male rats, it revealed acceleration and enhance of the mechanical fixation of femoral medullary implants, by increasing the volume of cortical and trabecular bone around the implants,[37] and for alveolar bone defects, there was an increase in bone-implant contact (BIC), bone volume fraction (BVF), and bone area fill at 14 days, which was more significant at 28 days, indicating an improvement in bone regeneration and implant osseointegration.[38]

Furthermore, in clinical studies (phase I and II), antisclerostin has induced robust increases in BMD, being suggested as a promising treatment option for osteoporosis.[39-41] With all these approaching, it has awaked, thus, the interesting for the Dentistry area, either in bone regenerations as implants osseointegration. Also, recent publication[42] confirmed aforementioned data, which reached a relevant systemic result contrasting with local application, with a different result related to an enhanced deposition of cellular cement.

Nonetheless, successful patents were already registered using the aScl, such as U.S. patent number 9913900 and 9657090 about alveolar bone loss through the use of anti-sclerostin antibodies, Spanish patent number ES2445792T3 for use in a method to inhibit bone resorption in a human being, Global Patent Index number 3478719A1 for treatment of osteogenesis imperfecta, U.S. patent application number 20180099046 for treatment of osteoporosis, and European patent EP2195026B1 studying the modulation of the bone density.

In the implant dentistry field, it is known either the high success rate for dental implants as the survival rate, with more than 95%[43] found and, specifically observed in a long-term study which presented 96.4% after ten-years follow-up.[44] Thereby, it is a predictable and reliable treatment method which can treat 69% of adults aged between 35 and 44 that lost at least one permanent tooth, or the elder people with more than 70 years old who 26% already lost all their permanent teeth.[45] Moreover, an estimative revealed that the use of dental implants is between 100,000-300,000 per year,[46] achieving an expectation in the US and European markets of $4.2 billion up to 2022.[47] Nonetheless, a great challenge still exists and it is matched with the acceleration of implants' osseointegration, which wants to benefit patients, permitting a more rapid functional loading and esthetic. With this purpose, two methods are highlighted, one by implant surface modifications and another related to bone antiresorptive[48, 49] or anabolic agents, which may involve the association with the aScl.

Thus, within this background observing the aScl approaching and its possible relation to the dental implant area, the goal of this systematic study was to verify systematically the literature analyzing whether there was acceleration on the implant osseointegration–after administration of systemic or local antisclerostin. A secondary goal was defined in order to verify if the stimulation of bone remodeling was achieved by aScl administration.

MATERIALS AND METHODS

2. Materials and Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines[50] with the focused question being determined according to the Population, Intervention, Comparison and Outcome (PICO) strategy.[51] The protocol for this systematic review was registered on PROSPERO (CRD42021236778).

2.1. Focused Question

The focused question for the present systematic review was as follows: “In partially and fully edentulous patients requiring dental implant or *in vivo* animal studies (P), does the antisclerostin application systemic or locally (I), when compared with no use, in the control group (C), resulted in the acceleration of the osseointegration, and bone remodeling (O)?

2.2. Information sources and search strategy

An extensive electronic search was conducted through MEDLINE (PubMed®), PubMed Central® and Web of Science® databases, and specific Journals peer-reviewed (Biomed Research International, Cancers, Current Osteoporosis Reports, Frontiers in Bioengineering and Biotechnology, International Journal of Molecular Sciences, International Journal of Nanomedicine, Journal of dental research, Journal of functional biomaterials, Materials, Osteoporosis International, and PloS one), using the following keywords, sclerotin OR antisclerostin OR sclerostin antibody OR Romosozumab OR Blosozumab AND osseointegration AND bone formation OR "newly formed bone" OR "new bone" AND dental implant OR "dental implants" OR implant, with a platform-specific search strategy combining terms and text words with Booleans. An additional manual search was performed on the references of included articles to identify relevant publications. There is no restriction of date and language.

Two reviewers (G.V.O.F and B.A.A.C.) independently performed the electronic and manual search. The publications obtained from the search through all mentioned databases were imported into a reference management software (EndNote 20.1) and subsequently screened.

2.3. Inclusion criteria

This systematic review was based on any experimental *in vivo* (animal or human) study, which involved the aScl effectiveness analysis, when administrated systemic or locally, resulting on the dental implant osseointegration, or bone remodeling. Case report, case series, randomized controlled trial, clinical trial, and animal studies were included. The additional inclusion criteria for study

selection were restriction for English language and no restriction for period; clinical needed of the implant placement; animal studies analyzing implant osseointegration; detailed information on the implant osseointegration; reported details regarding survival and/or failure rates; if applicable, only the longest follow-up published was included when involving the same patient cohort (population).

2.4. Exclusion criteria

Book or chapter, posters and e-posters, editorial letter, patents, reports based on questionnaires, interviews, *in vitro* study, *in silico* study, and systematic review/meta-analysis. Also, a lack of information about osseointegration or bone remodeling, dose/period of the drug administrated conducted to the exclusion.

2.5. Selection of studies

Duplicates studies were excluded, and the remaining articles screened, initially, by tittle and abstract for eligibility. Further examination regarding inclusion and exclusion was subsequently made by full-text analysis. The full text of any title or abstract that did not provide enough information regarding the inclusion criteria was also obtained. Any disagreement between the reviewers was discussed with a third author (J.C.H.F.). Cohen's kappa test was adopted to evaluate reviewers' agreement on both title and abstract and full-text selection.

2.6. Risk of bias and quality assessment

The assessment of risk of bias and study quality of the included investigations was performed independently by two reviewers (G.V.O.F. and J.C.H.F.), where randomization process, groups similar at baseline, blinded group allocation, random housing, blinded interventions, random and blinded outcome assessment, reporting of dropouts and other biases (funding) domains were addressed.

RESULTS

3. Results

3.1.Study Selection

A total of 385 records were identified after research on databases, PubMed Central® (290), Web of Science® (92), PubMed/MEDLINE (3), and 14 records identified through additional manual search on cross-references within the included articles. After removing duplicates, 361 records were screened and 341 were excluded. Thus, 20 records remained which were evaluated by full-text analysis, with 1 record being excluded for not having available data to compare with baseline data. In the end, 19 articles were included in the study (Figure 1).

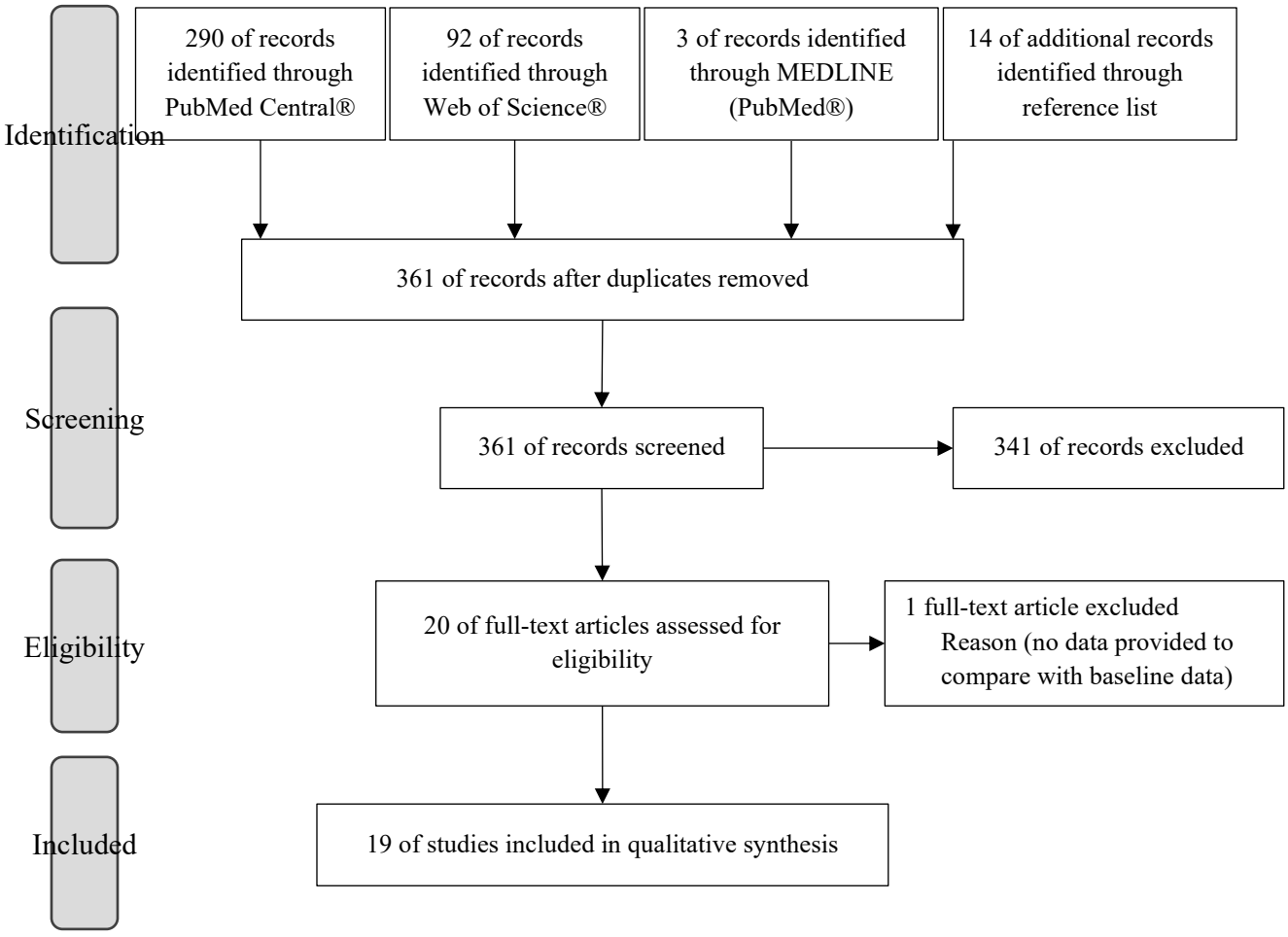

Figure 1: *Search Strategy and Studies Selection*

3.2.Study Characteristics

Of the 19 articles selected, 16 articles were animal studies while 3 were randomized control trials (RCTs) (Table 1). Initially were identified a total of 5751 "participants" were identified, of which 4560 humans and 1191 animals (906 Sprague-Dawley rats, 128 Wistar rats, 102 Lewis rats e 55 Cynomolgus monkeys), with at least 1017 excluded from the studies (981 humans and 36 animals). A total of 4724 "participants" completed the studies, 3579 humans and 1145 animals.

Liu *et al.* 2018, Virk *et al.* 2013 and Ominsky *et al.* 2011[52-54] described in their articles two independent studies. (Tables 1 and 2) The first one[52] used two different samples, in one study female and the other male Sprague-Dawley rats. The studies described by Ominsky *et al.* 2011 were performed in two different species.[54] One of them used Sprague-Dawley mice, and the other used Cynomolgus monkeys, which underwent osteotomy in fibular midshaft.

In four studies[31, 33, 52, 55] an ovariectomy surgery was performed to induce osteopenia. In the initial sample size, a total of 223 ovariectomized (OVX) and 153 Sham-ovariectomized (Sham) rats was identified. After exclusions, one of the studies[31] only mentioned that 5 rats were excluded from the study after surgery but didn't mention which group, they were excluded from. In the remaining studies, a total of 151 OVX and 81 Sham rats completed the studies (Table I).

One article[31] did not mention the age of the animals used. In animal studies, after exclusions, 582 female and 522 male rats, 12 female and 29 male monkeys were used and in human studies, were identified 3564 women and 15 men (Table I).

In animal studies, one article reported that no antibody was applied as control.[56] Seven studies[31, 32, 37, 52, 57, 58] reported the use of saline solution as control, with two studies corresponding to the same article,[52] and six studies reported the use of vehicle,[33, 36, 54, 55, 59] with two studies referring to the same article.[54] Three studies referred the use of phosphate-buffered saline solution (PBS)[38, 53]. One study reported the use of two different controls,[60] using PBS in healthy animals and vehicle in animals in which an experimental periodontitis model was induced. Another study[61] reported the use of intraarticular (ia) particle vehicle and subcutaneous (sc) antibody vehicle as control (Table 2). Whereas, in human studies, two articles[39, 41] referred placebo used as control, and in one study[62] was used Alendronate.

In animal studies, five articles reported the administration of 25 mg/kg sc of Scl-Ab III (sclerostin antibody III/murine sclerostin antibody, Amgen and UCB Pharma, Thousand Oaks, California) twice a week in rats[31, 33, 53, 54, 58]. Virk *et al.* 2013,[53] described another study, in which was administered 25 mg/kg of Scl-Ab III but did not mention the administration route. Ominsky *et al.*

2011,[54] also describes another study, performed in monkeys, in which referred the administration of 30 mg/kg sc of Scl-Ab V (Humanized sclerostin antibody, Amgen and UCB Pharma), every 2 weeks.

Three studies[32, 36, 57] used two different dosages of Scl-Ab III, 5 mg/kg, or 25 mg/kg sc twice a week. Two studies[38, 56] didn't reported the type of antibody used. Korn *et al.* 2019,[56] administered 100 mg/kg of Sclerostin Antibody intravenous (iv), and Yu *et al*. 2018[38] referred the administration of 25 mg/kg of Scl-Ab subcutaneously.

Liu *et al.* 2018,[52] reported the administration of Scl-Ab VI and the association of Scl-Ab VI with DKK1 antibody (Scl-Ab VI + DAB) in OVX rats, in both studies they performed, however, the drug dosage used differed between them. In one study administered 18.2 mg/kg sc twice a week (Scl-Ab VI) and 18.2 mg/kg and 18.1 mg/kg sc twice a week (Scl-Ab VI + DAB), and in the other 25 mg/kg sc twice a week (Scl-Ab VI) and 25 mg/kg and 25 mg/kg sc twice a week (Scl-Ab VI + DAB).

One study[55] reported the administration of 25 mg/kg of Scl-Ab (Sclerostin antibody, Amgen, Thousand Oaks, California) sc twice a week, 60μg/kg of PTH 1-34 (human Parathyroid Hormone 1-34, Bachem, Torrance, California) sc thrice a week, and the administration of the association of these two drugs mentioned above (Scl-Ab + PTH 1-34), in OVX rats. Other study[60] reported a systemic administration of 25 mg/kg sc twice a week of Scl-Ab III, and a local administration of 5 μL of 35.6 mg/mL of solution per site twice a week, giving a total of 15 μL per animal per treatment session, in rats submitted to experimental periodontitis model (EP rats).

Liu *et al.* 2012,[61] referred an administration of 50 μL ia of polyethylene (PE) suspension once a week associated with antibody vehicle or 25 mg/kg sc of Scl-Ab III twice a week. Virdi et al. 2012,[37] used 25 mg/kg subcutaneously of Scl-Ab (murine sclerostin antibody Amgen, Thousand Oaks, California). And finally, Ominsky *et al.* 2010,[59] administered 3 different dosages, 3 mg/kg, 10 mg/kg, or 30 mg/kg, sc of Scl-Ab IV (humanized sclerostin-neutralizing monoclonal antibody) once a month, in monkeys.

In human studies, Saag *et al.* 2017 study,[62] during an initial period, administered 210 mg sc of Romosozumab once a month, followed by oral administration of 70 mg of Alendronate once a week. In McClung *et al.* 2014 study,[39] was administrated 140 mg, or 210 mg once every 3 months, or 70 mg, 140 mg, or 210 mg once a month sc of Romosozumab, 70 mg sc of Alendronate once a week or 20 μg sc of Teriparatide once a day. In the last study,[35] Romosozumab was administrated subcutaneously and divided into 6 cohorts, 4 female cohorts (1mg/kg every 2 weeks, 2mg/kg every 4 weeks, 2mg/kg every 2 weeks, 3mg/kg every 4 weeks, Cohorts 1, 2 ,3 and 4, respectively) and 2 male cohorts (1mg/kg every 2 weeks, 3mg/kg every 4 weeks, Cohorts 5 and 6, respectively). When the last woman to receive the dose from cohort 2 was followed for 6 weeks, they evaluated safety and

laboratory findings before moving to the following cohorts (Cohorts 3 and 4). Cohort 5 ran simultaneously with any of the ongoing cohorts, and cohort 4 and 6 started at same time.

Four other studies reported the placement of implants[33, 37, 38, 56]. One study used titanium implants with two types of surface treatment, titanium sandblasted thermally acid-etched surface (reference-coated implant) or zoledronate-stearate spray coated surface (ZOL-coated implant).[56] Another study[38] commercially pure titanium (cp-Ti) cylindrical solid with titanium plasma-sprayed surface implant was placed one month after the extraction of the first right maxillary molar. Finally, Virdi *et al.* 2015 and Virdi *et al.* 2012 studies used cp-Ti with dual acid-etched surface implants.[33, 37]

Only one study[61] used titanium screws with dual acid-etched surface. One of the studies in the Omnisky *et al.* 2011 article used stainless steel K-wire.[54] And one last study used stainless steel screws for mechanical tests and polymethylmethacrylate (PMMA) screws for micro-CT, to avoid radiographic artifacts.[58] Nevertheless, the remaining studies did not install any implant.

Table 1: *Main Characteristics of Selected Articles – Part I.*

Author (et al.)	**Year**	**Country** (study)	**Study Center**	**Study Type**	**Species**	**Sample Size** (Initial)		**Sample Size** (Final)		**Age** (mean)	**Gender**
Korn *et al.* [56]	2019	Switzerland	Basel-Stadt Cantonal Veterinary Office	Animal	Wistar rats	128		124		6-month-old	female
Liu *et al.* [52]	2018	USA	-	Animal	Sprague-Dawley rats	50	40 OVX[a] 10 Sham[b]	50	40 OVX[a] 10 Sham[b]	6-month-old	female
					Sprague-Dawley rats	45		45		8-month-old	male
Wu *et al.* [55]	2018	China	-	Animal	Sprague-Dawley rats	50	5 Sham 5 OVX 40 OVX	40 OVX		3-month-old	female
Yu *et al.* [38]	2018	USA	University of Michigan	Animal	Sprague-Dawley rats	60		60		8-month-old	male
Virdi *et al.* [33]	2015	USA	-	Animal	Sprague-Dawley rats	144	72 OVX[a] 72 Sham[b]	142	71 OVX[a] 71 Sham[b]	4.5-month-old	female
Taut *et al.* [60]	2013	USA	-	Animal	Sprague-Dawley rats	69		69		9–10-week-old	male
Virk *et al.* [53]	2013	USA	University of Connecticut Health Center	Animal	Lewis rats	72		72		14-week-old	male
					Lewis rats	30		30		14-week-old	male
Liu *et al.* [61]	2012	USA	-	Animal	Sprague-Dawley rats	36		36		-	male
McDonald *et al.* [31]	2012	Australia	-	Animal	Sprague-Dawley rats	132	66 Sham[b] 66 OVX[a]	127		-	female
Virdi *et al.* [37]	2012	USA	-	Animal	Sprague-Dawley rats	90		88		6-month-old	male
Ominsky *et al.* [54]	2011	Canada	Charles River Laboratories	Animal	Sprague-Dawley rats	35		32		7-7.5-month-old	male
					Cynomolgus monkeys	43		29		4–5 years old	male
Tian *et al.* [32]	2011	USA	University of Utah	Animal	Sprague-Dawley rats	67		67		10-month-old	female
Agholme *et al.* [58]	2010	Sweden	-	Animal	Sprague-Dawley rats	68		64		10-month-old	male
Li *et al.* [36]	2010	USA	-	Animal	Sprague-Dawley rats	28		26		16-month-old	male
Ominsky *et al.* [59]	2010	Canada	Charles River Laboratories	Animal	Cynomolgus monkeys	12		12		3–5 years old	female
Tian *et al.* [57]	2010	USA	University of Utah	Animal	Sprague-Dawley rats	32		32		10-month-old	female
Saag *et al.* [62]	2017	-	Multicenter international	RCT, ph.3[c]	Human	4093		3150		55–90 years old	women
McClung *et al.* [39]	2014	-	Multicenter international (28 centers)	RCT, ph.2[d]	Human	419		383		55-89 years old	women
Padhi *et al.* [41]	2014	USA	4 centers	RCT[e]	Human	48	32 women 16 men	46	31 women 15 men	45-80 years old	Postmenopausal women & men

[a]**OVX** – Ovarectomized rats; [b]**Sham** – Sham-ovarectomized rats; [c]**RCT, ph 3** – Phase 3, randomized, double-blind trial; [d]**RCT, ph 2** – Phase 2, randomized, placebo-controlled; [e]**RCT** - Randomized, double-blind, placebo-controlled

Table 2: *Main Characteristics of Selected Articles – Part II.*

	Sample Size (Inicial)		Sample Size (Final)		Control	Drug (name)	Administration Route	Dosage (unit)	Period of Treatment	Implant
Korn *et al.* (2019) [56]	128		124		non antibody applied	sclerostin antibody	intravenous	100mg/kg once week	2 or 4 weeks	Reference-coated implant
										ZOL-coated implant
Liu *et al.* (2018) [52]	50	40 OVX	50	40 OVX	saline solution	Scl-Ab VI	subcutaneous	18.2mg/kg twice week	5 weeks	not placed
						Scl-Ab VI + DAB[d]		18.1mg/kg + 18.1mg/kg twice week		
		10 Sham		10 Sham		-		-		
	45		45		saline solution	Scl-Ab VI	subcutaneous	25mg/kg twice week	15 weeks	not placed
						Scl-Ab VI + DAB[d]		25mg/kg + 25mg/kg twice week		
Wu *et al.* (2018) [55]	50	5 Sham	-		-	-	-	-	-	-
		5 OVX	-		-	-	-	-	-	-
		40 OVX	40 OVX		vehicle	Scl-Ab[e]	subcutaneous	25mg/kg twice week	12 weeks	not placed
						PTH 1-34[f]		60μg/kg thrice week		
						Scl-Ab[e] + PTH 1-34[f]		25mg/kg twice week + 60μg/kg thrice week		
Yu *et al.* (2018) [38]	60		60		PBS[a]	Scl-Ab	subcutaneous	25mg/kg	10, 14 or 28 days	cp-Ti, solid cylinder with titanium plasma-sprayed surface implant
Virdi *et al.* (2015) [33]	144	72 OVX	142	71 OVX	vehicle	Scl-Ab III[g]	subcutaneous	25 mg/kg twice week	4, 8 or 12 weeks	cp-Ti with dual acid-etched surface implant
		72 Sham		71 Sham						
Taut *et al.* (2013) [60]	69		69		EP[b]: vehicle healthy: PBS	EP[b]: Scl-Ab III[g]	subcutaneous	25 mg/kg twice week	3 or 6 weeks	not placed
							locally	15 μL of 35.6mg/mL solution[m] twice week		
Virk *et al.* (2013) [53]	72		72		PBS[a]	Scl-Ab III[g]	subcutaneous	25mg/kg twice week	0-12 weeks[n]	not placed
									0-2 weeks[o]	
									2-4 weeks[p]	
	30		30		PBS[a]	Scl-Ab III[g]	-	25mg/kg	12 weeks	not placed
Liu *et al.* (2012) [61]	36		36		particle vehicle + antibody vehicle	PE suspension[h] + antibody vehicle	intraarticular + subcutaneous	50μL once week + vehicle twice week	12 weeks	titanium rods, dual acid-etched surface
						PE suspension[h] + Scl-Ab III[g]		50μL once week + 25 mg/kg twice week		
McDonald *et al.* (2012) [31]	132	66 Sham	127		saline solution	Scl-Ab III[g]	subcutaneous	25mg/kg twice week	1, 2 or 3 weeks	not placed
		66 OVX								
Virdi *et al.* (2012) [37]	90		88		saline solution	Scl-Ab[i]	subcutaneous	25mg/kg	2, 4 or 8 weeks	cp-Ti with dual acid-etched surface implant
Ominsky *et al.* (2011) [54]	35		32		vehicle	Scl-Ab III[g]	subcutaneous	25mg/kg twice week	7 weeks	not placed
	43		29		vehicle	Scl-Ab V[j]	subcutaneous	30mg/kg every 2 weeks	10 weeks	stainless steel K-wire

Tian *et al.* (2011) [32]	67		67		saline solution	Scl-Ab III[g]	subcutaneous	5mg/kg twice week	4 weeks	not placed
								25mg/kg twice week		
Agholme *et al.* (2010) [58]	68		64		saline solution	Scl-Ab III[g]	subcutaneous	25mg/kg twice weeks	2 or 4 weeks	stainless steel screws (mechanical tests); PMMA screws (μCT)
Li *et al.* (2010) [36]	28		26		vehicle	Scl-Ab III[g]	subcutaneous	25mg/kg twice week	5 weeks	not placed
								5mg/kg twice week		
Ominsky *et al.* (2010) [59]	12		12		vehicle	Scl-Ab IV[k]	subcutaneous	3mg/kg once month	29 days	not placed
								10mg/kg once month		
								30mg/kg once month		
Tian *et al.* (2010) [57]	32		32		saline solution	Scl-Ab III[g]	subcutaneous	5mg/kg twice week	4 weeks	not placed
								25mg/kg twice week		
Saag *et al.* (2017) [62]	4093		3150		alendronate[c] → alendronate[c]	romosozumab[l] → alendronate[c]	subcutaneous → oral	210mg once month → 70mg once week	0-12 months[q] → 12-36 months[r]	not placed
McClung *et al.* (2014) [39]	419		383		placebo	romosozumab	subcutaneous	140mg every 3 months	12 months	not placed
								210mg every 3 months		
								70mg once month		
								140mg once month		
								210mg once month		
						alendronate	oral	70 mg once week		
						teriparatide	subcutaneous	20μg once day		
Padhi *et al.* (2014) [41]	48	32 women	46	31 women	placebo	romosozumab	subcutaneous	1mg/kg every 2 weeks	12 weeks	not placed
								2mg/kg every 4 weeks		
								2mg/kg every 2 weeks		
								3mg/kg every 4 weeks		
		16 men		15 men		romosozumab	subcutaneous	1mg/kg every 2 weeks		
								3mg/kg every 4 weeks		

[a]**PBS** – Phosphate-buffered saline solution; [b]**EP** – Experimental periodontitis model; [c]**Alendronate** – Alendronate, Merck; [d]**DAB** – DKK1 Antibody; [e]**Scl-Ab** – Sclerostin antibody, Amgen, Thousand Oaks, California; [f] **PTH 1-34** – human Parathyroid Hormone 1-34, Bachem, Torrance, California; [g]**Scl-Ab III** – Sclerostin antibody III (murine sclerostin antibody), Amgen and UCB Pharma, Thousand Oaks, California; [h]**PE suspension** – Polyethylene particle suspension; [i]**Scl-Ab** – Murine sclerostin antibody, Amgen, Thousand Oaks, California; [j]**Scl-Ab V** – Humanized sclerostin antibody, Amgen and UCB Pharma; [k]**Scl-Ab IV** – Humanized sclerostin-neutralizing monoclonal antibody; [l]**Romosozumab** – AMG 785/CDP7851, Amgen and UCB Pharma; [m]**15 μL of 35.6mg/mL solution** – 5 μL of 35.6 mg/mL of solution per site twice a week, giving a total of 15 μL per animal per treatment session [n]**0-12 weeks** – continuous group; [o]**0-2 weeks** – early group; [p]**2-4 weeks** – delayed group [q]**0-12 months** – Double blind period; [r]**12-36 months** – Open label period [s] **reference-coated implant** – Ti implant w/ sandblasted and thermally acid-etched surface [t]**ZOL-coated implant** – Ti implant w/ ZOL-stearate spray coated surface

3.3. Osseointegration

The seven studies, described in Supplementary Tables S1 to S6, were used for the description of osseointegration.

3.3.1. Bone Formation Parameters

Several bone formation parameters were identified, which are described below.

3.3.1.1. Bone-to-Implant Contact

The studies performed by Korn *et al.* 2019, Yu *et al.* 2018, Virdi *et al.* 2015 and Virdi *et al* 2012[33, 37, 38, 56] reported the Bone-to-Implant Contact (BIC). The remaining studies did not mention this parameter.

Korn *et al.* 2019[56] analyzed the BIC by histomorphometry and μCT.[56] With histomorphometry, they reported similar BIC values 2 weeks following sclerostin antibody application in both reference-coated and ZOL-coated implants. But at 4 weeks, the BIC values increased to 57.4 ± 15.0 % and decreased to 24.1 ± 9.7 % in the ZOL-coated and reference-coated implants, respectively. With μCT, they reported the highest increase in BIC 4 weeks after administration of the sclerostin antibody combined with ZOL-coated implants (60.0 ± 2.5 %). (Table S1)

The other three studies just reported qualitative information.[33, 37, 38] Yu *et al.* 2018 reported a significantly greater BIC than control, at 28 days and non-significant differences in early points.[38] This evidence is also supported by Virdi *et al.* 2012.[37] Virdi *et al.* 2015 reported an increase over time after Scl-Ab treatment, more notable with Sham rats.[33]

3.3.1.2. Bone Mineral Density

Four studies approach Bone Mineral Density (BMD)[38, 54, 56, 58] (Table S1).

Korn *et al.* 2019,[56] reported a significant increase in cancellous BMD with ZOL-coated implant and a decrease with reference-coated implants, 4 weeks after implant placement. Also, reported an increase almost two-fold in ZOL-coated implant + sclerostin antibody group compared to the reference-coated implant group. One study only reported that there were no differences between groups control and Scl-Ab.[38]

Two studies reported values in some anatomical points.[58, 59]

One study[59] registered the percentage of change from baseline values on total hip (TH), femoral neck (FN), third distal radius (DR), and lumbar spine (LS) of the primates, for both groups studied. In the control group, is reported an increase of 9.3 ± 1.5 %, 7.6 ± 2.1 %, 3.3 ± 0.6 % and 4.4 ± 0.5 % in TH, FN, DR, and LS, respectively. While in the Scl-AB V group, the increase was 14.5 ± 1.8 %, 17.4 ± 1.6 %, 5.6 ± 0.9 % e 16.6 ± 1.2 % in TH, FN, DR, and LS, respectively.

Agholme *et al.* 2011 referred to the mean values observed, from the μCT performed around all screw (AS), marrow surrounding (MS), cortical surrounding (CS), in the implanted tibia (IT), and the contralateral tibia (CT), for both groups control and Scl-Ab III.[58] For the control group were recorded the values 1.12 ± 0.05 g/cm^3, 1.10 ± 0.02 g/cm^3, 1.14 ± 0.065 g/cm^3, 0.96 ± 0.02 g/cm^3 e 0.98 ± 0.03 g/cm^3 in AS, MS, CS, IT e CT, respectively. For the Scl-Ab III group, were reported the values 1.17 ± 0.04 g/cm^3, 1.14 ± 0.04 g/cm^3, 1.20 ± 0.055 g/cm^3, 1.04 ± 0.01 g/cm^3 e 1.05 ± 0.01 g/cm^3 in AS, MS, CS, IT e CT, respectively.

3.3.1.3. Bone Area per Total Area

Only one study analyzed the Bone Area per Total Area (BA/TA).[56] It was reported, in all groups, a greater relative bone area close to the implant surface than in distant regions, with better results with the combination of ZOL-coated implant and sclerostin antibody. Furthermore, referred to the mean values of BA/TA, such as 4.5 ± 4.2%, 10.9 ± 4.4%, 23.8 ± 8.6% and 32.3 ± 11.5%, for the groups reference-coated implant without and with sclerostin antibody administration, and ZOL-coated implant without and with antibody application, respectively (Table S1).

3.3.1.4. Bone Volume Fraction

All studies approached the Bone Volume Fraction, also referred to as Relative Bone Volume and Bone Volume per Total Volume (BV/TV or BVF). Korn *et al.* 2019,[56] referred to the increase in BV/TV for ZOL-coated implant groups, indicating 31.0 ± 7.6 % to the ZOL-coated implant plus sclerostin antibody administration. They reported a decrease in the reference-coated implants after 4 weeks. (Table S1)

Yu *et al.* 2018[38] referred that the BFV was approximately 2 and 2.5 times higher in the Scl-Ab than the control group, at 14 and 28 days, respectively. (Table S1)

Other study[33] reported a most significant increase with the Scl-Ab III application in the Sham rats. Liu et al. 2012 reported the values 17.5 ± 5.8 %, 31.2 ± 7.7 %, and 7.6 ± 2.5 % for the control, PE suspension plus Scl-Ab III and PE suspension plus antibody vehicle administration, respectively.[61]

Virdi et al. 2012 study referred that, with the Scl-Ab administration, the relative bone volume was two and more than two-fold the value in the control group, at 4 and 8 weeks, respectively.[37] Omnisky *et al.* 2011[54] reported the BV/TV values at FN, with 27.5 ± 2.3 % and 33.6 ± 2.1%, for the control and Scl-Ab V group, respectively.

Finally, Agholme *et al.* 2010 reported the BV/TV data for the same points referred to BMD. The values have described in Table S1.[58] There was a trend towards higher values when administered Scl-Ab III to rats after screw placement at all points analyzed in the study.

3.3.1.5. Cortical, medullary, and subperiosteal areas

The Cortical Area (Ct.Ar) was described by two studies, Virdi *et al.* 2012 and Omnisky *et al.* 2011.[37, 54] The remaining studies didn't mention this parameter.

In Virdi *et al.* 2012 study, they reported a significantly greater Ct.Ar at 4 and 8 weeks, in Scl-Ab group.[33] Ominsky *et al.* 2011, reported the Ct.Ar values in FD, 56.0 ± 6.7 mm^2 and 54.7 ± 2.0 mm^2, for Scl-Ab V and vehicle groups, respectively.[54] (Table S2)

The Medullary or Marrow Area (M.Ar) and Subperiosteal Area, also known as Total cross-sectional Area, (Tt.Ar) only was reported by Virdi *et al.* 2012 study.[37]

This study referred to that did not detect differences between Scl-Ab and control groups in peri-implant M.Ar. And reported a greater Tt.Ar, with the administration of Scl-Ab, at 8 weeks.

3.3.1.6. Bone Fill

Only one study approached the Bone Fill parameter.[38] Reporting that it was significantly greater in the Scl-Ab group at 28 days.

3.3.1.7. Bone Thickness, Trabecular Thickness and Cortical Thickness

The only study which reported Bone Thickness was by Virdi *et al.* 2012.[37] Bone thickness was greater in the Scl-Ab group than in the control at 8 weeks.

Only two studies did not report information on Trabecular Thickness (Tb.Th).

A higher Tb.Th was reported by Korn *et al.* 2019, in both groups which received sclerostin antibody treatment.[56] Virdi *et al.* 2015 referred that Tb.Th increased in Sham rats treated with Scl-Ab III.[33]

Three studies reported the mean values of Trabecular Thickness in control and drug tested groups, described in Table S3. Liu *et al.* 2012 study reported the 192 ± 26 μm Tb.Th value in PE

suspension plus Scl-Ab III group, as the greater of the three groups.[61] Ominsky *et al.* 2011 reported the values on the FN, and the highest value was observed with the application of Scl-Ab V (194 ± 6 μm).[54] As well as the other studies, Agholme et al. 2010 reported the greater values in the drug test group.[58] However, it demonstrated better results in contralateral tibia than in implanted tibia (121 ± 3.8 μm and 117 ± 5.7μm, respectively).

The Cortical Thickness (Ct.Th) was only mentioned by Virdi *et al.* 2015 and Virdi *et al.* 2012. Virdi *et al.* 2015 verified an increase over time with the application of Scl-Ab in OVX and Sham rats, however the effect was more pronounced in Sham rats.[33] Virdi *et al.* 2012 reported that with the administration of Scl-Ab the peri-implant Ct.Th was greater at 8 weeks, and in contralateral femur it was greater at 4 and 8 weeks.[37]

3.3.1.8. Trabecular Number

No information about Trabecular Number (Tb.N) was provided by four studies. Yu *et al.* 2018 reported a greater Tb.N in Scl-Ab than control group at 8 weeks[38] and Virdi *et al.* 2015 referred that a little or no effect was observed in Sham rats, after the Scl-Ab III administration.[33]

Liu *et al.* 2012 and Agholme *et al.* 2010 reported the mean values in the groups analyzed.[58, 61] In the first study, they reported the values of 1,31 ± 0.34 mm^{-1}, 2.01 ± 0.32 mm^{-1}, and 0.92 ± 0.18 mm^{-1} in the control, PE suspension plus Scl-Ab III and PE suspension plus antibody vehicle, respectively.[61] The last study related higher values of Tb.N in control group (2.4 ± 0,40 μm^{-1} and 2.1 ± 0,48 μm^{-1}, in CT and IT, respectively), compared to Scl-Ab III group.[58] (Table S3)

3.3.1.9. Trabecular Separation

Only Liu *et al.* 2012 e Agholme *et al.* 2010 approached the Trabecular Separation (Tb.Sp) in their studies. The remaining studies did not mention the Tb.Sp (Table S3).

Liu *et al.* 2012 reported a higher value in PE suspension plus antibody vehicle group, followed by control and PE suspension plus Scl-Ab III groups (1182 ± 216 μm, 869 ± 216 μm and 502 ± 93 μm, respectively).[61] Contrasting to that, Agholme *et al.* 2010 referred that Tb.Sp has higher values in Scl-Ab III group, both Implanted and Contralateral Tibia (304 ± 54 μm and 277 ± 56 μm, respectively).[58]

3.3.1.10. Structural Model Index

The studies performed by Liu *et al.* 2012 and Virdi *et al.* 2012 referred the Structural Model Index (SMI). The remaining studies did not mention this parameter.

Liu *et al.* 2012 reported SMI data for each group analyzed in his study, with the lowest value identified in PE suspension plus antibody vehicle group[61] (Table S4). While Virdi *et al.* 2012 just related a decrease of SMI over time with the administration Scl-Ab.[37]

3.3.1.11. Mineralizing Surface and Mineral Apposition Rate

The Relative Mineralizing Surface (MS/BS) and the Mineral Apposition Rate (MAR) was only approached by Liu *et al.* 2012 study.[61] It is related that there was a higher MS/BS with the combination of intraarticular PE suspension application and with subcutaneous administration of Scl-Ab III (17.64 ± 3.5 %). And the values of MAR were reported, such as 1.11 ± 0.16 μm/day, 1.56 ± 0.26 μm/day and 0.77 ± 0.16 μm/day in control, PE suspension plus Scl-Ab III and PE suspension plus antibody vehicle, respectively.

3.3.1.12. Bone Formation Rate

The Bone Formation Rate (BFR/BS) was identified by three groups.[33, 54, 61] Virdi *et al.* 2015 reported a higher increase of BFR/BS in both OVX and Sham rats that received the Scl-Ab III treatment.[33] However, was verified a decrease of BFR/BS over time.

Ominsky *et al.* 2011 study also supported the evidence of a higher increase with Scl-Ab administration.[54] Nevertheless, they reported an increase over time of Ec.BFR/BS (endocortical BFR/BS) in FD and BFR/BS in FN in the Scl-Ab and control group, respectively (Table S4).

Liu *et al.* 2012 reported a higher BFR/BS with the application of PE suspension ia plus Scl-Ab III sc (102.14 ± 34.47 $\mu m^3/\mu m^2/day \times 100$).[61]

3.3.1.1. Eroded Surface, Osteoclast Surface, and Cortical Porosity

Three studies[33, 54, 61] reported the Eroded Surface (ES/BS) (Table S5). It was reported by Virdi et al. 2015 that, after the Scl-Ab III administration was a decrease higher than 50% of Eroded Surface in both OVX and Sham rats.[33]

Liu *et al.* 2012, referred to a 10.26 ± 2.71 %, 10.83 ± 1.92 % and 17.10 ± 3.17 % of the relative Eroded Surface, in control, PE suspension plus Scl-Ab III and PE suspension plus antibody vehicle group, respectively.[61] Omnisky et al. 2011 reported a lower ES/BS in the femoral neck of the primates treated by the Scl-Ab V.[54]

Ominsky *et al.* 2011 was the only study that approached Osteoclast Surface (Oc.S/BS) and Cortical Porosity.[54] They reported that, in FN, the Osteoclast Surface was 0.26 ± 0.09 % and 0.33 ±

0.08 % in the Scl-Ab V and control groups, respectively. And in FD, the Cortical Porosity was 0.99 ± 0.07 % and 1.13 ± 0.10 % in the Scl-Ab V and control groups, respectively.

3.3.2. Implant Fixation Properties

Three implant fixation properties were identified, such as Fixation Strength, Stiffness, and Energy. Only four studies approached these properties in their articles,[33, 37, 54, 61] but one of them only reported the Stiffness.[54] The remaining studies did not make any reference to them.

3.3.2.1. Fixation Strength

Virdi, *et al.* 2015 study reported an increase in the fixation strength over time, in the Scl-Ab III group, both in OVX and Sham rats.[33] However, was reported a greater increase in the Sham group compared to the OVX group. And a two-fold than the control group.

In Liu, *et al.* 2012 study, was described the mean values of 1.32 ± 0.45 N/mm^2, 2.00 ± 0.29 N/mm^2, and 0.79 ± 0.40 N/mm^2 for the control, PE suspension and antibody vehicle administration, and PE suspension and Scl-Ab III application groups, respectively.[61]

The last study[37] reported that the Scl-Ab group presented a fixation strength 1.9 and 2.2 times higher than the control group, at 4 and 8 weeks, respectively. Beyond that, determine if the fixation strength was correlational with some parameters of bone formation around the implant. The parameters BV/TV, SMI, Tb.Th, Ct.Ar, Ct.Th, and Tt.Ar demonstrated this correlation in the Scl-Ab group (Table S6).

3.3.2.2. Stiffness

One study[33] reported a significant increase over time with the Scl-Ab III administration, with better results in Sham rats. The next study[61] indicated mean values for Stiffness, such as 221 ± 127 N/mm, 186 ± 114 N/mm, and 127 ± 89 N/mm for the control, PE suspension plus Scl-Ab III, and PE suspension plus vehicle antibody application groups, respectively.

Virdi et al. 2012 study reported a significant increase over time, but it was not equally verified overall Scl-Ab group justified by his effect only have been apparent at 8 weeks.[37] To determine the correlation between the bone formation around implant variables and stiffness, they reported a correlation between SMI and stiffness in both control and Scl-Ab groups and a correlation between stiffness and BV/TV, Tb.Th, Ct.Ar, and M.Ar in Scl-Ab group (Table S6).

Ominsky *et al.* 2011 reported an increase in torsional stiffness, as well in peak load of 48% and 32%, respectively, compared to control in the fractured fibular, provided by increase in amount of mature callus area and bone mineral content (BMC).[54]

3.3.2.1. Energy

The first study[33] reported a significant increase at 8 and 12 weeks with Scl-Ab administration, with the energy being higher in the Sham group.

Liu, *et al.* 2012 study described a higher mean value in PE suspension plus Scl-Ab III application (348 ± 156 Nmm) than the other groups.[61] The mean value for control and PE suspension plus antibody vehicle application groups was 154 ± 81 Nmm and 104 ± 67 Nmm, respectively.

The last study[37] was reported a significant increase was described at 2 and 4 weeks with a pattern suchlike Fixation Strength. As for the properties described before, correlation analysis was also performed. They reported a significant correlation between energy and BV/TV, SMI, Tb.Th, Ct.Ar, Ct.Th, and Tt.Ar in Scl-Ab group (Table S6).

3.4. Bone Remodeling

The twelve studies, identified in Supplementary Tables S7 to S15, were used for Bone Remodeling's description.

3.4.1. Bone Formation Parameters

3.4.1.1. Bone Mineral Density and Bone Mineral Content

Eight studies reported BMD, of which three are RCT studies. And four studies reported the Bone Mineral Content (BMC).

In the animal studies, generally was reported an increase of BMD with sclerostin antibody treatment. Wu *et al.* 2018[55] reported the initial BMD of the tibia metaphysis (TM) to determine the success of ovariectomy in Sham and OVX rats. Also referred the BMD increased 1.24, 1.25, and 1.35 times with the Scl-Ab, PTH 1-34, and Scl-AB + PTH 1-34 administration, compared to control. In the control group, they observed a significant decrease at 12 weeks.

Taut *et al.* 2013[60] referred a limited increase of BMD with local Scl-Ab III after 3 or 6 weeks. They reported that systemic therapy demonstrated a trend toward increased BMD compared to vehicle-treated EP rats. However, no significant differences were reported compared to healthy rats. They also showed that vehicle-treated EP rats had a BMD increase after 3 weeks but, those levels stabilized until 6 weeks (plateau effect). Ominsky *et al.* 2011 only noticed an increase of 11% in BMD, in the fractured femur, with the Scl-Ab III treatment.

Li *et al.* 2010[36] showed the mean values of BMD and BMC in LV, FD, and FN, Tb.BMD in LV and DF and Ct.BMD in LV, in all groups (see Table S7). In all sites, they reported higher BMD values in the rats after administration of 25mg/kg or 5 mg/kg Scl-Ab III treatment compared to the control group, without significant differences related to the treatment dosage. They also reported a correlation between the increase of vBMD and both vBMC and bone area.

The next study[59] reported the percent change from baseline using DXA and pQCT to show the areal BMD of the LS, FN, and UDR (ultra-distal radius) and volumetric BMD (vBMD) of DR and PT (proximal tibia), respectively. They reported a non-significant higher increase in areal BMD with the higher dosage of Scl-Ab IV treatment in LS, FN, and UDR. But was also reported a significant increase in vBMD in DRM and PTM, and in Trabecular vBMD in PTM with the administration of 30 mg/kg sc once a month of Scl-Ab IV. (See Table S7)

The three human studies reported the baseline BMD T-score mean values in LS, TH, and FN in each test and control group.[39, 41, 62] But McClung *et al.* 2014[39] and Padhi *et al.* 2014[41] also reported the BMD T-score in DR.

Saag *et al.* 2017[62] referred that the higher increases in BMD were observed in those patients who received the Romosozumab therapy, with a higher increase reported after 12 months. Since that, transitioned to Alendronate therapy until 36 months, maintaining the values (see Table S7).

In McClung *et al.'s* 2014[39] study, they reported that the greatest increase in BMD were seen with sc. administration of 210 mg of Romosozumab once a month, being significantly greater in LS, TH, and FN. In the DR, they affirmed that no significant differences were observed. (Table S7)

Padhi *et al.* 2014[41] indicated that in each cohort were observed BMD increases in LS and verified that after Romosozumab treatment that increase was significantly higher than placebo. And in TH, they referred that Cohorts 3 and 4 obtained the higher BDM increases, which persisted until the end of follow-up.

Liu *et al.* 2018[52] reported, in one of the studies they performed, that the administration of Scl-Ab VI lead to an increase of vertebral and leg BMC in OVX rats, but the increase was significantly higher with the combined Scl-Ab VI and DAB treatment.

In Ominsky *et al.'s* 2011[54] study performed in Sprague-Dawley rats; they noticed a greater increase of BMC in both fractured and intact femur after Scl-Ab III treatment. Li *et al.* 2010[36] reported in all sites increased BMC values in the rats treated with Scl-Ab III compared to control group. Was also noticed a dose-dependently increase in vBMC and Ct.BMC in LV.

Ominsky et al. 2010 reported significant dose-dependent increases in areal BMC at WB and FN and in vBMC at DR and PT, showing increased of 24.0 ± 2.2 %, 35.2 ± 7.2 %, 19.8 ± 7.2 %, and 27.3 ± 6.2 %, respectively, two months after the administration of the higher dose of Scl-Ab IV treatment.

3.4.1.2. Bone Area per Total Area and Bone Volume Fraction

Both BA/TA and BV/TV only were reported in animal studies.

The Relative Bone Area was reported by the two studies described by Virk *et al.* 2013.[53] They referred to higher BA/TA in both studies after Scl-Ab III administration compared to the control group. And in study 1, they reported the highest percentage in the continuous group but, that difference was not significant.

Eleven studies reported results about Bone Volume Fraction.

In one of *Liu et al.'s* 2018 studies,[52] they reported restoration of the BVF levels, with exceeding both OVX and Sham-saline groups, after finishing both treatments (Scl-Ab VI and Scl-Ab+DAB). The other referred that the bone volume fraction was 13.9% lower in the underloaded mandible with the saline vehicle application. In both test groups (Scl-Ab VI and Scl-Ab VI+DAB), after 15 weeks, this evidence was not identified by them. However, they noticed an increase in BVF compared to the control group.

Wu *et al.* 2018[55] reported a higher increase of BV/TV with the combined treatment with Scl-Ab and PTH 1-34 compared to the control and the other drugs tested in their study. Taut *et al.* 2013[60] a limited increase of BVF with the local application of the antibody, with worst and little better results than vehicle at 3 weeks and 6 weeks, respectively. Both studies reported by Virk *et al.* 2013[53] showed significantly higher increases with the continuous Scl-Ab treatment (12 weeks after the begging of treatment). (See Table S7)

The other five studies reported that the BV/TV was enhanced by Scl-Ab at 25 mg/kg twice a week administration compared to control or lower dosages.

McDonald *et al.* 2012[31] showed a significant increase of BV/TV in OVX (with or without Scl-Ab treatment) compared to the application of saline solution in Sham rats. At 2 and 3 weeks, they referred a diminution of BV/TV in OVX without Scl-Ab treatment while, in Sham, with the same treatment, verified an increase. The Scl-Ab treatment tended to improve the BV/TV at 2 and 3 weeks. (Table S7) Ominsky *et al.* 2011 reported higher increases in callus BV/TV in the fractured femur and BV/TV in the intact contralateral femur, with Scl-Ab III treatment.[54]

In Tian *et al.'s* 2011 study,[32] they did not report differences in BV/TV between under or normal-loaded sites (UL and NL, respectively) in the control group. But significant differences were referred between both administration dosages (5 or 25 mg/kg sc twice a week) and the control group, with a dose-dependent increase, with a tendency to higher BV/TV with the higher dosage. (See Table 9) The Li *et al.'s* 2010 study[36] also indicated a higher BV/TV in PT and FN and Tb.BV/TV in LV and DR with higher treatment dosage. The Tian *et al.* 2010 study,[57] reported similar results about trabecular BV/TV, in yellow marrow CVB (5th caudal vertebral body) and red marrow LVB (4th lumbar vertebral body) as the studies aforementioned (Table S7).

3.4.1.3. Bone volume, bone height, and bone area

Three studies reported the Bone Volume,[52, 53] one study the Bone Height[52] and four studies the Bone Area.[36, 53, 59]

In Liu *et al.'s* 2018[52] study they reported a 38% decrease of initial ridge bone volume 9 weeks after extraction of right maxillary molars. With the vehicle was reported further decreases over time. With both Scl-Ab and Scl-Ab + DAB treatment, they noticed a significant increase in bone volume, 2 and 4 weeks after the beginning of treatment, with further increases over time with an increase of 42% and 81% in alveolar bone ridge volume with Scl-Ab and Scl-Ab + DAB, respectively, after 15 weeks of the therapeutic period. Both studies reported by Virk *et al.* 2013[53] showed a greater bone volume with the continuous Scl-Ab treatment (29.7 ± 11.2 mm^3 in the first study, and 17.6 ± 7.4 mm^3 in the second). (See Table S8)

Referring to bone height, Liu et al. 2018, reported fast vertical resorption in the first 9 weeks post-extraction, with additional resorption over time, totalizing a 0.41mm of height loss with the saline vehicle administration. The combined treatment of Scl-AB with DAB was reported as the group with the best result, with a full recovery of height loss 9 weeks after therapy began.

Both Virk *et al.* 2013 and Li *et al.* 2010 studies reported higher bone area after Scl-Ab treatment. In the first study,[53] better results were obtained with continuous period treatment, and in the second,[36] with a higher treatment dose. (See Table S8)

Ominsky et al. 2010 referred that, in Cynomolgus monkeys, the administration of 30 mg/kg of Scl-Ab VI led to the biggest bone area increase[59] (Table S8).

3.4.1.4. Trabecular, Cortical, Medullary and Subperiosteal Areas

Trabecular, Medullary and Subperiosteal Area (Tb.Ar, M.Ar and Tt.Ar, respectively) were only reported by Li *et al.* 2010.[36] Reporting a significantly higher Tb.Ar, in LV, with Scl-Ab treatment than control, with 5 mg/kg and 25 mg/kg (3.15 ± 0.20 mm^2 and 2.55 ± 0.14 mm^2, respectively), with a dose-dependent relation. In TS, reported with both 5 mg/kg and 25 mg/kg Scl-Ab application a greater Tt.Ar (6.76 ± 0.51 mm^2 and 7.72 ± 0.26 mm^2, respectively) and a significantly lower M.Ar (0.97 ± 0.09 mm^2 and 0.92 ± 0.04 mm^2, respectively) than vehicle.

The Cortical Area (Ct.Ar) was reported by Li *et al.* 2010 and Ominsky *et al.* 2010.[36, 59] In general, both studies reported higher Ct.Ar values with Scl-Ab treatment, with all doses, at all sites studied, in Sprague-Dawley rats[36] and Cynomolgus monkeys[59] (Table S9).

3.4.1.5. Cortical Area per Total Cross-sectional Area

The percentage of Cortical Area per Total Area (Ct.Ar/Tt.Ar) was reported by Li *et al.* 2010[36] as significantly greater in higher doses Scl-Ab treatment than control. (Table S9) No other studies mentioned this parameter.

3.4.1.6. Trabecular Thickness and Cortical Thickness

Seven studies reported the Trabecular Thickness (Tb.Th)[31, 32, 36, 52, 54, 55, 57] and four studies the Cortical Thickness (Ct.Th).[32, 36, 54, 59]

Liu *et al.* 2018[52] reported a higher increase of Tb.Th with Scl-Ab VI treatment in OVX rats than Sham and OVX saline vehicle controls, as well as Wu *et al.'s* 2018 and McDonald *et al.*'s 2012 studies.[31, 55] However, Wu *et al.'s* 2018 reported an even higher increase with the Scl-Ab and PTH 1-34 combined treatment (1.27 vs. 1.66 times higher, in Scl-Ab and Scl-Ab + PTH 1-34 treatments). And McDonald *et al.*'s 2012 noticed a higher increase of Tb.Th with Scl-Ab III treatment in the OVX rats compared to the Sham rats, who received the same treatment, more pronounced at later times. (See Table S10)

Ominsky *et al.* 2011[54] referred that the Trabecular Thickness was higher after Scl-Ab III treatment in DF of the intact femur, compared to control (97.4 ± 2.7 μm vs. 56.5 ± 1.4 μm, respectively).

And the following three studies reported higher Tb.Th values with the highest dose of Scl-Ab administered (25 mg/kg twice a week) at all sites compared to the control.[32, 36, 57] (Table 12) Tian *et al.* 2011[32] and Tian *et al.* 2010[57] also verified that increase compared to baseline values, with higher expression in the normal-loaded proximal tibia reported by Tian *et al.'s* 2011 study[32]. (See Table S10)

Ominsky *et al.* 2011[54] reported a higher increase of Cortical Thickness after Scl-Ab III treatment in DF of the intact femur, compared to control (922 ± 18 μm vs. 838 ± 19 μm, respectively).

Generally, Tian *et al.* 2011[32] and Li *et al.* 2010[36] reported a greater increase in Ct.Th with the administration of higher doses of Scl-Ab (25 mg/kg twice a week) in Sprague-Dawley rats. Ominsky *et al.* 2010,[59] reported higher Ct.Th values with the lowest doses applied in Cynomolgus monkeys (3 mg/kg twice a week) (Table S10).

3.4.1.7. Trabecular Number

Five studies approach the Trabecular Number (Tb.N).

Wu *et al.* 2018 reported greater increases with the three tested treatments (Scl-Ab, PTH 1-34, and Scl-AB + PTH 1-34) than control, with the higher effect observed by them with the Scl-Ab + PTH 1-34 combined treatment.

McDonald et al. 2012[31] showed higher Tb.N values in OVX rats, 1 week after the beginning of Scl-Ab treatment, with decreases since then (2.87 ± 0.86 N/mm, 2.40 ± 0.53 N/mm, and 1.09 ± 0.48 N/mm, at 1, 2 and 3 weeks, respectively). In Sham rats, the higher value was reported after 2 weeks (3.30 ± 0.57 N/mm), decreasing until 3 weeks (2.16 ± 0.46 N/mm). Despite that, they referred that the Trabecular Number was increased by Scl-Ab III treatment.

Tian *et al.* 2011[32] reported higher increase in normal-loaded tibia (3.7 ± 0.3 N/mm) with higher dosage (25 mg/kg twice a week) treatment, but a decrease in under-loaded tibia (2.9 ± 0.7 N/mm) compared to baseline and control. (See Table S10)

Li *et al.* 2010[36] noticed a higher Tb.N with 25mg/kg dosage of Scl-Ab III twice a week, at all sites, PT, LV, and DF (1.31 ± 0.11 *n*/mm, 3.45 ± 0.15 mm^{-1} and 2.15 ± 0.20 mm^{-1}) compared to vehicle.

In Tian *et al.'s* 2010 study,[57] they referred that a higher increase (5.7 ± 0.6 #/mm) had been observed with higher dose treatment (25 mg/kg twice a week) in CVB, compared to baseline. However, in LVB was observed a decrease in Tb.N with the two doses treatment tested, compared to baseline. (See Table S10)

3.4.1.8. Trabecular Separation

Four studies reported the Trabecular Separation.[32, 36, 55, 57]

Wu *et al.* 2018[55] noticed greater decreases of Tb.Sp with Scl-Ab, PTH 1-34 and Scl-Ab + PTH 1-34 treatments compared to control group, with higher expression of that decrease in the combined treatment. (Table S10)

Tian *et al.* 2011[32] reported a baseline Tb.Sp value of 297 ± 99.0 μm, at PTM (proximal tibia metaphysis). Comparing with this value, they reported a decrease of values with subcutaneous administration of 5 mg/kg of Scl-Ab in UL bone, 25 mg/kg in NL bone, and saline solution in both

UL and NL bones. They also reported an increase in Tb.Sp with 5mg/kg in NL and 25mg/kg in UL bones. (See Table S10)

Li *et al.* 2010[36] described the Tb.Sp data, assessed by histomorphometry and μCT, at PT and LV and DF, with the subcutaneous administration of vehicle, 5 mg/kg or 25 mg/kg twice a week. At all sites, were reported a greater decrease with the higher dose administration (PT: 661 ± 66 μm; LV: 267 ± 31 μm and DF: 512.3 ± 49.2 μm), compared to the other groups. Tian *et al.* 2010[57] had similar results, with baseline values of 149.8 ± 24.7 μm and 195.4 ± 22.5 μm, at CVB and LVB, respectively, that decrease significantly with the higher dose treatment. (Table S10)

3.4.1.9. Structural Model Index

Li *et al.'s* 2010[36] study was the only one that reported SMI, which was significantly lower after Scl-Ab treatment, either with 5mg/kg or 25 mg/kg doses. (Table S11)

3.4.1.10. Mineralizing Surface and Mineral Apposition Rate

These two parameters were reported by the same three studies.[32, 36, 57] Tian *et al.* 2011 reported initial MS/BS values at proximal tibia metaphysis and Ps.MS/BS and Ec.MS/BS in the tibial shaft (24.6 ± 7.3 %, 26.1 ± 7.8 %, and 17.3 ± 7.0 %, respectively). They noticed a higher increase of this with the higher dose of Scl-Ab treatment, at all sites, in both NL and UL bones. Tian *et al.* 2010[57] reported similar results, with MS/BS values of 47.5 ± 13.2 % and 78.7 ± 4.1 %, with the administration of 25 mg/kg twice a week of Scl-Ab, in the caudal vertebral body and lumbar vertebral body, respectively. Li *et al.* 2010[36] also showed higher increases in MS/BS in PT and Ps.MS/BS and Ec.MS/BS in TS with Scl-Ab treatment, compared to the control group, with dose-dependent increase. (See Table S11)

Tian *et al.* 2011 reported higher increases in MAR values at PTM and Ps.MAR and Ec.MAR values at TS, in both NL and UL bones, with the administration of Scl-Ab III in 25 mg/kg dose twice a week. (See Table S11) Li *et al.* 2010 referred that the administration of 25 mg/kg of Scl-Ab III provided an increase in MAR at the proximal tibia (1.59 ± 0.08 μm/day) and in Ec.MAR at tibial shaft (1.66 ± 0.14 μm/day) but, in Ps.MAR at tibial shaft the maximum increase was obtained with the administration of 5 mg/kg (2.13 ± 0.11 μm/day), compared to the control group. Tian *et al.* 2010[57] reported that, compared to baseline and saline solution control groups, the increase in MAR with the

administration of 25mg/kg dose at CVB, but no differences described between the administration of 5 or 25 mg/kg at LVB.

3.4.1.11. Bone Formation Rate

The Bone Formation Rate (BFR/BS) were reported by 5 studies.[32, 36, 52, 57, 59] In the Liu *et al.* 2018 study with the administration of 18.2 mg/kg of Scl-Ab VI twice a week or 18.1mg/kg of Scl-Ab VI plus 18.1 mg/kg of DAB twice a week, they reported a significantly higher BFR/BS in basal and alveolar bone in both groups, compared to control. However, the combined treatment showed a better effect in basal bone compared to the Scl-Ab group.

Similar results were reported by Tian *et al.* 2011, Li *et al.* 2010 and Tian *et al.* 2010 studies. (Values described in Table S11). Ominsky *et al.* 2010 reported a significant increase in Ec.BFR/BS and a non-significant increase in Ps.BFR/BS, with the administration of 30 mg/kg of Scl-Ab IV once a month.

3.4.1.12. Eroded Surface, Osteoclast Surface, and Fat Cell Volume

Three studies approached the Eroded Surface (ES/BS).[32, 52, 57] Liu *et al.* 2018[52] only reported qualitative information, referring that ES/BS was significantly lower with the application of both Scl-Ab VI treatment or Scl-Ab VI and DAB combined treatment, compared to administration of saline vehicle in OVX rats. Tian *et al.* 2011[32] referred that the ES/BS and Ec.ES/BS significantly decreased with the administration of Scl-Ab III (5 mg/kg or 25 mg/kg) in both PTM and TS, respectively, in normal-loaded and under-loaded bones, and verified a dose-dependent relation, with greater decreases in NL bones. (Table S12) Tian *et al.* 2010[57] also reported similar results in both yellow and red marrow.

The Osteoclast surface (Oc.S/BS) was only reported by Li *et al.* 2010,[36] referring to be increased with the administration of 25 mg/kg Scl-Ab twice a week, compared to both other groups. However, that difference between groups was not significant.

The Fat Cell Volume was only reported by Tian et al. 2010.[57] They noticed that the yellow marrow was mainly occupied by fat cells according to almost 100 % in all groups. While in red marrow (LVB), the volume of fat cells varied between groups without significance.

McDonald *et al.* 2012[31] reported the number of TRAP-positive cells per bone surface unit (Oc.N/BS), with some differences observed between Sham and OVX rats and with or without administration of Scl-Ab, in the center or cortical of the defect, at 2 and 3 weeks. (Table S12) They also referred to nonsignificant differences with or without Scl-Ab treatment in OVX rats and significant differences with saline control administration, with decrease of Oc.N/BS in center of defects in OVX rats (0.002 ± 0.001 N/mm) compared with Sham rats (0.004 ± 0.001 N/mm), at 2 weeks, and normalization of values until 3 weeks (0.002 ± 0.001 N/mm, in both OVX and Sham saline control groups). However, in the cortical point of the defect, they related the maintaining of decrease at 3 weeks with saline control administration in OVX rats (0.001 ± 0.001 N/mm) compared to Sham rats (0.002 ± 0.001 N/mm).

3.4.2. Bone Formation/Resorption Markers

Three markers of bone formation were identified: bone-specific alkaline phosphatase (BSAP), osteocalcin, and procollagen type 1 N-terminal Propeptide (P1NP); and markers for bone resorption were: serum C-telopeptide (sCTX), C-terminal telopeptides of type I collagen (CTX-1), β-isomer of C-terminal telopeptides of type I collagen (β-CTX), and tartrate-resistant acid phosphatase 5b (TRACP-5b).

Liu *et al.* 2018[52] reported a higher increase of BSAP with Scl-Ab VI or Scl-Ab VI + DAB treatments compared to both Sham and OVX saline vehicle controls. Also noticed a higher enhance of osteocalcin and P1NP with the administration of 25 mg/kg of Scl-Ab VI, twice a week, compared to saline vehicle in intact or extracted mandible. (Table S13) The same study reported a decrease of TRACP-5b marker with both treatments tested (Scl-Ab and Scl-Ab + DAB) compared to the control group, with higher expression with the combined treatment (Table S14).

Wu *et al.* 2018[55] referred that the administration of Scl-Ab or PTH 1-34 increased the osteocalcin and P1NP, compared to vehicle and without differences between them, at 12 weeks. But an even greater increase was reported with the combined treatment with Scl-Ab plus PTH 1-34. (Table S13) Also noticed were no differences between all groups in the CTX-1 resorption marker (Table S14).

Taut *et al.* 2013[60] reported increases of osteocalcin and P1NP compared to vehicle EP and PBS healthy controls at 3 weeks after the beginning of treatment. After six weeks, they referred that an increase in osteocalcin was maintained but did not report differences to P1NP. (Table S13) In TRACP-5b, they didn't report changes compared to vehicle-EP control, at 6 weeks. (Table S14)

In the second study performed by Virk *et al.* 2013,[53] they reported a significantly higher increase of osteocalcin and P1NP, at 6 and 12 weeks, respectively. But did not notice differences between both groups at any time of the study.

Ominsky *et al.* 2011[54] also reported greater increases in osteocalcin and P1NP with Scl-Ab treatment (90.0 ± 4.6 ng/mL and 16.0 ± 4.0 ng/mL, respectively) (Table S13). Li *et al.* 2010[36] referred to observed increases in osteocalcin marker, 1 week after the beginning of Scl-Ab treatment, with both doses tested, maintaining greater values over time. A dose-dependent effect was reported, with greater values identified with 25 mg/kg of Scl-Ab twice a week (Table S13). In the CTX-1 marker, they reported that the administration of Scl-Ab did not have significant effects. Ominsky *et al.* 2010 reported similar information in CTX serum marker in Cynomolgus monkeys.

In Saag *et al.'s* 2017 study,[62] they reported an increase of P1NP levels in the first 12 months of study with the administration of Romosozumab. But after that, with the transition to Alendronate therapy, the P1NP levels decreased and remained below initial values. In contrast, with full Alendronate treatment, the P1NP levels decrease since month 1 and remained below basal values until the end of the study. (Table S13) A decrease of βCTX levels was also noticed at 12 months (end of Romosozumab treatment) and was maintained below baseline until 36 months (after transition for Alendronate). Compared to treatment made only with Alendronate, at 12 months, the decrease was greater with Romosozumab. (Table S14)

McClung et al. 2014[39] reported transitional increases, verifying increases 1 week after beginning treatment maintaining until 1 month. Since then, were reported decreases to baseline or even lower values, depending on doses and markers (BSAP, osteocalcin, or P1NP). The teriparatide seemed to have higher increases on bone formation markers over time since the third month. (See Table S13) Also reported a decrease from baseline values of the βCTX resorption marker in all groups that received Romosozumab treatment, with a higher decrease observed on the first week. With the administration of Romosozumab monthly (all doses) and 210 mg/kg once every 3 months, they reported that values remained below baseline after 12 months (See Table S14).

Padhi *et al.* 2014[41] reported baseline values and the maximum increase observed, in the P1NP marker, compared to that in each group they analyzed, with the greater increase observed with the administration of 2mg/kg of Romosozumab every 2 weeks in women and 3mg/kg of Romosozumab every 4 weeks in men. For BSAP and osteocalcin, they reported increases like those observed to P1NP but didn't report data. (Table S13) They also showed higher decreases from baseline in sCTX with the Romosozumab administration, compared to placebo control (Table S14).

3.4.3. Bone Strength Endpoints

The Bone Strength Endpoints identified in the studies analyzed were Maximum Load, Stiffness, Energy to Failure, and Peak Load, which are described below.

3.4.3.1. Maximum Load

The Maximum Load was reported by two studies, Wu *et al.* 2018[55] and Li *et al.* 2010.[36] Wu *et al.* 2018 noticed significant increases with Scl-Ab, PTH 1-34, and Scl-Ab + PTH 1-34, compared to the vehicle, but non-significant differences between them, 12 weeks after the beginning of treatment. Li *et al.* 2010 reported a significant increase on maximum load with the administration of Scl-Ab III compared to vehicle control. A dose-dependent increase was reported, in LV, with a significantly higher increase with the administration of 25mg/kg twice a week (693 ± 37 N). (Table S15)

3.4.3.2. Stiffness

Five studies reported qualitative or quantitative information about Stiffness.[36, 53, 55, 59] Wu *et al.* 2018[55] reported a significant increase in Stiffness with Scl-Ab, PTH 1-34, and Scl-Ab + PTH 1-34, compared to the vehicle. They also showed significant increases with the administration of Scl-Ab + PTH 1-34 treatment compared to the other tested groups 12 weeks after the beginning of treatment. One of the studies reported by Virk *et al.* 2013[53] only referred that, after 6 weeks of treatment, they verified a significantly higher increase vs. the PBS control.

Li *et al.* 2010[36] referred that the Stiffness was higher with a higher treatment dose (25 mg/kg of Scl-Ab III twice a week), in LV (4623 ± 549 N/mm), and FD (781 ± 53 N/mm). In FN, they described a higher Stiffness increase with Scl-Ab III in dosage of 5 mg/kg twice a week (805 ± 70 N/mm), compared to vehicle and Scl-Ab III (25 mg/kg), without significant relation. Ominsky et al. 2011[54] reported increases in Stiffness in both fractured and intact femurs with Scl-Ab therapy compared to the control group. (Table S15)

Similar results were reported by Ominsky et al. 2010[59] in Cynomolgus monkeys, with a 1040 ± 192 N/mm of Stiffness with 30 mg/kg of Scl-Ab VI once a month treatment compared to 888 ± 97 N/mm with vehicle control. With lower doses was reported a non-significant decrease of values, compared to vehicle.

3.4.3.3. Energy to Failure

The Energy to Failure was reported by four studies. Wu *et al.* 2018[55] reported similar results as Stiffness. Virk *et al.* 2013,[53] in one of the studies they performed, described a higher increase in Energy to Failure with Scl-Ab III treatment, compared to PBS control, at 12 weeks. Li *et al.* 2010[36] referred that the higher increase was obtained with higher dose Scl-Ab treatment, at all sites (82.6 ± 10.0 mJ, 172 ± 22 mJ and 68.6 ± 9.5 mJ, at LV, FD and FN, respectively). And in Cynomolgus monkeys, Ominsky *et al.* 2010[59] also reported the higher increase with the higher dose, in FD (4994 ± 904 N). (See Table S15)

3.4.3.4. Peak Load

The Peak Load was approach by Ominsky *et al.* 2011[54] and Ominsky *et al.* 2010.[59] Ominsky *et al.* 2011 reported an increase of Peak Load with the administration of Scl-Ab III (223 ± 10 N), compared to vehicle control (191 ± 8 N). And Ominsky *et al.* 2010 reported higher increase of Peak Load, in femoral diaphysis, with the administration of 30mg/kg once a month of Scl-Ab IV (1285 ± 241 N) compared to vehicle control (1008 ± 102N).

3.5. Adverse Events

Adverse Events was only reported in RCT's studies performed by Saag *et al.* 2017,[62] McClung *et al.* 2014[39] and Padhi *et al.* 2014.[41]

Saag *et al.'s* 2017 study[62] reported similar incidences of adverse events, serious adverse events and deaths, in the double-blind period, with both Alendronate or Romosozumab administration and cumulative incidences, in the primary analysis period. They also noticed some serious adjudicate cardiac events, such as cardiac ischemic and cerebrovascular events, heart failure, noncoronary revascularization, or peripheral vascular ischemic event not requiring revascularization. In general, the Romosozumab group had higher relation with these events in both double-blind and primary analysis periods. Although, less evidence has been reported with the last three events (See Table 3).

McClung *et al.* 2014[39] referred that the incidence of adverse events and serious adverse events were similar between Placebo and Romosozumab groups but, no serious adverse event was related to treatment. The pain at injection site was greater with Romosozumab treatment, compared to Placebo, but no relation was mentioned about dose administered.

Padhi *et al.* 2014[41] referred that almost every person included in the study (receiving placebo or Romosozumab) had at least one adverse event. They only reported in their study the most reported adverse events, which are described in Table 3. Also referred that only two subjects with serious adverse events, but did not refer to which group it corresponding, giving only the information that it was not related to the study treatment.

Table 3: *Adverse Events*

	Saag, *et al.* (2017)				**McClung, *et al.* (2014)**								**Padhi, *et al.* (2014)**						
Drug/control	Double-Blind Period		Primary Analysis Period		Placebo	Alendronate	Teraparatide	Romosozumab					Placebo	Romosozumab					
	Alendronate → Alendronate	Romosozumab → Alendronate	Alendronate → Alendronate	Romosozumab → Alendronate										Women				Men	
Dosage (unit)	70mg → 70mg once week	210mg once month → 70mg once week	70mg → 70mg once week	210mg once month → 70mg once week	-	70mg once week	20μg once day	140mg every 3 moths	210mg every 3 months	70mg once month	140mg once month	210mg once month	-	1mg/kg every 2 weeks	2mg/kg every 4 weeks	2mg/kg every 2 weeks	3mg/kg every 4 weeks	1mg/kg every 2 weeks	3mg/kg every 4 weeks
Number of participants	2014	2040	2014	2040	50	51	54	53	53	50	48	51	12	6	6	6	6	6	6
Adverse Events	1584 (78.6%)	1544 (75.7%)	1784 (88.6%)	1766 (86.6%)	45 (90%)	44 (86.3%)	37 (68.5%)	43 (81.1%)	46 (86.8%)	48 (96%)	42 (87.5%)	42 (87.4%)	10 (83%)	6 (100%)	6 (100%)	6 (100%)	5 (83%)	5 (83%)	5 (83%)
Headache	-	-	-	-	8 (16%)	4 (7.8%)	3 (5.6%)	7 (13.2%)	3 (5.7%)	4 (8.0%)	3 (6.3%)	5 (9.8%)	4 (33%)	1 (17%)	1 (17%)	1 (17%)	2 (33%)	3 (50%)	2 (33%)
Upper respiratory tract infection	-	-	-	-	-	-	-	-	-	-	-	-	1 (8%)	3 (50%)	1 (17%)	2 (33%)	0	2 (33%)	0
Arthralgia	-	-	-	-	4 (8%)	5 (9.8%)	5 (9.3%)	19 (17%)	5 (9.4%)	8 (16%)	6 (12.5%)	3 (5.9%)	2 (17%)	0	2 (33%)	0	1 (17%)	1 (17%)	1 (17%)
Pain in Extremity	-	-	-	-	2 (4%)	2 (3.9%)	5 (9.3%)	7 (13.2%)	3 (5.7%)	10 (20%)	5 (10.4%)	6 (11.8%)	2 (17%)	0	2 (33%)	0	1 (17%)	0	1 (17%)
Abdominal pain	-	-	-	-	-	-	-	-	-	-	-	-	1 (8%)	0	1 (17%)	1 (17%)	0	1 (17%)	0
Back pain	228 (11.3%)	186 (9.1%)	393 (19.5%)	329 (16.1%)	3 (6.0%)	5 (9.8%)	3 (5.6%)	4 (7.5%)	7 (13.2%)	5 (10%)	7 (14.6%)	3 (5.9%)	2 (17%)	3 (50%)	0	0	0	0	0
Injection site pain	-	-	-	-	0	0	0	2 (3.8%)	4 (7.5%)	3 (6%)	4 (8.3%)	3 (5.9%)	0	0	0	2 (33%)	0	1 (17%)	0
Injection site reaction	53 (2.6%)	90 (4.4%)	53 (2.6%)	90 (4.4%)	-	-	-	-	-	-	-	-	0	0	0	1 (17%)	1 (17%)	0	1 (17%)
Lymphadenopathy	-	-	-	-	-	-	-	-	-	-	-	-	0	1 (17%)	0	1 (17%)	1 (17%)	0	0
Nasopharyngitis	218 (10.8%)	213 (10.4%)	373 (18.5%)	363 (17.8%)	7 (14%)	3 (5.9%)	4 (7.4%)	10 (18.9%)	5 (9.4%)	19 (38.0%)	13 (27.1%)	8 (15.7%)	-	-	-	-	-	-	-
Gastroenteritis	-	-	-	-	3 (6%)	2 (3.9%)	1 (1.9%)	2 (3.8%)	5 (9.4%)	3 (6%)	4 (8.3%)	8 (15.7%)	-	-	-	-	-	-	-
Cough	-	-	-	-	2 (4%)	4 (7.8%)	0	3 (5.7%)	1 (1.9%)	8 (16%)	4 (8.3%)	4 (7.8%)	-	-	-	-	-	-	-
Constipation	-	-	-	-	2 (4%)	3 (5.9%)	2 (3.7%)	2 (3.8%)	5 (9.4%)	4 (8%)	4 (8.3%)	2 (3.9%)	-	-	-	-	-	-	-
Bronchitis	-	-	-	-	2 (4%)	1 (2%)	2 (3.7%)	5 (9.4%)	1 (1.9%)	5 (10%)	3 (6.3%)	2 (3.9%)	-	-	-	-	-	-	-

Urinary tract infection	-	-	-	-	0	4 (7.8%)	3 (5.6%)	3 (5.7%)	5 (9.4%)	0	3 (6.3%)	5 (9.8%)	-	-	-	-	-	-	-
Fatigue	-	-	-	-	2 (4.0%)	2 (3.9%)	0	1 (1.9%)	1 (1.9%)	5 (10%)	5 (10.4%)	2 (3.9%)	-	-	-	-	-	-	-
Musculoskeletal pain	-	-	-	-	2 (4.0%)	2 (3.9%)	2 (3.7%)	3 (5.7%)	3 (5.7%)	4 (8%)	2 (4.2%)	1 (2%)	-	-	-	-	-	-	-
Adjuticated serious cardiovascular event	38 (1.9%)	50 (2.5%)	122 (6.1%)	133 (6.5%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cardiac ischemic event	6 (0.3%)	16 (0.8%)	20 (1.0%)	30 (1.5%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cerebrovascular event	7 (0.3%)	16 (0.8%)	27 (1.3%)	45 (2.2%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heart failure	8 (0.4%)	4 (0.2%)	23 (1.1%)	12 (0.6%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Noncoronary revascularization	5 (0.2%)	3 (0.1%)	10 (0.5%)	6 (0.3%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1%)	0	5 (0.2%)	2 (<0.1%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Osteoarthritis	146 (7.2%)	138 (6.8%)	268 (13.3%)	247 (12.2%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypersensitivity	118 (5.9%)	122 (6%)	185 (9.2%)	205 (10%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cancer	28 (1.4%)	31 (1.5%)	85 (4.2%)	84 (4.1%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperostosis	12 (0.6%)	2 (<0.1%)	27 (1.3%)	23 (1.1%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypocalcemia	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	4 (0.2%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Atypical femoral fracture	0	0	4 (0.2%)	2 (<0.1%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Osteonecrosis of the Jaw	0	0	1 (<0.1%)	1 (<0.1%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serious adverse event	278 (10.8%)	262 (12.8%)	605 (30.0%)	586 (28.7%)	7 (14%)	4 (7.8%)	5 (9.3%)	4 (7.5%)	2 (3.8%)	5 (10%)	1 (2.1%)	5 (9.8%)	-	-	-	-	-	-	-
Fatal adverse events (Deaths)	21 (1.0%)	30 (1.5%)	90 (4.5%)	90 (4.4%)	1 (2%)	0	0	0	0	1 (2%)	0	0	-	-	-	-	-	-	-

DISCUSSION

4. Discussion

The main objective of this systematic review was to verify whether the local or systemic administration of aScl improved the osseointegration of implants, dental, or orthopedics. A secondary aim was defined to verify if the administration of anti-sclerotin also stimulated bone remodeling.

In order to identify new therapies that could accelerate the osseointegration of dental implants, noting the growing number of implants placed in actuality and the benefits that the patient could obtain with a faster functional load and esthetic, this study gains particular relevance in Dentistry.

4.1. Osseointegration

Regarding the osseointegration, we verified that only a few studies evaluate the effect of aScl treatment in osseointegration of implants, and only one study[38] was performed to evaluate if the aScl could improve the osseointegration of dental implants.

In this review, we observed that, in general, BIC was greater at later times with aScl treatment. That is corroborated by Virdi *et al.* 2012,[37] who reported higher BIC at later times, and Virdi *et al.* 2015,[33] referring to were verified an increase over time, with a higher effect in Sham rats. Similar results were observed with the placement of dental implants. Yu *et al.* 2018[38] reported a significantly greater BIC with aScl treatment at 28 days of study. Korn *et al.'s* 2019[56] partially corroborate this information, reporting greater increases at later times with the aScl treatment. However, the implants with a sandblasted and thermally acid-etched surface reported a decrease in BIC at 4 weeks of study.

We noted that aScl treatment had a positive effect in BMD around the implants placed, as we could observe by the Korn *et al.* 2019[56] and Agholme *et al.* 2010[58] studies, who reported higher increases after receiving aScl treatment. The treatment with aScl also showed a systemic effect, as Agholme *et al.* 2010[58] showed, with the higher value obtained with the aScl, in the contralateral femur (1.05 ± 0.01 g/cm^3), and by Ominsky *et al.* 2011[54], who reported values in different sites from which the K-wire had placed. In contrast, Yu *et al.* 2018[38] reported no differences in BMD between aScl treatment and control.

In general, we identified the increase of BVF around the implant after aScl therapy. This information is supported by the results of the Korn *et al.* 2019,[56] Virdi *et al.* 2015,[33] Liu *et al.* 2012,[61] Virdi *et al.* 2012,[37] and Agholme *et al.* 2010.[58] Increases in systemic BFV also were identified, as reported by Ominsky *et al.* 2011, with a higher value in FN, and Agholme *et al.* 2010, with the higher BV/TV in contralateral tibia.[58]

We observed higher Trabecular and Cortical Thickness around implants and systemically after aScl therapy.

Several studies corroborated the information about the increase in Tb.Th around implants. Namely, Korn *et al.'s* 2019 study, reporting the enhance on Tb.Th with both implants surfaces analyzed. Liu *et al.* 2012 referring to the higher value with Scl-Ab III associated with PE suspension intraarticular application therapy, and Agholme et al. 2010, noticing the higher result in the implanted tibia. The systemic increase of Tb.Th was reported by Agholme *et al.* 2010[58], with greater increase after aScl therapy reported in the contralateral tibia, and Ominsky *et al.* 2011[54], with higher values reported in FN, after Scl-Ab V treatment.

The Cortical Thickness improvement around implants by Scl-Ab treatment is supported by Virdi *et al.'s* 2015 study, with the increase over time in both OVX and Sham rats, and Virdi *et al.'s* 2012 study, which was greater at later times peri-implant.

The Trabecular Number increased with aScl therapy, as reported by Yu *et al.* 2018[38] describing a greater Tb.N at 8 weeks around the dental implants placed, and Liu *et al.* 2012[61] reported a higher increase with Scl-Ab III plus PE suspension treatment. However, different results were reported by two studies. One of them mentioned that the aScl treatment had little or no effect in Tb.N,[33] and the other noticed higher values in the control group.[58]

We identified different results in Trabecular Separation in both studies that analyzed this parameter. Liu *et al.* 2012[61] reported the lowest Tb.Sp with the Scl-Ab III plus PE suspension treatment, while Agholme *et al.* 2010[58] mentioned an enhance on Tb.Sp values, with the Scl-Ab III therapy.

Different results have also been observed in SMI results, with Virdi *et al.* 2012[37] reporting a higher decrease in SMI, with Scl-Ab III treatment, and Liu *et al.* 2012[61] noticing higher SMI values with the Scl-Ab III + PE suspension treatment.

We verified increases brought about by Scl-Ab treatment in bone formation rate in three studies, identifying two studies reporting the increase around the implant and one reporting the systemically increasing. The local increase in BFR/BS was reported by Liu *et al.* 2012[61] and Virdi *et al.* 2015[33]. However, Virdi *et al.* 2015 noticed a decrease over time. Only Ominsky *et al* 2011[54] reported systemic effect, with the BFR/BS increase over time.

We observed a decrease of peri-implant and systemic eroded surface with the aScl treatment, corroborated by Virdi *et al.* 2015[33] and Ominsky *et al.* 2011[54], respectively. Contrasting with that,

Liu *et al.'s* 2012 study reported a lower ES/BS in the control group compared to the administration of Scl-Ab III plus PE suspension.

Generally, the aScl therapies provided increase in the proprieties of implant fixation.

The Fixation Strength was increased by aScl treatment, as reported by Virdi *et al.* 2015[33], with an increase over time with the administration of Scl-Ab III in both OVX and Sham rats, with a higher enhance in Sham rats. Liu *et al.* 2012[61] reported a higher increase with Scl-Ab III plus PE suspension administration. And Virdi *et al.* 2012[37] reported an enhanced Fixation Strength by 1.9 and 2.2 h Scl-Ab III, compared to the control group.

The Stiffness increased after aScl therapies. This information was supported by Virdi et al. 2015,[33] reporting a significant increase over time, with better results in Sham rats. Virdi et al. 2012,[37] referring to a significant increase over time, but not equitably verified overall Scl-Ab group justified by his effect only have been apparent at eight weeks. And Ominsky et al. 2011,[54] reported an increase in torsional Stiffness of 48%. But, in contrast, Liu et al. 2012[61] reported the highest value of Stiffness in the control group (221 ± 127 N/mm).

The Energy was increased by aScl treatment, as reported by Virdi *et al.* 2015[33], with a significant increase at 8 and 12 weeks after the administration of Scl-Ab III Sham rats. Liu *et al.* 2012[61] reported a higher increase with Scl-Ab III plus PE suspension administration (348 ± 156 Nmm). And Virdi *et al.* 2012[37] reported a significant increase in Energy, compared to control group.

4.2. Bone Remodeling

To evaluate the effect of aScl treatment in bone remodeling, we verified that more studies than osseointegration had been done.

We verified that the treatment with antisclerostin had a positive effect on BMD, promoting his increase. In general, the eight studies in which we identified the analysis of BMD showed an increase of this parameter with the administration of this antibody, in both animal and human studies.

In the animal studies, Wu et al. 2018, reported an increase of BMD with the Scl-Ab, compared to vehicle control. But the higher effect was noticed with the combined treatment, with Scl-Ab and PTH 1-34. Li et al. 2010 reported an increase in BMD, with either dose they tested in their study. Ominsky et al. 2011, reported an increase of 11% in BMD. On the other hand, Taut *et al.* 2013, reported that the systemically Scl-Ab III treatment trend to increase the BMD. However, in case of locally administration, the increase was very limited. All of that evidence corroborates the initial premise that BMD is increased by aScl treatment.

Even if Ominsky *et al.* 2010, had reported a greater increase of volumetric BMD, with a greater dose of treatment in cynomolgus monkeys, they referred that the increase in areal BMD was not significant with the same doses.

Regarding human studies, Saag *et al.* 2017, reported an increase on BMD with the Romosozumab therapy. Similar to that, McClung *et al.* 2014 and Padhi *et al* 2014 also reported the increase in BMD with the Romosozumab. McClung *et al.* 2014 also reported the highest increase with the administration 210 mg once a month.

We noted that the BMC was increase with the different aScl therapies. Ominsky *et al.* 2011 reported the increase in BMC. In Liu *et al.* 2018 we could note an increase of BMC in OVX rats, with Scl-Ab VI treatment, with a higher expression of effect with the combined treatment with Scl-Ab VI and DAB. And in both Li *et al.* 2010 and Ominsky *et al.* 2010, with the rats and Cynomolgus monkeys' studies, respectively, we observed an increase in BMC, depending on dose used, with greater effect with higher doses.

Both studies performed by Virk *et al.* 2013[53] reported the increase of BA/TA, with a higher increase with continuous therapy. The bone area also showed to increase significantly with the Scl-Ab treatment, being that higher effects on increases were reported with a continuous period of treatment[53] and with higher treatment doses, in both Sprague-Dawley rats[36] and Cynomolgus monkeys.[59]

The BV/TV increased after Scl-Ab treatment. All the studies reported the increasing BV/TV, but some particularities were noted in some studies. Liu *et al.* 2018 reported the increases in BV/TV with Scl-Ab VI treatment alone, but also with the combined treatment (Scl-Ab VI + DAB). Similar results were identified by Wu *et al.* 2018, reporting a greater increase with the therapy with Scl-Ab III and PTH 1-34. Taut *et al.* 2013 showed that local treatment had only a few effects in the BV/TV improvement, compared to systemic. And finally, Tian *et al.'s* 2011 study referred to the higher increases with higher doses of treatment, comparing 5 and 25 mg/kg twice a week, in Sprague-Dawley rats.

Similar to the increase in bone volume fraction, some studies also reported an increase in bone volume. Liu *et al.* 2018[52] in their second study, recognized the increase in bone volume with only Scl-Ab VI treatment but, the higher increase in alveolar ridge volume was reported with the combination of Scl-Ab VI and DAB. Virk *et al.* 2013,[53] referred to higher increases with the continuous treatment.

The increase in Tb.Th, in those studies which tested the effect of aScl in OVX rats,[31, 52, 55] were verified higher exactly in OVX rats, compared to vehicles used in OVX rats and vehicle and drug tested in Sham rats. The other studies that compared the effect of higher and lower doses of Scl-Ab III treatment,[32, 36, 57] showed, in general, the higher increase with the 25mg/kg twice a week, with some particularity in Tian *et al.'s* 2011[32] study reported a higher increase in NL tibia.

Generally, there were identified greater results with higher therapeutic doses (25 mg/kg twice a week), in Sprague-Dawley rats, in the studies we identified.[32, 36, 54] However, a different effect was obtained by the only study performed in primates, with a higher increase in Ct.Th with the lower dose.[59]

In the Trabecular Number we noticed some divergences in our results. Some studies reported increases on the Tb.N values. Wu *et al.* 2018 reported increases with all the treatment options they studied, with higher increases observed in combined treatment (Scl-AB + PTH 1-34). Same as Li *et al.* 2012 who referred to higher Tb.N with Scl-Ab treatment (25 mg/kg twice a week). However, McDonald *et al.* 2012,[31] Tian *et al.* 2011[32] and Tian *et al.* 2010[57] showed some divergences in the values they reported.

The Trabecular Separation seems to decrease with the administration of aScl treatments, as referred by Wu *et al.* 2018,[55] Li *et al.* 2010[36] and Tian *et al.* 2010.[57] As other parameters discussed before, Wu *et al.* 2018 related a greater decrease with combined treatment, even if with the Scl-Ab isolated the decrease also occurred. Li *et al.* 2010[36] and Tian *et al.* 2010[57] reported greater results in Tb.Sp with the administration of higher dose of Scl-Ab. But, contrasting with these evidences, we

noticed the Tian *et al.'s* 2011 study, who reported decrease of decrease of values with saline solution in UL and NL bones, and with administration of 5 mg/kg of Scl-Ab in UL bone and 25 mg/kg in NL bone but, they reported an increase in Tb.Sp with 5mg/kg in NL and 25mg/kg in UL bones.

For the Mineralizing Surface all the studies reported similar results. Tian *et al.* 2011[32] reported greater results with the higher dose of Scl-Ab III treatment in both NL and UL bones sites. Tian *et al.* 2010[57] reported similar results in yellow and red marrow. And Li *et al.* 2010 also reported increases in MS/BS, Ps.MS/BS, and Ec.MS/BS with the higher dose of treatment (25 mg/kg twice a week of Scl-Ab III).

In general, the studies[32, 36, 57] showed similar results in Mineral Apposition Rate, with greater increases with the administration of 25mg/kg twice a week of Scl-Ab III. But Tian *et al.* 2010,[57] reported that were no differences at red marrow (LVB) related to the dose administration.

The Bone Formation Rate seemed to have greater increases after Scl-Ab treatment, compared to control groups. All the studies[32, 36, 52, 57] performed in Sprague-Dawley rats, reported similar results in Bone Formation Rate, which was significantly higher with the aScl treatments. Some particularities of each study showed little differences in their results. Liu *et al.* 2018,[52] reported a significantly higher increase in basal bone with the association of Scl-Ab VI (18.1 mg/kg) com DAB (18.1 mg/kg), compared to the administration of Scl-Ab VI alone. Tian *et al.* 2011, Li *et al.* 2010 and Tian *et al.* 2010 reported greater increases in BFR/BS with higher Scl-Ab treatment doses. Ominsky *et al.* 2010, with their study performed in primates, reported a significant increase in Ec.BFR/BS with the administration of 30 mg/kg once a month of Scl-Ab IV.

We observed in all studies a decrease of Eroded Surface associated with Scl-Ab treatment. Liu *et al.* 2018 reported lower values, both with the administration of Scl-Ab alone or the association of Scl-Ab and DAB. Tian *et al.* 2011 and Tian *et al.* 2010 reported a significantly higher decrease of ES/BS with the Scl-Ab therapy in NL and UL bones, and CVB and LVB, respectively.

In animal studies, we observed an increase of bone formation markers, after the beginning of treatment. Liu *et al.* 2018[52] reported an increase of BSAP with both Scl-Ab VI (18.2 mg/kg twice a week) or Scl-Ab VI + DAB (18.1 mg/kg + 18.1 mg/kg twice a week), and an increase in osteocalcin and P1NP with Scl-Ab VI (25 mg/kg twice a week). Similar results were obtained by Wu *et al.* 2018,[55] with increasing in osteocalcin and P1NP with a greater increase reported with Scl-Ab + PTH 1-34. Taut *et al.* 2013,[60] Virk *et al.* 2013[53] and Ominsky *et al.* 2011[54] reported greater increases in osteocalcin and P1NP with the administration of Scl-Ab III. Li *et al.* 2010[36] reported the greatest increase from baseline at 1 week of Scl-Ab III (25 mg/kg twice a week) of treatment, with a little decrease over time, but maintaining the greatest values compared to lower dose and vehicle control.

A decrease was observed in bone resorption markers. Liu *et al.* 2018[52] reported a decrease in TRACP-5b, with both Scl-Ab and Scl-Ab + DAB, with higher effect in the last one. Contrasting with this, Wu *et al.* 2018[55] and Li *et al* 2010[36] did not reported differences between Scl-Ab treatment and control. Taut *et al.* 2013[60] and Ominsky *et al.* 2010[59] referred that no differences were found in TRACP-5b and CTX serum, respectively.

Generally, aScl treatment provided increase in the bone strength endpoints.

We identified an increase on Maximum Load in both Wu *et al.* 2018[55] and Li *et al.* 2010[36] studies, with the Scl-Ab treatment. Li *et al.* 2010[36] reported that the increase of Maximum Load was related to the dose of Scl-Ab treatment administered in the 5th lumbar vertebra.

We noted that the Stiffness and Energy to Failure had a significantly higher increase with the Scl-Ab treatment in both rats[36, 53-55] and primates.[59] Wu *et al.* 2018[55] referred to a greater increase in Stiffness with the association of Scl-Ab with PTH 1-34. Li *et al.* 2010[36] reported some contrasting information from Stiffness, once they referred to a higher Stiffness as being related to higher treatment doses in LV and FD but, in FN, they reported a greater effect in Stiffness with lower doses. At Energy to Failure, they reported an increase with higher dose administration at all sites. Ominsky *et al.* 2010 reported that the increase in both Stiffness and Energy to Failure was obtain with higher dose of Scl-Ab VI treatment.

4.3. Limitations of the Study

This systematic review does present some limitations.

Those limitations are related to the low number of human studies identified, the high divergence in the model of the studies (animal or human models), the variance verified in the type of aScl administered and doses of administration on the treatment group, and to the lack of reference quantitative or reference of few quantitative values in the parameters analyzed by authors studies. Many articles only reported qualitative information.

CONCLUSIONS

5. Conclusions

Within the limitations of the systematic study developed, we can see antisclerostin as a promising treatment option to improve and accelerate the osseointegration of dental implants. Also could help in the treatment of oral pathologies that lead to loss of bone structure, stimulating the bone remodeling and neoformation.

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APPENDIX

Table S1: *Osseointegration - Bone Formation Parameters - Part I.*

	Sample Size (Initial)	Sample Size (Final)	Drug/Control	Dosage & Administration Route	Implant	BIC	BMD	BA/TA	BV/TV
Korn *et al.* (2019)[56]	128	124	sclerostin antibody	100mg/kg iv once week	reference-coated implant	**HMM**: 2 weeks: 33.2 ± 18.5 %; 4 weeks: 24.1 ± 9.7 % **μCT**: -	-	**HMM**: 4 weeks: 10.9 ± 4.4 %	-
					ZOL-coated implant	**HMM**: 2 weeks: comparable to reference implant; 4 weeks: 57.4 ± 15.0 % **μCT**: 4 weeks: 60.0 ± 2.5 %	**μCT**: 4 weeks: ≈ 2 times increase, comparing to reference implant	**HMM**: 4 weeks: 32.3 ± 11.5 %	**μCT**: 4 weeks: 31.0 ± 7.6 %
			non antibody applied	-	reference-coated implant	**μCT**: 4 weeks: nonsignificant decrease	-	**HMM**: 4 weeks: 4.5 ± 4.2 %	-
					ZOL-coated implant	**μCT**: 4 weeks: 47.8 ± 10.4 %	-	**HMM**: 4 weeks: 23.8 ± 8.6 %	-
Yu *et al.* (2018)[38]	60	60	Scl-Ab	25mg/kg sc	cp-Ti, solid cylinder with titanium plasma-sprayed surface implant	10 & 14 days: no differences compared to control group 28 weeks: significantly greater than control group	No differences between both groups	-	14 days: ≈ 2x greater 28 days: 2.5x greater
			PBS	-		-		-	-
Virdi *et al.* (2015)[33]	144: 72 OVX	142: 71 OVX	Scl-Ab III	25 mg/kg sc twice week	cp-Ti with dual acid-etched surface implant	increase over time, lower than sham group	-	-	-
			vehicle	-		-	-	-	-
	144: 72 Sham	142: 71 Sham	Scl-Ab III	25 mg/kg sc twice week		increase over time, higher than OVX group	-	-	most significant increase than OVX group
			vehicle	-		-	-	-	-
Liu *et al.* (2012)[61]	36	36	PE suspension + Scl-Ab III	50μL ia once week + 25 mg/kg sc twice week	titanium rods with dual acid-etched surface	-	-	-	31.2 ± 7.7 %
			PE suspension + antibody vehicle	50μL ia once week + vehicle sc twice week		-	-	-	7.6 ± 2.5 %
			particle vehicle + antibody vehicle	-		-	-	-	17.5 ± 5.8 %
Virdi *et al.* (2012)[37]	90	88	Scl-Ab	25mg/kg sc	cp-Ti with dual acid-etched surface implant	higher at later times	-	-	4 weeks: 2x control grp 8 weeks: more than 2x
			saline solution	-		-	-	-	-
Ominsky *et al.* (2011)[54]	43	29	Scl-Ab V	30mg/kg sc every 2 weeks	stainless steel K-wire	-	TH: 14.5 ± 1.8 % FN: 17.4 ± 1.6 % DR: 5.6 ± 0.9 % LS: 16.6 ± 1.2 %	-	FN: 33.6 ± 2.1 %
			vehicle	-		-	TH: 9.3 ± 1.5 % FN: 7.6 ± 2.1 % DR: 3.3 ± 0.6 % LS: 4.4 ± 0.5 %	-	FN: 27.5 ± 2.3 %

Agholme *et al.* (2010)[58]	68	64	Scl-Ab III	25mg/kg sc twice weeks	stainless steel screws (mechanical tests); PMMA screws (μCT)	-	AS: 1.17 ± 0.04 g/cm^3 MS: 1.14 ± 0.04 g/cm^3 CS: 1.20 ± 0.055 g/cm^3 IT: 1.04 ± 0.01 g/cm^3 CT: 1.05 ± 0.01 g/cm^3	-	AS: 37 ± 7.7 % MS: 31 ± 6.6 % CS: 65 ± 11 % IT: 23 ± 4.4 % CT: 26 ± 4.7%
			saline solution	-		-	AS: 1.12 ± 0.05 g/cm^3 MS: 1.10 ± 0.02 g/cm^3 CS: 1.14 ± 0.065 g/cm^3 IT: 0.96 ± 0.02 g/cm^3 CT: 0.98 ± 0.03 g/cm^3	-	AS: 28 ± 6.9 % MS: 25 ± 6.1 % CS: 51 ± 12 % IT: 19 ± 4.0 % CT: 23 ± 3.8%

BIC – Bone-to-Implant Contact; **BMD** – Bone Mineral Density; **BA/TA** – Bone Area per Total Area; **BV/TV** – Bone Volume Fraction; **HMM** – Histomorphometry; **μCT** – Micro Computed Tomography; **TH** – Total Hip; **FN** – Femoral Neck; **DR** – Third Distal Radius; **LS** – Lumbar Spine; **AS** – Around Entire Screw; **MS** – Marrow Surrounding; **CS** – Cortical Surrounding; **IT** – Implanted Tibia; **CT** – Contralateral Tibia.

Table S2: *Osseointegration - Bone Formation Parameters – Part II.*

	Sample Size (Initial)	Sample Size (Final)	Drug/Control	Dosage & Administration Route	Implant	Ct.Ar	M.Ar	Tt.Ar	Bone Fill
Korn *et al.* (2019)[56]	128	124	sclerostin antibody	100mg/kg iv once week	reference-coated implant	-	-	-	-
					ZOL-coated implant	-	-	-	-
			non antibody applied	-	reference-coated implant	-	-	-	-
					ZOL-coated implant	-	-	-	-
Yu *et al.* (2018)[38]	60	60	Scl-Ab	25mg/kg sc	cp-Ti, solid cylinder implants with titanium plasma-sprayed surface	-	-	-	28 days: significantly greater than control
			PBS	-		-	-	-	-
Virdi *et al.* (2015)[33]	144 (72 OVX)	142 (71 OVX)	Scl-Ab III	25 mg/kg sc twice week	cp-Ti, dual acid-etched surface	-	-	-	-
			vehicle	-		-	-	-	-
	144 (72 Sham)	142 (71 Sham)	Scl-Ab III	25 mg/kg sc twice week		-	-	-	-
			vehicle	-		-	-	-	-
Liu *et al.* (2012)[61]	36	36	PE suspension + Scl-Ab III	50μL ia once week + 25 mg/kg sc twice week	titanium rods, dual acid-etched surface	-	-	-	-
			PE suspension + antibody vehicle	50μL ia once week + vehicle sc twice week		-	-	-	-
			particle vehicle + antibody vehicle	-		-	-	-	-
Virdi *et al.* (2012)[37]	90	88	Scl-Ab	25mg/kg sc	cp-Ti, dual acid-etched surface	4 & 8 weeks: significantly greater	No detectable differences	8 weeks: greater	-
			saline solution	-		-		-	-
Ominsky *et al.* (2011)[54]	43	29	Scl-Ab V	30mg/kg sc every 2 weeks	stainless steel K-wire	FD: 56.0 ± 6.7 mm^2	-	-	-
			vehicle	-		FD: 54.7 ± 2.0 mm^2	-	-	-
Agholme *et al.* (2010)[58]	68	64	Scl-Ab III	25mg/kg sc twice week	stainless steel screws (mechanical tests); PMMA (μCT)	-	-	-	-
			saline solution	-		-	-	-	-

Tt.Ar – Total cross-sectional Area/Subperiosteal Area; **Ct.Ar** – Cortical Area; **M.Ar** – Medullary Area; **FD** – Femoral Diaphysis.

Table S3: *Osseointegration - Bone Formation Parameters - Part III.*

	Sample Size (Initial)	Sample Size (Final)	Drug/Control	Dosage & Administration Route	Implant	Bone Thickness	Tb.Th	Tb.N	Tb.Sp	Ct.Th
Korn *et al.* (2019)[56]	128	124	sclerostin antibody	100mg/kg iv once week	reference-coated implant	-	**μCT** higher than control group	-	-	-
					ZOL-coated implant	-		-	-	-
			non antibody applied	-	reference-coated implant	-	-	-	-	-
					ZOL-coated implant	-	-	-	-	-
Yu *et al.* (2018)[38]	60	60	Scl-Ab	25mg/kg sc	cp-Ti, solid cylinder implants with titanium plasma-sprayed surface	-	-	8 weeks: greater than control group	-	-
			PBS	-		-	-	-	-	-
Virdi *et al.* (2015)[33]	144 72 OVX	142 71 OVX	Scl-Ab III	25 mg/kg sc twice week	cp-Ti, dual acid-etched surface	-	-	-	-	increase over time
			vehicle	-		-	-	-	-	-
	72 Sham	71 Sham	Scl-Ab III	25 mg/kg sc twice week		-	increase	little or no effect	-	increase over time, more significant than OVX group
			vehicle	-		-	-	-	-	-
Liu *et al.* (2012)[61]	36	36	PE suspension + Scl-Ab III	50μL ia once week + 25 mg/kg sc twice week	titanium rods, dual acid-etched surface	-	192 ± 26 μm	2.01 ± 0.32 mm^{-1}	502 ± 93 μm	-
			PE suspension + antibody vehicle	50μL ia once week + vehicle sc twice week		-	137 ± 19 μm	0.92 ± 0.18 mm^{-1}	1182 ± 216 μm	-
			particle vehicle + antibody vehicle	-		-	142 ± 20 μm	1.31 ± 0.34 mm^{-1}	869 ± 216 μm	-
Virdi *et al.* (2012)[37]	90	88	Scl-Ab	25mg/kg sc	cp-Ti, dual acid-etched surface	8 weeks: greater than control group	-	-	-	8 weeks: greater
			saline solution	-		-	-	-	-	-
Ominsky *et al.* (2011)[54]	43	29	Scl-Ab V	30mg/kg sc every 2 weeks	stainless steel K-wire	-	FN: 194 ± 6 μm	-	-	-
			vehicle	-		-	FN: 152 ± 12 μm	-	-	-
Agholme *et al.* (2010)[58]	68	64	Scl-Ab III	25mg/kg sc twice weeks	stainless steel screws (mechanical tests); PMMA (μCT)	-	IT: 117 ± 5.7μm CT: 121 ± 3.8μm	IT: 1.9 ± 0.34 μm^{-1} CT: 2.2 ± 0.36 μm^{-1}	IT: 304 ± 54μm CT: 277 ± 56μm	-
			saline solution	-		-	IT: 92 ± 4.1μm CT: 93 ± 3.1μm	IT: 2.1 ± 0.48 μm^{-1} CT: 2.4 ± 0.40 μm^{-1}	IT: 273 ± 48μm CT: 244 ± 42μm	-

Tb.Th – Trabecular Thickness; **Tb.N** – Trabecular Number; **Tb.Sp** – Trabecular Separation; **Ct.Th** – Cortical Thickness; **FN** – Femoral Neck; **IT** – Implanted Tibia; **CT** – Contralateral Tibia.

Table S4: *Osseointegration - Bone Formation Parameters - Part IV.*

	Sample Size (Initial)	Sample Size (Final)	Drug/Control	Dosage & Administration Route	Implant	SMI	MS/BS	MAR	BFR/BS
Korn *et al.* (2019)[56]	128	124	sclerostin antibody	100mg/kg iv once week	reference-coated implant	-	-	-	-
					ZOL-coated implant	-	-	-	-
			non-antibody applied	-	reference-coated implant	-	-	-	-
					ZOL-coated implant	-	-	-	-
Yu *et al.* (2018)[38]	60	60	Scl-Ab	25mg/kg sc	cp-Ti, solid cylinder implants with titanium plasma-sprayed surface	-	-	-	-
			PBS	-		-	-	-	-
Virdi *et al.* (2015)[33]	144 (72 OVX)	142 (71 OVX)	Scl-Ab III	25 mg/kg sc twice week	cp-Ti, dual acid-etched surface	-	-	-	<u>4 weeks:</u> 4.6-fold increase vs control increase attenuated overtime
			vehicle	-		-	-	-	-
	144 (72 Sham)	142 (71 Sham)	Scl-Ab III	25 mg/kg sc twice week		-	-	-	<u>4 weeks:</u> 7-fold increase vs control increase attenuated overtime
			vehicle	-		-	-	-	-
Liu *et al.* (2012)[61]	36	36	PE suspension + Scl-Ab III	50μL ia once week + 25 mg/kg sc twice week	titanium rods, dual acid-etched surface	1.09 ± 0.46	17.64 ± 3.25 %	1.56 ± 0.26 μm/day	102.14 ± 34.47 $\mu m^3/\mu m^2$/day×100
			PE suspension + antibody vehicle	50μL ia once week + vehicle sc twice week		2.18 ± 0.60	9.83 ± 4.78 %	0.77 ± 0.16 μm/day	29.69 ± 19.77 $\mu m^3/\mu m^2$/day×100
			particle vehicle + antibody vehicle	-		1.55 ± 0.43	12.04 ± 2.12 %	1.11 ± 0.16 μm/day	49.53 ± 15.18 $\mu m^3/\mu m^2$/day×100
Virdi *et al.* (2012)[37]	90	88	Scl-Ab	25mg/kg sc	cp-Ti, dual acid-etched surface	decrease over time	-	-	-
			saline solution	-		-	-	-	-
Ominsky *et al.* (2011)[54]	43	29	Scl-Ab V	30mg/kg sc every 2 weeks	stainless steel K-wire	-	-	-	**2-3.5 wks:** <u>FN:</u> 157.6 ± 20.1 $\mu m^3/\mu m^2$/yr; <u>Ps.FD:</u> 187 ± 36 $\mu m^3/\mu m^2$/yr; <u>Ec.FD:</u> 238 ± 42 $\mu m^3/\mu m^2$/yr
									8-9.5 wks: <u>FN:</u> 100.4 ± 17.9 $\mu m^3/\mu m^2$/yr; <u>Ps.FD:</u> 15.0 ± 5.2 $\mu m^3/\mu m^2$/yr; <u>Ec.FD:</u> 270 ± 37 $\mu m^3/\mu m^2$/yr
			vehicle	-		-	-	-	**2-3.5 wks:** <u>FN:</u> 44.8 ± 8.0 $\mu m^3/\mu m^2$/yr; <u>Ps.FD:</u> 79.3 ± 15.8 $\mu m^3/\mu m^2$/yr; <u>Ec.FD:</u> 50.5 ± 14.8 $\mu m^3/\mu m^2$/yr
									8-9.5 wks: <u>FN:</u> 62.4 ± 12.1 $\mu m^3/\mu m^2$/yr; <u>Ps.FD:</u> 6.4 ± 3.4 $\mu m^3/\mu m^2$/yr; <u>Ec.FD:</u> 35.5 ± 10.6 $\mu m^3/\mu m^2$/yr
Agholme *et al.* (2010)[58]	68	64	Scl-Ab III	25mg/kg sc twice weeks	stainless steel screws (mechanical tests); PMMA (μCT)	-	-	-	-
			saline solution	-		-	-	-	-

SMI – Structural Model Index; **MS/BS** – Mineralizing Surface; **MAR** – Mineral Apposition Rate; **BFR/BS** – Bone Formation Rate; **FN** – Femoral Neck; **FD** – Femoral Diaphysis; **Ps** – Periosteal; **Ec** – Endocortical.

Table S5: *Osseointegration - Bone Formation Parameters - Part V.*

	Sample Size (Initial)	Sample Size (Final)	Drug/Control	Dosage & Administration Route	Implant	ES/BS	Oc.S/BS	Cortical Porosity
Korn *et al.* (2019)[56]	128	124	sclerostin antibody	100mg/kg iv once week	reference-coated implant	-	-	-
					ZOL-coated implant	-	-	-
			non antibody applied	-	reference-coated implant	-	-	-
					ZOL-coated implant	-	-	-
Yu *et al.* (2018)[38]	60	60	Scl-Ab	25mg/kg sc	cp-Ti, solid cylinder implants with titanium plasma-sprayed surface	-	-	-
			PBS	-		-	-	-
Virdi *et al.* (2015)[33]	144 (72 OVX)	142 (71 OVX)	Scl-Ab III	25 mg/kg sc twice week	cp-Ti, dual acid-etched surface	decrease greater than 50%	-	-
			vehicle	-		-	-	-
	144 (72 Sham)	142 (71 Sham)	Scl-Ab III	25 mg/kg sc twice week		decrease greater than 50%	-	-
			vehicle	-		-	-	-
Liu *et al.* (2012)[61]	36	36	PE suspension + Scl-Ab III	50μL ia once week + 25 mg/kg sc twice week	titanium rods, dual acid-etched surface	17.10 ± 3.17 %	-	-
			PE suspension + antibody vehicle	50μL ia once week + vehicle sc twice week		10.83 ± 1.92 %	-	-
			particle vehicle + antibody vehicle	-		10.26 ± 2.71 %	-	-
Virdi *et al.* (2012)[37]	90	88	Scl-Ab	25mg/kg sc	cp-Ti, dual acid-etched surface	-	-	-
			saline solution	-		-	-	-
Ominsky *et al.* (2011)[54]	43	29	Scl-Ab V	30mg/kg sc every 2 weeks	stainless steel K-wire	FN: 0.86 ± 0.19 %	FN: 0.26 ± 0.09 %	FD: 0.99 ± 0.07 %
			vehicle	-		FN: 1.95 ± 0.33 %	FN: 0.33 ± 0.08 %	FD: 1.13 ± 0.10 %
Agholme *et al.* (2010)[58]	68	64	Scl-Ab III	25mg/kg sc twice weeks	stainless steel screws (mechanical tests); PMMA (μCT)	-	-	-
			saline solution	-		-	-	-

ES/BS – Eroded Surface; **Oc.S/BS** – Osteoclast Surface; **FN** – Femoral Neck; **FD** - Femoral Diaphysis.

Table S6: *Implant Fixation Properties*

	Sample Size (Initial)	Sample Size (Final)	Drug/Control	Dosage & Administration Route	Implant	Fixation Strength	Stiffness	Energy
Korn *et al.* (2019)[56]	128	124	sclerostin antibody	100mg/kg iv once week	reference-coated implant	-	-	-
					ZOL-coated implant	-	-	-
			non antibody applied	-	reference-coated implant	-	-	-
					ZOL-coated implant	-	-	-
Yu *et al.* (2018)[38]	60	60	Scl-Ab	25mg/kg sc	cp-Ti, solid cylinder with Ti plasma-sprayed surface implant	-	-	-
			PBS	-		-	-	-
Virdi *et al.* (2015)[33]	144: 72 OVX	142: 71 OVX	Scl-Ab III	25 mg/kg sc twice week	cp-Ti, dual acid-etched surface	increase over time	-	-
			vehicle	-		-	-	-
	144: 72 Sham	142: 71 Sham	Scl-Ab III	25 mg/kg sc twice week		increase over time greater than OVX group 2x higher than control group	sig. increase over time, with better results than OVX	greater than OVX group 8 & 12 wks: significant increase
			vehicle	-		-	-	-
Liu *et al.* (2012)[61]	36	36	PE suspension + Scl-Ab III	50μL ia once week + 25 mg/kg sc twice week	titanium rods, dual acid-etched surface	2.00 ± 0.29 N/mm^2	186 ± 114 N/mm	348 ± 156 Nmm
			PE suspension + antibody vehicle	50μL ia once week + vehicle sc twice week		0.79 ± 0.40 N/mm^2	127 ± 89 N/mm	104 ± 67 Nmm
			particle vehicle + antibody vehicle	-		1.32 ± 0.45 N/mm^2	221 ± 127 N/mm	154 ± 81 Nmm
Virdi *et al.* (2012)[37]	90	88	Scl-Ab	25mg/kg sc	cp-Ti, dual acid-etched surface	4 wks: 1,9 times higher 8 wks: 2,2 times higher	sig. increase over time, but not overall group effect. 8 wks: drug effect apparent	4 & 8 wks: sig. increase with similar pattern as fixation strength
						Univariate correlation with	**Univariate correlation with**	**Univariate correlation with**
						BV/TV: 0.596 SMI: -0.678 Tb.Th: 0.719 Tb.Sp: 0.078 Tb.N: -0.121 Ct.Ar: 0.671 Ct.Th: 0.666 Tt.Ar: 0.502 M.Ar: -0.255	BV/TV: 0.436 SMI: -0.519 Tb.Th: 0.517 Tb.Sp: 0.053 Tb.N: -0.120 Ct.Ar: 0.428 Ct.Th: 0.485 Tt.Ar: 0.205 M.Ar: -0.358	BV/TV: 0.577 SMI: -0.662 Tb.Th: 0.717 Tb.Sp: 0.069 Tb.N: -0.094 Ct.Ar: 0.636 Ct.Th: 0.595 Tt.Ar: 0.538 M.Ar: -0.135
			saline solution	-		**Univariate correlation with**	**Univariate correlation with**	**Univariate correlation with**
						BV/TV: -0.016 SMI: -0.187 Tb.Th: 0.019 Tb.Sp: 0.124 Tb.N: -0.148 Ct.Ar: 0.052 Ct.Th: 0.111 Tt.Ar: -0.193 M.Ar: -0.260	BV/TV: 0.115 SMI: -0.540 Tb.Th: 0.017 Tb.Sp: 0.062 Tb.N: -0.031 Ct.Ar: -0.222 Ct.Th: -0.094 Tt.Ar: -0.266 M.Ar: -0.255	BV/TV: -0.015 SMI: -0.027 Tb.Th: 0.082 Tb.Sp: 0.065 Tb.N: -0.129 Ct.Ar: 0.047 Ct.Th: 0.180 Tt.Ar: -0.102 M.Ar: -0.204
Ominsky *et al.* (2011)[54]	43	29	Scl-Ab V	30mg/kg sc every 2 weeks	stainless steel K-wire	-	increase of 48% in torsional stiffness	-
			vehicle	-		-	-	-
Agholme *et al.* (2010)[58]	68	64	Scl-Ab III	25mg/kg sc twice week	stainless steel screws (mechanical tests); PMMA (μCT)	-	-	-
			saline solution	-		-	-	-

BV/TV – Bone Volume per Total Volume; **SMI** – Structural Model Index; **Tb.Th** – Trabecular Thickness; **Tb.Sp** – Trabecular Separation; **Tb.N**. – Trabecular Number; **Ct.Ar** – Cortical Area; **Ct.Th** – Cortical Thickness; **Tt.Ar** - Total cross-sectional Area/Subperiosteal Area; **M.Ar** – Medullary Area

Table S7: *Bone Remodeling - Bone Formation Parameters – Part I.*

	Sample Size (Initial)		**Sample Size** (Final)		**Drug/Control**	**Dosage & Administration Route**	**BMD**	**BMC**	**BA/TA**	**BV/TV**
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	-	Vertebral & Leg: increase vs control group	-	levels restored and exceeded both control groups
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week	-	Vertebral & Leg: sig. increase vs control and Scl-Ab groups	-	
					saline vehicle	-	-	-	-	-
		10 Sham		10 Sham	saline vehicle	-	-	-	-	-
	45		45		Scl-Ab VI	25mg/kg sc twice week	-	-	-	**15 weeks** higher in loaded and underloaded sites vs control no sig. differences between loaded & underloaded sites
					Scl-Ab VI + DAB	25mg/kg sc + 25mg/kg sc twice week	-	-	-	
					saline vehicle	-	-	-	-	13.9% lower in underloaded mandible vs loaded mandible
Wu *et al.* (2018)[55]	50	5 Sham	50	5 Sham	**Baseline**		TM: 231 ± 30.14 mg/cm^3	-	-	-
		5 OVX		5 OVX	**Baseline**		TM: 165 ± 27.65 mg/cm^3	-	-	-
		40 OVX		40 OVX	Scl-Ab	25mg/kg sc twice week	1.24x higher increase vs control	-	-	1.75x higher increase vs control
					PTH 1-34	60μg/kg sc thrice week	1.25x higher increase vs control	-	-	1.77x higher increase vs control
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week	1.35x higher increase vs control	-	-	2.31x higher increase vs control
					vehicle	-	12 weeks: sig. decrease	-	-	-
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	**3 wks** higher increase vs vehicle	-	-	**3 wks** higher than vehicle group
							6 wks sig. higher increase vs veh no differences vs healthy			**6 wks** sig. higher vs vehicle and no sig. difference vs healthy
						15 μL of 35.6mg/mL solution locally twice week	3 & 6 weeks: limited increase	-	-	limited increase
							3 wks lower than vehicle			**3 wks** lower increase than veh
							6 wks little higher than vehicle			**6 wks** little higher increase vs veh
					EP: vehicle	-	3 wks: increase, stabilizing at 6 wks	-	-	3 wks: increased, stabilizing 6 wks
					healthy: PBS	-	6 weeks: sig. greater vs veh	-	-	significantly higher vs vehi
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc twice week	-	-	12 weeks: 44.4 ± 9.1 % 2 weeks: 33.5 ± 13.5 % 2-4 weeks: 40.4 ± 15 %	12 weeks: 60 ± 17 % 2 weeks: 44.4 ± 20 % 2-4 weeks: 49.6 ± 20.4 %
					PBS	-	-	-	37.3 ± 10.2 %	39.3 ± 15.3 %
	30		30		Scl-Ab III	25mg/kg	-	-	28.2 ± 10.9 %	37.4 ± 0.1 %
					PBS	-	-	-	15.2 ± 9.1 %	19.2 ± 9.5 %

McDonald *et al.* (2012)[31]	132	66 Sham	127	Scl-Ab III	25mg/kg sc twice week	-	-	-	1 week: 8.5 ± 6.3 % 2 weeks: 32.0 ± 7.9 % 3 weeks: 35.8 ± 7.9 %
				saline solution	-	-	-	-	1 week: 8.3 ± 4.9 % 2 weeks: 28.0 ± 5.5 % 3 weeks: 28.9 ± 11.0 %
		66 OVX		Scl-Ab III	25mg/kg sc twice week	-	-	-	1 week: 18.6 ± 8.6 % 2 weeks: 25.3 ± 7.4 % 3 weeks: 18.9 ± 9.2 %
				saline solution	-	-	-	-	1 week: 21.3 ± 14.3 % 2 weeks: 15.5 ± 5.2 % 3 weeks: 13.7 ± 3.4 %
Ominsky *et al.* (2011)[54]	35		32	Scl-Ab III	25mg/kg sc twice week	11 % increase compared to vehicle, in fractured femur	**Fractured Femur:** 19% increase compared to vehicle	-	**Fractured Femur:** 41 % greater compared to vehicle
							Intact Femur: FN: 3.68 ± 0.14 mg/mm Tb.DF: 4.26 ± 0.31 mg/mm Ct.FD: 10.05 ± 0.29 mg/mm		**Intact Femur:** Tb.DF: 23.1 ± 2.0 %
				vehicle	-	-	**Intact Femur:** FN: 3.23 ± 0.08 mg/mm Tb.DF: 3.07 ± 0.15 mg/mm Ct.FD: 9.10 ± 0.23 mg/mm	-	**Intact Femur:** Tb.DF: 16.4 ± 3.8 %
Tian *et al.* (2011)[32]	67		67	-	-	-	-	-	**Baseline** PTM: 14.3 ± 4.8 %
				Scl-Ab III	5mg/kg sc twice week	-	-	-	NL.PTM: 24.6 ± 9.2 % UL.PTM: 19.4 ± 3.3 %
					25mg/kg sc twice week	-	-	-	NL.PTM: 34.7 ± 6.5 % UL.PTM: 21.2 ± 6.3 %
				saline solution	-	-	-	-	NL.PTM: 13.9 ± 2.7 % UL.PTM: 13.4 ± 1.1 %
Li *et al.* (2010)[36]	28		26	Scl-Ab III	25mg/kg sc twice week	LV: 678 ± 16 mg/mL FD: 1360 ± 8 mg/mL FN: 1090 ± 31 mg/mL Tb.LV: 561 ± 22 mg/mL Tb.DF: 428.1 ± 21.9 mg/mL Ct.LV: 674 ± 10 mg/mL	LV: 9.07 ± 0.26 mg/mm FD: 15.87 ± 1.22 mg/mm FN: 5.88 ± 0.33 mg/mm Tb.LV: 4.02 ± 0.16 mg/mm Tb.DF: 5.63 ± 0.36 mg/mL Ct.LV: 5.1 ± 0.1 mg/mm	-	Tb.LV: 43.9 ± 2.8 % Tb.DF: 24.5 ± 2.7 % FN: 88.5 ± 3.5 % PT: 19.0 ± 2.1 %
					5mg/kg sc twice week	LV: 626 ± 21 mg/mL FD: 1363 ± 9 mg/mL FN: 1064 ± 12 mg/mL Tb.LV: 499 ± 26 mg/mL Tb.DF: 411.5 ± 22.3 mg/mL Ct.LV: 633 ± 16 mg/mL	LV: 8.15 ± 0.22 mg/mm FD: 15.85 ± 0.63 mg/mm FN: 4.90 ± 0.32 mg/mm Tb.LV: 3.55 ± 0.13 mg/mm Tb.DF: 4.89 ± 0.35 mg/mL Ct.LV: 4.6 ± 0.1 mg/mm	-	Tb.LV: 36.1 ± 3.1 % Tb.DF: 22.5 ± 2.8 % FN: 87.6 ± 2.0 % PT: 17.0 ± 3.3 %
				vehicle	-	LV: 500 ± 14 mg/mL FD: 1343 ± 10 mg/mL FN: 975 ± 21 mg/mL Tb.LV: 375 ± 16 mg/mL Tb.DF: 290.2 ± 10.8 mg/mL Ct.LV: 508 ± 13 mg/mL	LV: 6.22 ± 0.24 mg/mm FD: 13.00 ± 0.48 mg/mm FN: 4.83 ± 0.23 mg/mm Tb.LV: 2.81 ± 0.13 mg/mm Tb.DF: 3.79 ± 0.22 mg/mL Ct.LV: 3.4 ± 0.1 mg/mm	-	Tb.LV: 22.4 ± 1.6 % Tb.DF: 9.5 ± 1.3 % FN: 74.8 ± 2.3 % PT: 7.1 ± 0.8 %

Ominsky *et al.* (2010)[59]	12	12	Scl-Ab IV	3mg/kg sc once month	%Change	DXA	WB: 4.4 ±5.4 % LS: 9.8 ± 1.4 % FN: 10.2 ± 10.9 % UDR: 8.5 ± 0.9 %	%Change	DXA	WB: 5.8 ± 6.2 % LS: 15.0 ± 0.3 % FN: 17.3 ± 11.6 % UDR: 9.7 ± 5.5 %	-	-
						pQCT	DRM: 1.8 ± 2.4 % PTM: 3.2 ± 4.5 % Tb.DRM: 13.1 ± 26.0 % Tb.PTM: 8.4 ± 18.7 % Ct.DRD: 0.2 ± 1.2 % Ct.PTD: -1.2 ± 3.3 %		pQCT	DRM: 4.1 ± 5.1 % PTM: 9.4 ± 15.0 % Ct.DRD: 7.3 ± 7.2 % Ct.PTD: 9.7 ± 9.6 %		
				10mg/kg sc once month	%Change	DXA	WB: 10.8 ± 3.2 % LS: 4.2 ± 3.8 % FN: 11.5 ± 5.8 % UDR: 6.2 ± 5.6 %	%Change	DXA	WB: 19.2 ± 6.7 % LS: 8.1 ± 6.6 % FN: 10.5 ± 2.8 % UDR: 11.3 ± 8.3 %	-	-
						pQCT	DRM: 8.5 ± 2.2 % PTM: 10.9 ± 3.7 % Tb.DRM: 21.7 ± 6.8 % Tb.PTM: 21.1 ± 6.7 % Ct.DRD: -1.6 ± 1.4 % Ct.PTD: -1.1 ± 0.9 %		pQCT	DRM: 7.7 ± 1.7 % PTM: 17.4 ± 5.9 % Ct.DRD: 3.3 ± 1.9 % Ct.PTD: 11.0 ± 3.8 %		
				30mg/kg sc once month	%Change	DXA	WB: 9.4 ± 2.8 % LS: 11.1 ± 3.0 % FN: 19.5 ± 3.4 % UDR: 15.1 ± 1.0 %	%Change	DXA	WB: 24.0 ± 2.2 % LS: 16.5 ± 6.2 % FN: 35.2 ± 7.2 % UDR: 19.8 ± 4.4 %	-	-
						pQCT	DRM: 14.2 ± 3.4 % PTM: 18.8 ± 4.7 % Tb.DRM: 34.3 ± 14.4 % Tb.PTM: 34.9 ± 8.2 % Ct.DRD: -0.9 ± 1.6 % Ct.PTM: 1.0 ± 1.0 %		pQCT	DRM: 19.8 ± 7.2 % PTM: 27.3 ± 6.2 % Ct.DRD: 8.8 ± 2.5 % Ct.PTM: 13.6 ± 2.8 %		
			vehicle	-	%Change	DXA	WB: 1.6 ± 3.0 % LS: 1.7 ± 1.8 % FN: 4.6 ± 1.8 % UDR: 2.7 ± 4.0 %	%Change	DXA	WB: 6.4 ± 3.0 % LS: 2.8 ± 2.7 % FN: 5.4 ± 5.1 % UDR: 5.3 ± 3.7 %	-	-
						pQCT	DRM: 2.6 ± 2.0 % PTM: 2.9 ± 3.5 % Tb.DRM: -3.2 ± 4.0 % Tb.PTM: -1.7 ± 4.9 % Ct.DRD: -0.3 ± 0.5 % Ct.PTD: 1.3 ± 0.7 %		pQCT	DRM: 0.8 ± 1.6 % PTM: -1.0 ± 3.2 % Ct.DRD: 2.4 ± 0.7 % Ct.PTD: 2.5 ± 3.2 %		
Tian *et al.* (2010)[57]	32	32	-	-	-			-			-	**Baseline**	CVB: 25.7 ± 4.1 % LVB: 25.1 ± 4.1 %
			Scl-Ab III	5mg/kg sc twice week	-			-			-	CVB: 29.4 ± 4.1 % LVB: 31.9 ± 7.9 %	
				25mg/kg sc twice week	-			-			-	CVB: 37.5 ± 6.5 % LVB: 45.2 ± 4.6 %	

			saline solution	-	-		-	-	CVB: 23.8 ± 3.5 % LVB: 24.4 ± 3.7 %
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → Alendronate	210mg sc once month → 70mg po once week	**T-score Baseline**		LS: -2.94 ± 1.25 TH: -2.78 ± 0.68 FN: -2.89 ± 0.49	-	-	-
					%Change	**12 mo**	LS: 13.7%; TH: 6.2%; FN: 4.9%			
						24 mo	LS: 15.2%; TH: 7.1%; FN: 5.9%			
						36 mo	LS: 14.9%; TH: 7.0%; FN: 5.9%			
			Alendronate → Alendronate	70mg po once week → 70mg po once week	**T-score Baseline**		LS: -2.99 ± 1.24 TH: -2.18 ± 0.67 FN: -2.90 ± 0.50	-	-	-
					%Change	**12 mo**	LS: 5.0%; TH: 2.8%; FN: 1.7%			
						24 mo	LS: 7.1%; TH: 3.4%; FN: 3.6%			
						36 mo	LS: 8.5%; TH: 3.6%; FN: 2.7%			
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc every 3 months	**T-score Baseline**		LS: -2.44 ± 0.70 TH: -1.58 ± 0.51 FN: -2.00 ± 0.54 DR: -2.24 ± 1.06	-	-	-
					%Change	**3 mo**	LS: 2.4%; TH: 0.3%; FN: 0.4%			
						6 mo	LS: 4.2%; TH: 0.9%; FN: 0.4%			
						12 mo	LS: 5.4%; TH: 1.3%; FN: 1.8%; DR: -1.1%			
				210mg sc every 3 months	**T-score Baseline**		LS: -2.21 ± 0.69 TH: 1.65 ± 0.63 FN: -2.02 ± 0.57 DR: -1.98 ± 1.04	-	-	-
					%Change	**3 mo**	LS: 3.1%; TH: 0.8%; FN: 0.9 %			
						6 mo	LS: 4.4%; TH: 1.1%; FN: 0.9%			
						12 mo	LS: 5.5%; TH: 1.9%; FN: 1.4%; DR: -0.4 %			
				70mg sc once month	**T-score Baseline**		LS: -2.35 ± 0.79 TH: 1.69 ± 0.67 FN: -2.06 ± 0.55 DR: -1.78 ± 1.14	-	-	-
					%	**3 mo**	LS: 1.9%; TH: 0.4%; FN: -0.4%			

						6 mo	LS: 4.1%; TH: 0.5%; FN: 0.2%			
						12 mo	LS: 5.4%; TH: 1.3%; FN: 0.6%; DR: -1.8%			
				140mg sc once month	**T-score Baseline**		LS: -2.27 ± 0.77 TH: -1.67 ± 0.65 FN: -2.03 ± 0.58 DR: -2.11 ± 1.12	-	-	-
					%Change	**3 mo**	LS: 4.5%; TH: 1.0%; FN: 1.3%			
						6 mo	LS: 7.1%; TH: 2.2%; FN: 2.1%			
						12 mo	LS: 9.1%; TH: 3.4%; FN: 4.2%; DR: -1.0%			
				210mg sc once month	**T-score Baseline**		LS: -2.33 ± 0.57 TH: -1.45 ± 0.65 FN: -1.87 ± 0.58 DR: -2.03 ± 0.99	-	-	-
					%Change	**3 mo**	LS: 4.5%; TH: 1.1%; FN: 0.8%			
						6 mo	LS: 8.2%; TH: 2.9%; FN: 1.9%			
						12 mo	LS: 11.3%; TH: 4.1%; FN: 3.7%; DR: -1.2%			
			Alendronate	70 mg po once week	**T-score Baseline**		LS: -2.08 ± 0.69 TH: -1.55 ± 0.68 FN: -1.91 ± 0.61 DR: -2.08 ± 0.99	-	-	-
					%Change	**3 mo**	LS: 1.8%; TH: 0.6%; FN: 0.4%			
						6 mo	LS: 2.6%; TH: 0.9%; FN: 0.5%			
						12 mo	LS: 4.1%; TH: 1.9%; FN: 1.2%; DR: -0.3%			
			Teriparatide	20μg sc once day	**T-score Baseline**		LS: -2.29 ± 0.57 TH: -1.32 ± 0.78 FN: -1.79 ± 0.67 DR: -2.05 ± 1.21	-	-	-
					%Change	**3 mo**	LS: 2.8%; TH: 0.7%; FN: 1.1%			
						6 mo	LS: 4.8%; TH: 0.5%; FN: 0.5%			
						12 mo	LS: 7.1%; TH: 1.3%; FN: 1.1%; DR: -1.7%			

					placebo	-	**T-score Baseline**	LS: -2.29 ± 0.66 TH: -1.35 ± 0.65 FN: -1.76 ± 0.56 DR: -1.85 ± 1.04	-	-	-
							%Change 3 mo	LS: 0.5%; TH: -0.4%; FN: -0.2%			
							%Change 6 mo	LS: 0.3%; TH: -0.6%; FN: -0.4%			
							%Change 12 mo	LS: -0.1%; TH: -0.7%; FN: -1.1%; DR: -0.9%			
Padhi *et al.* (2014)[41]	48	32 women	46	31 women	Romosozumab	1mg/kg sc every 2 weeks	**T-score Baseline**	LS: -1.22 ± 0.93 TH: -0.88 ± 0.67 FN: -1.33 ± 0.41 DR: -0.93 ± 0.62	-	-	-
						2mg/kg sc every 4 weeks	**T-score Baseline**	LS: -1.24 ± 0.46 TH: -0.90 ± 0.68 FN: -1.72 ± 0.37 DR: -0.55 ± 1.25	-	-	-
						2mg/kg sc every 2 weeks	**T-score Baseline**	LS: -1.27 ± 0.29 TH: -1.17 ± 0.56 FN: -1.58 ± 0.64 DR: -1.37 ± 1.43	-	-	-
						3mg/kg sc every 4 weeks	**T-score Baseline**	LS: -1.58 ± 0.47 TH: -0.72 ± 0.54 FN: -1.10 ± 0.64 DR: -0.83 ± 0.48	-	-	-
					placebo	-	**T-score Baseline**	LS: -1.29 ± 0.67 TH: -1.12 ± 0.85 FN: -1.57 ± 0.79 DR: -1.18 ± 1.14	-	-	-
		16 men		15 men	Romosozumab	1mg/kg sc every 2 weeks	**T-score Baseline**	LS: -1.15 ± 0.76 TH: -0.90 ± 0.85 FN: -1.42 ± 0.89 DR: -0.23 ± 0.93	-	-	-
						3mg/kg sc every 4 weeks	**T-score Baseline**	LS: -0.75 ± 1.16 TH: -0.55 ± 0.67 FN: -0.97 ± 0.63 DR: -0.08 ± 0.76	-	-	-

BMD – Bone Mineral Density; **BMC** – Bone Mineral Content **BA/TA** – Bone Area per Total Area; **BV/TV** – Bone Volume Fraction; **TM** – Tibia Metaphysis; **FN** – Femoral Neck; **Tb** – Trabecular; **Ct** – Cortical; **DF** – Distal Femur; **FD** – Femoral Diaphysis; **PTM** – Proximal Tibia Metaphysis; **NL** – Normal-loaded; **UL** – Under-loaded; **LV** – 5th Lumbar Vertebra; **PT** – Proximal Tibia; **%Change** – Percent change from Baseline; **DXA** – Dual energy X-ray Absorptiometry; **pQCT** – Peripheral Quantitative Computed Tomography; **WB** – Whole Body; **LS** – Lumbar Spine; **UDR** – Ultra-distal Radius; **DRM** – Distal Radius Metaphysis; **DRD** – Distal Radius Diaphysis; **PTM** – Proximal Tibial Metaphysis; **CVB** – 5th Caudal Vertebral Body; **LVB** – 4th Lumbar Vertebral Body; **TH** – Total Hip; **DR** – Third Distal Radius; **mo** – months.

Table S8: *Bone Remodeling - Bone Formation Parameters - Part II.*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	Bone Volume		Bone Height		Bone Area
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	-		-		-
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week	-		-		-
					saline vehicle	-	-		-		-
		10 Sham		10 Sham	saline vehicle	-	-		-		-
	45		45		-	-	9 w post extraction: decrease of 38%		9 w post extraction: fast vertical resorption		
					Scl-Ab VI	25mg/kg sc twice week	**2 & 4 wks**	significant increase further increases over time	**2 & 4 wks**	significant increase, with further increases over time	-
							15 wks	42% higher alveolar bone ridge volume than control	**15 wks**	recovery of ≈2/3 of total loss of bone height	
					Scl-Ab VI + DAB	25mg/kg + 25mg/kg sc twice week	**2 & 4 wks**	significant increase further increases over time	**2 & 4 wks**	significant increase, with further increases over time	-
							15 wks	81% higher alveolar bone ridge volume than control	**9 wks**	full recovery of bone height loss	
					saline vehicle	-	decrease over time		**15 wks**	resorption over time total height loss = 0.41mm	-
Wu *et al.* (2018)[55]	40 OVX				Scl-Ab	25mg/kg sc twice week	-		-		-
					PTH 1-34	60μg/kg sc thrice week	-		-		-
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week	-		-		-
					vehicle	-	-		-		-
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	-		-		-
						15 μL of 35.6mg/mL solution locally twice week	-		-		-
					EP: vehicle	-	-		-		-
					healthy: PBS	-	-		-		-
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc twice week	12 weeks: 29.7 ± 11.2 mm^3 2 weeks: 22.7 ± 14.8 mm^3 2-4 weeks: 25.7 ± 16.5 mm^3		-		0-12 weeks: 46.8 ± 16.2 mm^2 0-2 weeks: 31.4 ± 20.1 mm^2 2-4 weeks: 36 ± 17.4 mm^2
					PBS	-	18.3 ± 8.6 mm^3		-		30.3 ± 8.8 mm^2
	30		30		Scl-Ab III	25mg/kg	17.6 ± 7.4 mm^3		-		38.6 ± 23.8 mm^2
					PBS	-	8.5 ± 3.3 mm^3		-		13.1 ± 9.6 mm^2
McDonald *et al.* (2012)[31]	132	66 Sham	127		Scl-Ab III	25mg/kg sc twice week	-		-		-
					saline solution	-	-		-		-
		66 OVX			Scl-Ab III	25mg/kg sc twice week	-		-		-
					saline solution	-	-		-		-
Ominsky *et al.* (2011)[54]	35		32		Scl-Ab III	25mg/kg sc twice week	-				-
					vehicle	-	-				-

Tian *et al.* (2011)[32]	67	67	Scl-Ab III	5mg/kg sc twice week	-	-	-	
				25mg/kg sc twice week	-	-	-	
			saline solution	-	-	-	-	
Li *et al.* (2010)[36]	28	26	Scl-Ab III	25mg/kg sc twice week	-	-	LV: 7.90 ± 0.30 mm^2 FN: 4.73 ± 0.21 mm^2	
				5mg/kg sc twice week	-	-	LV: 6.84 ± 0.23 mm^2 FN: 4.01 ± 0.18 mm^2	
			vehicle	-	-	-	LV: 4.75 ± 0.20 mm^2 FN: 3.69 ± 0.15 mm^2	
Ominsky *et al.* (2010)[59]	12	12	Scl-Ab IV	3mg/kg sc once month	-	-	**pQCT**	DRM: 2.2 ± 2.6 % PTM: 5.7 ± 9.9 %
				10mg/kg sc once month	-	-	**pQCT**	DRM: -0.7 ± 2.1 % PTM: 5.8 ± 2.6 %
				30mg/kg sc once month	-	-	**pQCT**	DRM: 4.7 ± 3.2 % PTM: 7.0 ± 2.4 %
			vehicle	-	-	-	**pQCT**	DRM: -1.7 ± 1.3 % PTM: -3.6 ± 2.1 %
Tian *et al.* (2010)[57]	32	32	Scl-Ab III	5mg/kg sc twice week	-	-	-	
				25mg/kg sc twice week	-	-	-	
			saline solution	-	-	-	-	
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → Alendronate	210mg sc once month → 70mg po once week	-	-	-	
			Alendronate → Alendronate	70mg po once week → 70mg po once week	-	-	-	
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc every 3 moths	-	-	-	
				210mg sc every 3 months	-	-	-	
				70mg sc once month	-	-	-	
				140mg sc once month	-	-	-	
				210mg sc once month	-	-	-	
			Alendronate	70 mg po once week	-	-	-	
			Teriparatide	20μg sc once day	-	-	-	
			placebo	-	-	-	-	
Padhi *et al.* (2014)[41]	48	32 women 16 men	46	31 women 15 men	Romosozumab	1mg/kg sc every 2 weeks	-	-	-
						2mg/kg sc every 4 weeks	-	-	-
						2mg/kg sc every 2 weeks	-	-	-
						3mg/kg sc every 4 weeks	-	-	-
					placebo	-	-	-	-
					Romosozumab	1mg/kg sc every 2 weeks	-	-	-
						3mg/kg sc every 4 weeks	-	-	-

Tb – Trabecular; **LV** – 5th Lumbar Vertebra; **DF** – Distal Femur; **FN** – Femoral Neck; **pQCT** – Peripheral Quantitative Computed Tomography; **DRM** – Distal Radius Metaphysis; **PTM** – Proximal Tibial Metaphysis.

Table S9: *Bone Remodeling - Bone Formation Parameters - Part III*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	Tb.Ar	Ct.Ar	M.Ar	Tt.Ar	Ct.Ar/Tt.Ar
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	-	-	-	-	-
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week	-	-	-	-	-
					saline vehicle	-	-	-	-	-	-
		10 Sham		10 Sham	saline vehicle	-	-	-	-	-	-
	45		45		Scl-Ab VI	25mg/kg sc twice week	-	-	-	-	-
					Scl-Ab VI + DAB	25mg/kg sc + 25mg/kg sc twice week	-	-	-	-	-
					saline vehicle	-	-	-	-	-	-
Wu *et al.* (2018)[55]	40 OVX		40 OVX		Scl-Ab	25mg/kg sc twice week	-	-	-	-	-
					PTH 1-34	60μg/kg sc thrice week	-	-	-	-	-
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week	-	-	-	-	-
					vehicle	-	-	-	-	-	-
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	-	-	-	-	-
						15 μL of 35.6mg/mL solution locally twice week	-	-	-	-	-
					EP: vehicle	-	-	-	-	-	-
					healthy: PBS	-	-	-	-	-	-
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc twice week	-	-	-	-	-
					PBS	-	-	-	-	-	-
	30		30		Scl-Ab III	25mg/kg	-	-	-	-	-
					PBS	-	-	-	-	-	-
McDonald *et al.* 2012)[31]	132	66 Sham	127		Scl-Ab III	25mg/kg sc twice week	-	-	-	-	-
					saline solution	-	-	-	-	-	-
		66 OVX			Scl-Ab III	25mg/kg sc twice week	-	-	-	-	-
					saline solution	-	-	-	-	-	-
Ominsky *et al.* (2011)[54]	35		32		Scl-Ab III	25mg/kg sc twice week	-	-	-	-	-
					vehicle	-	-	-	-	-	-
Tian *et al.* (2011)[32]	67		67		Scl-Ab III	5mg/kg sc. twice week	-	-	-	-	-
						25mg/kg sc. twice week	-	-	-	-	-
					saline solution	-	-	-	-	-	-

Li *et al.* (2010)[36]	28	26	Scl-Ab III	25mg/kg sc. twice week	LV: 3.15 ± 0.20 mm^2	**HMM**	TS 6.80 ± 0.24 mm^2	TS: 0.92 ± 0.04 mm^2	TS: 7.72 ± 0.26 mm^2	TS: 83.2 ± 1.1 %
						***μ*CT**	LV: 4.75 ± 0.12 mm^2 FD: 11.67 ± 0.32 mm^2			
				5mg/kg sc. twice week	LV: 2.55 ± 0.14 mm^2	**HMM**	TS 5.79 ± 0.48 mm^2	TS: 0.97 ± 0.09 mm^2	TS: 6.76 ± 0.51 mm^2	TS: 88.0 ± 0.5 %
						***μ*CT**	LV: 4.29 ± 0.12 mm^2 FD: 11.62 ± 0.43 mm^2			
			vehicle	-	LV: 1.67 ± 0.11 mm^2	**HMM**	TS 6.17 ± 0.13 mm^2	TS: 1.25 ± 0.09 mm^2	TS: 7.43 ± 0.15 mm^2	TS: 85.3 ± 1.3 %
						***μ*CT**	LV: 3.08 ± 0.11 mm^2 FD: 9.67 ± 0.32 mm^2			
Ominsky *et al.* (2010)[59]	12	12	Scl-Ab IV	3mg/kg sc. once month	-	**pQCT**	DRD: 7.2 ± 8.5 % PTD: 11.5 ± 13.5%	-	-	-
				10mg/kg sc. Once month	-	**pQCT**	DRD: 5.0 ± 3.3 % PTD: 12.1 ± 3.0 %	-	-	-
				30mg/kg sc. once month	-	**pQCT**	DRD: 10.0 ± 4.2 % PTD: 12.6 ± 3.7 %	-	-	-
			vehicle	-	-	**pQCT**	DRD: 2.8 ± 1.2 % PTD: 1.2 ± 3.2 %	-	-	-
Tian *et al.* (2010)[57]	32	32	Scl-Ab III	5mg/kg sc. twice week	-	-		-	-	-
				25mg/kg sc. twice week	-	-		-	-	-
			saline solution	-	-	-		-	-	-
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → Alendronate	210mg sc. once month → 70mg po. once week	-	-		-	-	-
			Alendronate → Alendronate	70mg po. once week → 70mg po. once week	-	-		-	-	-
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc. every 3 months	-	-		-	-	-
				210mg sc. every 3 months	-	-		-	-	-
				70mg sc. once month	-	-		-	-	-
				140mg sc. once month	-	-		-	-	-
				210mg sc. once month	-	-		-	-	-
			Alendronate	70 mg po. once week	-	-		-	-	-
			Teriparatide	20*μ*g sc. once day	-	-		-	-	-
			placebo	-	-	-		-	-	-
Padhi *et al.* (2014)[41]	48 (32 women / 16 men)	46 (31 women / 15 men)	romosozumab	1mg/kg sc. every 2 weeks	-	-		-	-	-
				2mg/kg sc. every 4 weeks	-	-		-	-	-
				2mg/kg sc. every 2 weeks	-	-		-	-	-
				3mg/kg sc. every 4 weeks	-	-		-	-	-
			placebo	-	-	-		-	-	-
			romosozumab	1mg/kg sc. every 2 weeks	-	-		-	-	-
				3mg/kg sc. every 4 weeks	-	-		-	-	-

Tb.Ar Trabecular Area; **Ct.Ar** – Cortical Area; **M.Ar** – Medullary Area; **Tt.Ar** - Total cross-sectional Area/Subperiosteal Area; **Ct.Ar/Tt.Ar** – Cortical Area per Total Cross-sectional Area; **LV** – 5th Lumbar Vertebra; **HMM** – Histomorphometry; ***μ*CT** – Micro computed tomography; **TS** – Tibial Shaft; **FD** – Femoral Diaphysis; **pQCT** – Peripheral Quantitative Computed Tomography; **pQCT** – Peripheral Quantitative Computed Tomography; **DRD** – Distal Radius Diaphysis; **PTD** – Proximal Tibial Diaphysis.

Table S10: *Bone Remodeling - Bone Formation Parameters - Part IV*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	Tb.Th	Tb.N	Tb.Sp	Ct.Th
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	higher increase than both control (Sham & OVX)	-	-	-
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week		-	-	-
					saline vehicle	-	-	-	-	-
		10 Sham		10 Sham	saline vehicle	-	-	-	-	-
	45		45		Scl-Ab VI	25mg/kg sc twice week	-	-	-	-
					Scl-Ab VI + DAB	25mg/kg sc + 25mg/kg sc twice week	-	-	-	-
					saline vehicle	-	-	-	-	-
Wu *et al.* (2018)	40 OVX		40 OVX		Scl-Ab	25mg/kg sc.twice week	1.27 higher increase vs control	1.59 higher increase vs control	2.1 higher decrease vs control	-
					PTH 1-34	60μg/kg sc thrice week	1.29 higher increase vs control	1.60 higher increase vs control	2.2 higher decrease vs control	-
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week	1.66 higher increase vs control	1.85 higher increase vs control	3.31 higher decrease vs control	-
					vehicle	-	-	-	-	-
Taut *et al.* (2013)	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	-	-	-	-
						15 μL of 35.6mg/mL solution locally twice week	-	-	-	-
					EP: vehicle	-	-	-	-	-
					healthy: PBS	-	-	-	-	-
Virk *et al.* (2013)	72		72		Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					PBS	-	-	-	-	-
	30		30		Scl-Ab III	25mg/kg	-	-	-	-
					PBS	-	-	-	-	-
McDonald *et al.* (2012)	132	66 Sham	127		Scl-Ab III	25mg/kg sc twice week	1 week: 53.5 ± 9.39 μm^2 2 weeks: 96.1 ± 10.5 μm^2 3 weeks: 169.8 ± 40.5 μm^2	1 week: 1.52 ± 0.91 N/mm 2 weeks: 3.30 ± 0.57 N/mm 3 weeks: 2.16 ± 0.46 N/mm	-	-
					saline solution	-	1 week: 58.3 ± 9.15 μm^2 2 weeks: 84.6 ± 9.1 μm^2 3 weeks: 148.9 ± 64.3 μm^2	1 week: 1.37 ± 0.73 N/mm 2 weeks: 3.30 ± 0.47 N/m 3 weeks: 2.02 ± 0.61 N/mm	-	-
		66 OVX			Scl-Ab III	25mg/kg sc twice week	1 week: 63.0 ± 11.3 μm^2 2 weeks: 105.3 ± 18.7 μm^2 3 weeks: 199.1 ± 95.9 μm^2	1 week: 2.87 ± 0.86 N/mm 2 weeks: 2.40 ± 0.53 N/mm 3 weeks: 1.09 ± 0.48 N/mm	-	-
					saline solution	-	1 week: 69.8 ± 27.2 μm^2 2 weeks: 89.5 ± 12.1 μm^2 3 weeks: 168.6 ± 77.2 μm^2	1 week: 2.84 ± 1.15 N/mm 2 weeks: 1.72 ± 0.50 N/mm 3 weeks: 0.88 ± 0.23 N/mm	-	-
Ominsky *et al.* (2011)	35		32		Scl-Ab III	25mg/kg sc twice week	**Intact Femur:** DF: 97.4 ± 2.7 μm	-	-	**Intact Femur:** FD: 922 ± 18 μm
					vehicle	-	**Intact Femur:** DF: 56.5 ± 1.4 μm	-	-	**Intact Femur:** FD: 838 ± 19 μm

Tian *et al.* (2011)	67	67	**Baseline**		PTM: 45.3 ± 6.4 μm		PTM: 3.1 ± 0.7 #/mm		PTM: 297.8 ± 99.0 μm		PTM: 645 ± 33 μm	
			Scl-Ab III	5mg/kg sc twice week	NL.PTM: 75.5 ± 9.9 μm UL.PTM: 57.9 ± 5.7 μm		NL.PTM: 3.2 ± 1.0 #/mm UL.PTM: 3.4 ± 0.4 #/mm		NL.PTM: 310.9 ± 271.9 μm UL.PTM: 245.0 ± 42.2 μm		NL.PTM: 677 ± 18 μm UL.PTM: 686 ± 37 μm	
				25mg/kg sc twice week	NL.PTM: 93.6 ± 10.7 μm UL.PTM: 71.3 ± 7.1 μm		NL.PTM: 3.7 ± 0.3 #/mm UL.PTM: 2.9 ± 0.7 #/mm		NL.PTM: 180.3 ± 33.3 μm UL.PTM: 300.3 ± 156.1 μm		NL.PTM: 723 ± 43 μm UL.PTM: 723 ± 44 μm	
			saline solution	-	NL.PTM: 44.5 ± 2.8 μm UL.PTM: 41.9 ± 3.3 μm		NL.PTM: 3.1 ± 0.5 #/mm UL.PTM: 3.2 ± 0.4 #/mm		NL.PTM: 285.2 ± 65.6 μm UL.PTM: 271.6 ± 36.7 μm		NL.PTM: 658 ± 36 μm UL.PTM: 651 ± 52 μm	
Li *et al.* (2010)	28	26	Scl-Ab III	25mg/kg sc twice week	**HMM**	PT: 144.7 ± 12.4 μm	**HMM**	PT: 1.31 ± 0.11 *n*/mm	**HMM**	PT: 661 ± 66 μm	**HMM**	PT: 1.14 ± 0.02 mm
					μCT	LV: 138.0 ± 4.6 μm DF: 124.5 ± 7.0 μm	**μCT**	LV: 3.45 ± 0.15mm^{-1} DF: 2.15 ± 0.20mm^{-1}	**μCT**	LV: 267 ± 31 μm DF: 512.3 ± 49.2 μm	**μCT**	LV: 325 ± 9 μm DF: 0.948 ± 0.021 mm
				5mg/kg sc twice week	**HMM**	PT: 137.8 ± 7.0 μm	**HMM**	PT: 1.22 ± 0.22 *n*/mm	**HMM**	PT: 829 ± 145 μm	**HMM**	PT: 1.03 ± 0.05 mm
					μCT	LV: 108.8 ± 4.6 μm DF: 109.7 ± 6.2 μm	**μCT**	LV: 3.37 ± 0.17 mm^{-1} DF: 2.12 ± 0.24 mm^{-1}	**μCT**	LV: 307 ± 31 μm DF: 518.7 ± 42.0 μm	**μCT**	LV: 291 ± 9 μm DF: 0.980 ± 0.040 mm
			vehicle	-	**HMM**	PT: 74.3 ± 2.8 μm	**HMM**	PT: 0.96 ± 0.10 *n*/mm	**HMM**	PT: 1086 ± 133 μm	**HMM**	PT: 1.02 ± 0.02 mm
					μCT	LV: 60.1 ± 1.9 μm DF: 60.6 ± 1.4 μm	**μCT**	LV: 3.34 ± 0.17 mm^{-1} DF: 1.27 ± 0.17 mm^{-1}	**μCT**	LV: 324 ± 23 μm DF: 741.0 ± 52.9 μm	**μCT**	LV: 231 ± 6 μm DF: 0.803 ± 0.037 mm
Ominsky *et al.* (2010)	12	12	Scl-Ab IV	3mg/kg sc once month	-		-		-		**pQCT**	DRD: 7.3 ± 7.1 % PTD: 13.4 ± 14.2 %
				10mg/kg sc once month	-		-		-		**pQCT**	DRD: 1.6 ± 1.1 % PTD: 10.8 ± 4.3 %
				30mg/kg sc once month	-		-		-		**pQCT**	DRD: 4.3 ± 2.4 % PTD: 10.2 ± 2.6 %
			vehicle	-	-		-		-		**pQCT**	DRD: 2.1 ± 0.9 % PTD: 0.6 ± 3.4 %
Tian *et al.* (2010)	32	32	**Baseline**		CVB: 50.8 ± 6.0 μm LVB: 65.1 ± 11.1 μm		CVB: 5.1 ± 0.7 #/mm LVB: 3.9 ± 0.3 #/mm		CVB: 149.8 ± 24.7 μm LVB: 195.4 ± 22.5 μm		-	
			Scl-Ab III	5mg/kg sc twice week	CVB: 54.5 ± 10.5 μm LVB: 91.6 ± 6.8 μm		CVB: 5.5 ± 0.7 #/mm LVB: 3.5 ± 0.2 #/mm		CVB: 130.5 ± 16.7 μm LVB: 197.1 ± 20.5 μm		-	
				25mg/kg sc twice week	CVB: 65.3 ± 7.0 μm LVB: 119.4 ± 17.7 μm		CVB: 5.7 ± 0.6 #/mm LVB: 3.8 ± 0.4 #/mm		CVB: 111.2 ± 21.9 μm LVB: 144.5 ± 18.7 μm		-	
			saline solution	-	CVB: 45.7 ± 6.8 μm LVB: 62.2 ± 7.2 μm		CVB: 5.2 ± 0.4 #/mm LVB: 3.9 ± 0.6 #/mm		CVB: 147.4 ± 15.3 μm LVB: 196.2 ± 35.7 μm		-	
Saag *et al.* (2017)	4093	3150	Romosozumab → Alendronate	210mg sc once month → 70mg po once week	-		-		-		-	
			Alendronate → Alendronate	70mg po once week → 70mg po once week	-		-		-		-	
McClung *et al.* (2014)	419	383	Romosozumab	140mg sc every 3 months	-		-		-		-	
				210mg sc every 3 months	-		-		-		-	
				70mg sc once month	-		-		-		-	
				140mg sc once month	-		-		-		-	
				210mg sc once month	-		-		-		-	
			alendronate	70 mg po once week	-		-		-		-	
			teriparatide	20μg sc once day	-		-		-		-	
			placebo	-	-		-		-		-	

Padhi *et al.* (2014)	48	32 women	46	31 women	Romosozumab	1mg/kg sc every 2 weeks	-	-	-	-
						2mg/kg sc every 4 weeks	-	-	-	-
						2mg/kg sc every 2 weeks	-	-	-	-
						3mg/kg sc every 4 weeks	-	-	-	-
					placebo	-	-	-	-	-
		16 men		15 men	Romosozumab	1mg/kg sc every 2 weeks	-	-	-	-
						3mg/kg sc every 4 weeks	-	-	-	-

Tb.Th – Trabecular Thickness; **Tb.N** – Trabecular Number; **Tb.Sp** – Trabecular Separation; **Ct.Th** – Cortical Thickness; **DF** – Distal Femur; **FD** – Femoral Diaphysis; **PTM** – Proximal Tibial Metaphysis; **NL** – Normal-loaded; **UL** – Under-loaded; **HMM** – Histomorphometry; **μCT** – Micro computed tomography; **PT** – Proximal Tibia; **LV** – 5th Lumbar Vertebra; **pQCT** – Peripheral Quantitative Computed Tomography; **DRD** – Distal Radius Diaphysis; **PTD** – Proximal Tibial Diaphysis; **CVB** – Caudal Vertebral Body; **LVB** – Lumbar Vertebral Body

Table S11: *Bone Remodeling – Bone Formation Parameters – Part V*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	SMI	MS/BS	MAR	BFR/BS
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	-	-	-	sig. higher in basal & alveolar bone vs control
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week	-	-	-	sig. higher in basal & alveolar bone vs control; higher than Scl-Ab group, in basal bone
					saline vehicle	-	-	-	-	-
		10 Sham		10 Sham	saline vehicle	-	-	-	-	-
	45		45		Scl-Ab VI	25mg/kg sc twice week	-	-	-	-
					Scl-Ab VI + DAB	25mg/kg sc + 25mg/kg sc twice week	-	-	-	-
					saline vehicle	-	-	-	-	-
Wu *et al.* (2018)[55]	40 OVX		40 OVX		Scl-Ab	25mg/kg sc twice week	-	-	-	-
					PTH 1-34	60μg/kg sc thrice week	-	-	-	-
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week	-	-	-	-
					vehicle	-	-	-	-	-
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	-	-	-	-
						15 μL of 35.6mg/mL solution locally twice week	-	-	-	-
					EP: vehicle	-	-	-	-	-
					healthy: PBS	-	-	-	-	-
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					PBS	-	-	-	-	-
	30		30		Scl-Ab III	25mg/kg	-	-	-	-
					PBS	-	-	-	-	-
McDonald *et al.* (2012)[31]	132	66 Sham	127		Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					saline solution	-	-	-	-	-
		66 OVX			Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					saline solution	-	-	-	-	-
Ominsky *et al.* (2011)[54]	35		32		Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					vehicle	-	-	-	-	-
Tian *et al.* (2011)[32]	67		67		**Baseline**		-	PTM: 24.6 ± 7.3 % Ps.TS: 26.1 ± 7.8 % Ec.TS: 17.3 ± 7.0 %	PTM: 0,7 ± 0,1 μm/day Ps.TS: 0.5 ± 0.2 μm/day Ec.TS: 0.5 ± 0.1 μm/day	PTM: 17.9 ± 6.1 $\mu m^3/\mu m^2$/day×100 Ps.TS: 12.7 ± 6.5 $\mu m^3/\mu m^2$/day×100 Ec.TS: 9.5 ± 5.4 $\mu m^3/\mu m^2$/day×100
					Scl-Ab III	5mg/kg sc twice week	-	**NL**: PTM: 55.1 ± 3.8 % Ps.TS: 46.3 ± 15.8 % Ec.TS: 65.1 ± 13.9 %	**NL**: PTM: 1.0 ± 0.1 μm/day Ps.TS: 0.7 ± 0.1 μm/day Ec.TS: 1.5 ± 0.2 μm/day	**NL**: PTM: 55.4 ± 8.7 $\mu m^3/\mu m^2$/day×100 Ps.TS: 34.9 ±17.7 $\mu m^3/\mu m^2$/day×100 Ec.TS: 99.5 ± 25.3 $\mu m^3/\mu m^2$/day×100
								UL: PTM: 44.4 ± 5.0 % Ps.TS: 48.2 ± 13.7 % Ec.TS: 51.0 ± 10.0 %	**UL**: PTM: 0.8 ± 0.1 μm/day Ps.TS: 1.0 ± 0.1 μm/day Ec.TS: 1.3 ± 0.3 μm/day	**UL**: PTM: 37.6 ± 6.9 $\mu m^3/\mu m^2$/day×100 Ps.TS: 48.6 ± 18.4 $\mu m^3/\mu m^2$/day×100 Ec.TS: 67.8 ± 23.2 $\mu m^3/\mu m^2$/day×100

				25mg/kg sc twice week	-	NL	PTM: 69.2 ± 2.6 % Ps.TS: 85.9 ± 11.0 % Ec.TS: 84.9 ± 12.5 %	NL	PTM: 1.1 ± 0.1 μm/day Ps.TS: 1.1 ± 0.2 μm/day Ec.TS: 1.7 ± 0.1 μm/day	NL	PTM: 75.7 ± 9.6 $\mu m^3/\mu m^2$/day×100 Ps.TS: 95.9 ± 27.9 $\mu m^3/\mu m^2$/day×100 Ec.TS: 148.9 ± 27.0 $\mu m^3/\mu m^2$/day×100
						UL	PTM: 56.8 ± 7.2 % Ps.TS: 72.7 ± 10.1 % Ec.TS: 84.5 ± 9.7 %	UL	PTM: 1.0 ± 0.2 μm/day Ps.TS: 1.7 ± 0.2 μm/day Ec.TS: 1.7 ± 0.2 μm/day	UL	PTM: 55.7 ± 15.1 $\mu m^3/\mu m^2$/day×100 Ps.TS: 120.0 ± 26.1 $\mu m^3/\mu m^2$/day×100 Ec.TS: 141 ± 26 $\mu m^3/\mu m^2$/day×100
			saline solution	-	-	NL	PTM: 27.6 ± 4.5 % Ps.TS: 30.6 ± 12.6 % Ec.TS: 25.1 ± 6.9 %	NL	PTM: 0,7 ± 0.1 μm/day Ps.TS: 0.5 ± 0.2 μm/day Ec.TS: 0.6 ± 0.2 μm/day	NL	PTM: 20.1 ± 3.1 $\mu m^3/\mu m^2$/day×100 Ps.TS: 17.1 ± 11.2 $\mu m^3/\mu m^2$/day×100 Ec.TS: 16.7 ± 8.7 $\mu m^3/\mu m^2$/day×100
						UL	PTM: 25.7 ± 2.3 % Ps.TS: 24.0 ± 8.8 % Ec.TS: 19.3 ± 2.3 %	UL	PTM: 0,6 ± 0.1 μm/day Ps.TS: 0.9 ± 0.3 μm/day Ec.TS: 0.5 ± 0.2 μm/day	UL	PTM: 14.1 ± 3.6 $\mu m^3/\mu m^2$/day×100 Ps.TS: 22.0 ± 12.7 $\mu m^3/\mu m^2$/day×100 Ec.TS: 10.2 ± 2.7 $\mu m^3/\mu m^2$/day×100
Li *et al.* (2010)[36]	28	26	Scl-Ab III	25mg/kg sc twice week	LV: -0.99 ± 0.32	PT: 74.7 ± 2.5 % Ps.TS: 99.8 ± 1.0 % Ec.TS: 84.5 ± 4.3 %		PT: 1.59 ± 0.08 μm/day Ps.TS: 1.92 ± 0.11 μm/day Ec.TS: 1.66 ± 0.14 μm/day		PT: 1.20 ± 0.08 $\mu m^3/\mu m^2$/day Ps.TS: 1.92 ± 0.12 $\mu m^3/\mu m^2$/day Ec.TS: 1.43 ± 0.17 $\mu m^3/\mu m^2$/day	
				5mg/kg sc twice week	LV: -0.49 ± 0.24	PT: 68.7 ± 2.7 % Ps.TS: 98.1 ± 2.1 % Ec.TS: 69.0 ± 6.9 %		PT: 1.57 ± 0.10 μm/day Ps.TS: 2.13 ± 0.11 μm/day Ec.TS: 1.24 ± 0.05 μm/day		PT: 1.09 ± 0.10$\mu m^3/\mu m^2$/day Ps.TS: 2.10 ± 0.13 $\mu m^3/\mu m^2$/day Ec.TS: 0.84 ± 0.07 $\mu m^3/\mu m^2$/day	
			vehicle	-	LV: 0.40 ± 0.14	PT: 26.0 ± 2.2 % Ps.TS: 20.7 ± 3.6 % Ec.TS: 36.7 ± 8.2 %		PT: 0.98 ± 0.02 μm/day Ps.TS: 0.79 ± 0.18 μm/day Ec.TS: 0.71 ± 0.17 μm/day		PT: 0.25 ± 0.02 $\mu m^3/\mu m^2$/day Ps.TS: 0.20 ± 0.06 $\mu m^3/\mu m^2$/day Ec.TS: 0.37 ± 0.11 $\mu m^3/\mu m^2$/day	
Ominsky *et al.* (2010)[59]	12	12	Scl-Ab IV	3mg/kg sc once month	-	-		-		-	
				10mg/kg sc once month	-	-		-		-	
				30mg/kg sc once month	-	-		-		sig. increase in Ec.BFR/BS & non sig. increase in Ps.BFR/BS	
			vehicle	-	-	-		-		-	
Tian *et al.* (2010)[57]	32	32	**Baseline**		-	CVB: 5.3 ± 4.8 % LVB: 25.9 ± 8.6 %		CVB: 0.4 ± 0.1 μm/day LVB: 0.7 ± 0.1 μm/day		CVB: 1.9 ± 1.4 $\mu m^3/\mu m^2$/day×100 LVB: 16.9 ± 6.3 $\mu m^3/\mu m^2$/day×100	
			Scl-Ab III	5mg/kg sc twice week	-	CVB: 22.2 ± 16.3 % LVB: 59.6 ± 5.7 %		CVB: 0.6 ± 0.1 μm/day LVB: 0.9 ± 0.0 μm/day		CVB: 12.6 ± 9.6 $\mu m^3/\mu m^2$/day×100 LVB: 54.2 ± 4.0 $\mu m^3/\mu m^2$/day×100	
				25mg/kg sc twice week	-	CVB: 47.5 ± 13.2 % LVB: 78.7 ± 4.1 %		CVB: 0.6 ± 0.0 μm/day LVB: 1.0 ± 0.1 μm/day		CVB: 30.2 ± 8.2 $\mu m^3/\mu m^2$/day×100 LVB: 79.0 ± 6.6 $\mu m^3/\mu m^2$/day×100	
			saline solution	-	-	CVB: 7.0 ± 3.3 % LVB: 23.7 ± 6.3 %		CVB: 0.4 ± 0.1 μm/day LVB: 0.6 ± 0.1 μm/day		CVB: 2.9 ± 1.4 $\mu m^3/\mu m^2$/day×100 LVB: 14.7 ± 5.1 $\mu m^3/\mu m^2$/day×100	
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → Alendronate	210mg sc once month → 70mg po once week	-	-		-		-	
			Alendronate → Alendronate	70mg po once week → 70mg po once week	-	-		-		-	
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc every 3 months	-	-		-		-	
				210mg sc every 3 months	-	-		-		-	
				70mg sc once month	-	-		-		-	
				140mg sc once month	-	-		-		-	
				210mg sc once month	-	-		-		-	
			Alendronate	70 mg po once week	-	-		-		-	
			Teriparatide	20μg sc once day	-	-		-		-	
			placebo	-	-	-		-		-	

Padhi *et al.* (2014)[41]	48	32 women	46	31 women	Romosozumab	1mg/kg sc every 2 weeks	-	-	-	-
						2mg/kg sc every 4 weeks	-	-	-	-
						2mg/kg sc every 2 weeks	-	-	-	-
						3mg/kg sc every 4 weeks	-	-	-	-
					placebo	-	-	-	-	-
		16 men		15 men	Romosozumab	1mg/kg sc every 2 weeks	-	-	-	-
						3mg/kg sc every 4 weeks	-	-	-	-

SMI – Structural Model Index; **MS/BS** – Mineralizing Surface; **MAR** – Mineral Apposition Rate; **BFR/BS** – Bone Formation Rate; **PTM** – Proximal Tibia Metaphysis; **Ps** – Periosteal; **Ec** – Endocortical; **TS** – Tibial Shaft; **NL** – Normal-loaded; **UL** – Under-loaded; **pQCT** – Peripheral Quantitative Computed Tomography; **DRD** – Distal Radius Diaphysis; **PTD** – Proximal Tibial Diaphysis; **LV** – 5th Lumbar Vertebra; **CVB** – Caudal Vertebral Body; **LVB** – Lumbar Vertebral Body.

Table S 12: *Bone Remodeling - Bone Formation Parameters - Part VI*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	ES/BS	Oc.S/BS	Oc.N/BS		Fat Cell Volume
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc. twice week	significantly lower than OVX-vehicle	-	-		-
					Scl-Ab VI + DAB	18.1mg/kg sc. + 18.1mg/kg sc. twice week		-	-		-
					saline vehicle	-	higher in alveolar and basal bone than Sham group	-	-		-
		10 Sham		10 Sham	saline vehicle	-	-	-	-		-
	45		45		Scl-Ab VI	25mg/kg sc. twice week	-	-	-		-
					Scl-Ab VI + DAB	25mg/kg sc. + 25mg/kg sc. twice week	-	-	-		-
					saline vehicle	-	-	-	-		-
Wu *et al.* (2018)[55]	40 OVX		40 OVX		Scl-Ab	25mg/kg sc. twice week	-	-	-		-
					PTH 1-34	60μg/kg sc. thrice week	-	-	-		-
					Scl-Ab + PTH 1-34	25mg/kg sc. twice week + 60μg/kg sc thrice week	-	-	-		-
					vehicle	-	-	-	-		-
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc. twice week	-	-	-		-
						15 μL of 35.6mg/mL solution locally twice week	-	-	-		-
					EP: vehicle	-	-	-	-		-
					healthy: PBS	-	-	-	-		-
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc. twice week	-	-	-		-
					PBS	-	-	-	-		-
	30		30		Scl-Ab III	25mg/kg	-	-	-		-
					PBS	-	-	-	-		-
McDonald *et al.* (2012)[31]	132	66 Sham	127		Scl-Ab III	25mg/kg sc. twice week	-	-	**Center**	2 weeks: 0.002 ± 0.001 N/mm 3 weeks: 0.002 ± 0.001 N/mm	-
									Cortical	2 weeks: 0.002 ± 0.001 N/mm 3 weeks: 0.002 ± 0.001 N/mm	
					saline solution	-	-	-	**Center**	2 weeks: 0.004 ± 0.001 N/mm 3 weeks: 0.002 ± 0.001 N/mm	-
									Cortical	2 weeks: 0.004 ± 0.001 N/mm 3 weeks: 0.002 ± 0.001 N/mm	
		66 OVX			Scl-Ab III	25mg/kg sc. twice week	-	-	**Center**	2 weeks: 0.002 ± 0.001 N/mm 3 weeks: 0.002 ± 0.001 N/mm	-
									Cortical	2 weeks: 0.003± 0.001 N/mm 3 weeks: 0.002 ± 0.001 N/mm	
					saline solution	-	-	-	**Center**	2 weeks: 0.002 ± 0.001 N/mm 3 weeks: 0.002 ± 0.001 N/mm	-
									Cortical	2 weeks: 0.003± 0.001 N/mm 3 weeks: 0.001 ± 0.001 N/mm	

Ominsky *et al.* (2011)[54]	35	32	Scl-Ab III	25mg/kg sc. twice week	-	-	-	
			vehicle	-	-	-	-	
Tian *et al.* (2011)[32]	67	67	**Baseline**		PTM: 3.2 ± 1.1 % Ec.TS: 3.3 ± 1.0 %	-	-	-
			Scl-Ab III	5mg/kg sc. twice week	**NL** PTM: 1.7 ± 0.6 % Ec.TS: 0.8 ± 0.4 %	-	-	-
					UL PTM: 3.2 ± 1.0 % Ec.TS: 1.2 ± 1.2 %			
				25mg/kg sc. twice week	**NL** PTM: 0.8 ± 0.3 % Ec.TS: 0.3 ± 0.2 %	-	-	-
					UL PTM: 2.7 ± 0.9 % Ec.TS: 0.5 ± 0.2 %			
			saline solution	-	**NL** PTM: 3.4 ± 0.8 % Ec.TS: 3.6 ± 1.2 %	-	-	-
					UL PTM: 4.7 ± 0.8 % Ec.TS: 4.4 ± 2.5 %			
Li *et al.* (2010)[36]	28	26	Scl-Ab III	25mg/kg sc. twice week	-	PT: 3.7 ± 0.9%	-	-
				5mg/kg sc. twice week	-	PT: 3.1 ± 0.8%	-	-
			vehicle	-	-	PT: 2.5 ± 0.2%	-	-
Ominsky *et al.* (2010)[59]	12	12	Scl-Ab IV	3mg/kg sc. once month	-	-	-	-
				10mg/kg sc. Once month	-	-	-	-
				30mg/kg sc. once month	-	-	-	-
			vehicle	-	-	-	-	-
Tian *et al.* (2010)[57]	32	32	**Baseline**		CVB: 1.3 ± 0.5 % LVB: 3.6 ± 0.7 %	-	-	CVB: ~ 100 ± 0 % LVB: 3.8 ± 2.2 %
			Scl-Ab III	5mg/kg sc. twice week	CVB: 1.2 ± 0.4 % LVB: 1.7 ± 0.3 %	-	-	CVB: ~ 100 ± 0 % LVB: 4.4 ± 1.8 %
				25mg/kg sc. twice week	CVB: 1.0 ± 0.3 % LVB: 0.7 ± 0.2 %	-	-	CVB: ~ 100 ± 0 % LVB: 3.1 ± 1.5 %
			saline solution	-	CVB: 1.4 ± 0.3 % LVB: 4.1 ± 0.8 %	-	-	CVB: ~ 100 ± 0 % LVB: 5.5 ± 3.6 %
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → alendronate	210mg sc. once month → 70mg po. once week	-	-	-	-
			alendronate → alendronate	70mg po. once week → 70mg po. once week	-	-	-	-
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc. every 3 months	-	-	-	-
				210mg sc. every 3 months	-	-	-	-
				70mg sc. once month	-	-	-	-
				140mg sc. once month	-	-	-	-
				210mg sc. once month	-	-	-	-
			alendronate	70 mg po. once week	-	-	-	-
			teriparatide	20μg sc. once day	-	-	-	-
			placebo	-	-	-	-	-

Padhi *et al.* (2014)[41]	48	32 women	46	31 women	romosozumab	1mg/kg sc. every 2 weeks	-	-	-	-
						2mg/kg sc. every 4 weeks	-	-	-	-
						2mg/kg sc. every 2 weeks	-	-	-	-
						3mg/kg sc. every 4 weeks	-	-	-	-
					placebo	-	-	-	-	-
		16 men		15 men	romosozumab	1mg/kg sc. every 2 weeks	-	-	-	-
						3mg/kg sc. every 4 weeks	-	-	-	-

ES/BS – Eroded Surface; **Oc.S/BS** – Osteoclast Surface; **Oc.N/BS** – Number of TRAP-positive Cells per Bone Surface; **PTM** – Proximal Tibia Metaphysis; **Ec** – Endocortical; **PT** – Proximal Tibia; **TS** – Tibial Shaft; **NL** – Normal-loaded; **UL** – Under-loaded; **CVB** – Caudal Vertebral Body; **LVB** – Lumbar Vertebral Body.

Table S13: *Bone Remodeling - Bone Formation Markers*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	BSAP	Osteocalcin		P1NP	
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	higher increase than both control (Sham & OVX)	-		-	
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week	higher increase than both control (Sham & OVX)	-		-	
					saline vehicle	-	-	-		-	
		10 Sham		10 Sham	saline vehicle	-	-	-		-	
	45		45		Scl-Ab VI	25mg/kg sc twice week	-	98.6 ± 8.0 ng/mL		91.4 ± 8.4 ng/mL	
					Scl-Ab VI + DAB	25mg/kg sc + 25mg/kg sc twice week	-	91.4 ± 8.4 ng/mL		29.94 ± 2.30 ng/mL	
					saline vehicle	-	-	Intact: 79.5 ± 2.1 ng/mL Extracted: 75.1 ± 5.3 ng/mL		Intact: 25.15 ± 0.84 ng/mL Extracted: 23.76 ± 1.63 ng/mL	
Wu *et al.* (2018)[55]	40 OVX		40 OVX		Scl-Ab	25mg/kg sc twice week		**12 wks**	higher increase vs vehicle no difference vs PTH	**12 wks**	higher increase vs vehicle no difference vs PTH
					PTH 1-34	60μg/kg sc thrice week		**12 wks**	higher increase vs vehicle no difference vs Scl-Ab	**12 wks**	higher increase vs vehicle no difference vs Scl-Ab
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week		**12 wks**	sig. higher increase vs all groups	**12 wks**	sig. higher increase vs all groups
					vehicle	-	-	-		-	
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	-	**3 wks**	sig. higher increase compared to vehicle EP and PSB healthy	**3 wks**	increase compared to vehicle EP and PSB healthy
								6 wks	maintenance of higher values compared to PBS healthy group	**6 wks**	no statistical differences between vehicle EP and PSB healthy
						15 μL of 35.6mg/mL solution locally twice week	-	-		-	
					EP: vehicle	-	-	-		-	
					healthy: PBS	-	-	-		-	
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc twice week	-	-		-	
					PBS	-	-	-		-	
	30		30		Scl-Ab III	25mg/kg	-	**6 wk**	significantly greater than control	**12 wk**	significantly greater than control
					PBS	-	-	-		-	
McDonald *et al.* (2012)[31]	132	66 Sham	127		Scl-Ab III	25mg/kg sc twice week	-	-		-	
					saline solution	-	-	-		-	
		66 OVX			Scl-Ab III	25mg/kg sc twice week	-	-		-	
					saline solution	-	-	-		-	
Ominsky *et al.* (2011)[54]	35		32		Scl-Ab III	25mg/kg sc twice week	-	90.0 ± 4.6 ng/mL		16.0 ± 4.0 ng/mL	
					vehicle	-	-	79.1 ± 2.1 ng/mL		13.2 ± 0.8 ng/mL	
Tian *et al.* (2011)[32]	67		67		Scl-Ab III	5mg/kg sc twice week	-	-		-	
						25mg/kg sc twice week	-	-		-	
					saline solution	-	-	-		-	

Li *et al.* (2010)[36]	28	26	Scl-Ab III	25mg/kg sc twice week	-				Baseline: 33.4 ± 2.0 ng/mL Week1: 92.3 ± 8.6 ng/mL Week3: 66.6 ± 5.0 ng/mL Week5: 62.8 ± 4.1 ng/mL				-			
				5mg/kg sc twice week	-				Baseline: 29.5 ± 3.1 ng/mL Week1: 72.4 ± 8.3 ng/mL Week3: 51.3 ± 3.1 ng/mL Week5: 46.7 ± 2.4 ng/mL				-			
			vehicle	-	-				Baseline: 32.4 ± 1.9 ng/mL Week1: 35.1 ± 2.6 ng/mL Week3: 33.1 ± 1.6 ng/mL Week5: 34.5 ± 2.3 ng/mL				-			
Ominsky *et al.* (2010)[59]	12	12	Scl-Ab IV	3mg/kg sc once month	-				-				-			
				10mg/kg sc once month	-				-				-			
				30mg/kg sc once month	-				-				-			
			vehicle	-	-				-				-			
Tian *et al.* (2010)[57]	32	32	Scl-Ab III	5mg/kg sc twice week	-				-				-			
				25mg/kg sc twice week	-				-				-			
			saline solution	-	-				-				-			
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → Alendronate	210mg sc once month → 70mg po once week	-				-				**12 mo**	levels increased vs. control		
													36 mo	levels decreased and maintained below baseline		
			Alendronate → Alendronate	70mg po once week → 70mg po once week	-				-				levels decreased since the 1st month, remaining below baseline at 36 months			
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc every 3 months	-				-				**Baseline**	49 (38, 67) μg/L		
					%Change	**1 wk**	15.6 (8.2, 21.8) %		**%Change**	**1 wk**	8.1 (−2.0, 20.4) %		**%Change**	**1 wk**	51.2 (37.6, 87.4) %	
						1 mo	33.1 (18.7, 51.2) %			**1 mo**	64.1 (38.5, 88.2) %			**1 mo**	61.6 (23.8, 104.7) %	
						2 mo	−9.7 (−20.2, 7.3) %			**2 mo**	7.1 (−5.7, 32.5) %			**2 mo**	−13.8 (−23.9, 1.0) %	
						3 mo	−18.7 (−30.1, −3.8) %			**3 mo**	−6.4 (−19.9, 19.6) %			**3 mo**	−17.4 (−22.5, −4.5) %	
						6 mo	−20.9 (−27.4, −1.5) %			**6 mo**	−9.7 (−30.7, 2.3) %			**6 mo**	−21.4 (−34.7, −11.5) %	
						9 mo	−14.1 (−27.4, 6.0) %			**9 mo**	−29.2 (−40.1, −17.3) %			**9 mo**	−25.4 (−32.6, −15.9) %	
						12 mo	−14.2 (−26.8, 3.3) %			**12 mo**	−26.8 (−36.2, −11.7) %			**12 mo**	−24.4 (−38.8, −4.9) %	
				210mg sc every 3 months	-				-				**Baseline**	49 (40, 62) μg/L		
					%Change	**1 wk**	17.5 (10.7, 25.1) %		**%Change**	**1 wk**	13.0 (2.5, 22.2) %		**%Change**	**1 wk**	77.5 (43.2, 98.3) %	
						1 mo	46.5 (21.5, 72.1) %			**1 mo**	84.3 (54.1, 102.2) %			**1 mo**	74.8 (46.5, 114.0) %	
						2 mo	−5.2 (−16.8, 10.2) %			**2 mo**	20.0 (−0.3, 34.4) %			**2 mo**	−22.1 (−34.4, -9.1) %	
						3 mo	−19.0 (−25.8, −7.0) %			**3 mo**	−5.0 (−17.6, 18.8) %			**3 mo**	−18.1 (−31.7, −4.1) %	
						6 mo	−22.0 (−29.3, −5.5) %			**6 mo**	−21.8 (−41.0, −15.5) %			**6 mo**	−25.7 (−36.0, −8.2) %	
						9 mo	−18.4 (−27.7, −6.3) %			**9 mo**	−24.8 (−41.4, 2.4) %			**9 mo**	−24.7 (−41.6, −14.1) %	
						12 mo	−10.1 (−26.2, 3.4) %			**12 mo**	−22.2 (−36.6, −8.1) %			**12 mo**	−28.5 (−40.0, −5.0) %	
				70mg sc once month	-				-				**Baseline**	50 (36, 61) μg/L		

					%Change	**1 wk**	5.5 (0.9, 15.9) %	%Change	**1 wk**	1.5 (−8.8, 10.7) %	%Change	**1 wk**	31.5 (19.4, 55.6) %
						1 mo	10.2 (0.8, 27.7) %		**1 mo**	28.9 (5.2, 46.3) %		**1 mo**	22.0 (7.1, 40.7) %
						2 mo	−0.2 (−11.6, 31.0) %		**2 mo**	11.1 (−0.3, 34.4) %		**2 mo**	−0.3 (−17.0, 12.4) %
						3 mo	−5.7 (−22.0, 9.4) %		**3 mo**	0.9 (−16.0, 22.6) %		**3 mo**	−8.2 (−20.1, 13.4) %
						6 mo	−9.9 (−21.3, 8.2) %		**6 mo**	−8.6 (−33.1, 21.1) %		**6 mo**	−18.5 (−32.6, −4.2) %
						9 mo	−3.1 (−23.0, 13.6) %		**9 mo**	−24.2 (−39.1, −2.3) %		**9 mo**	−25.5 (−43.1, −8.1) %
						12 mo	−6.9 (−20.2, 14.0) %		**12 mo**	−29.2 (−40.4, −8.0) %		**12 mo**	−26.5 (−43.9, −7.2) %
				140mg sc once month	-			-			**Baseline**		48 (38, 56) μg/L
					%Change	**1 wk**	14.0 (7.5, 21.0) %	%Change	**1 wk**	7.4 (−4.6, 19.6) %	%Change	**1 wk**	56.6 (42.2, 79.5) %
						1 mo	36.6 (14.0, 51.2) %		**1 mo**	58 (37.0, 82.4) %		**1 mo**	68.6 (23.1, 96.4) %
						2 mo	15.7 (−1.1, 31.8) %		**2 mo**	35.8 (17.5, 53.8) %		**2 mo**	9.7 (−13.6, 34.8) %
						3 mo	4.0 (−12.8, 22.3) %		**3 mo**	19.3 (−0.5, 41.0) %		**3 mo**	2.3 (−18.3, 27.8) %
						6 mo	−7.9 (−16.6, 11.9) %		**6 mo**	−5.3 (−27.7, 24.0) %		**6 mo**	−16.4 (−30.2, 8.0) %
						9 mo	−8.3 (−19.0, 11.0) %		**9 mo**	−28.4 (−44.0, −13.9) %		**9 mo**	−26.2 (−37.4, −5.1) %
						12 mo	−4.6 (−18.5, 11.1) %		**12 mo**	−32.9 (−44.3, −17.6) %		**12 mo**	−32.3 (−43.4, −14.3) %
				210mg sc once month	-			-			**Baseline**		53 (42, 64) μg/L
					%Change	**1 wk**	17.9 (7.8, 27.1) %	%Change	**1 wk**	4.3 (−0.2, 17.1) %	%Change	**1 wk**	82.7 (64.7, 101.1) %
						1 mo	51.8 (40.8, 82.1) %		**1 mo**	78.3 (54.1, 107.0) %		**1 mo**	91.2 (56.8, 126.7) %
						2 mo	36.7 (12.9, 52.6) %		**2 mo**	58.2 (29.1, 99.5) %		**2 mo**	36.4 (8.8, 73.8) %
						3 mo	26.6 (8.1, 47.7) %		**3 mo**	45.8 (19.3, 88.6) %		**3 mo**	31.8 (−3.8, 63.7) %
						6 mo	18.2 (−0.4, 35.7) %		**6 mo**	13.5 (−13.7, 37.1) %		**6 mo**	6.3 (−18.9, 32.3) %
						9 mo	6.8 (−9.1, 22.0) %		**9 mo**	1.1 (−25.6, 19.0) %		**9 mo**	−10.4 (−31.4, 12.9) %
						12 mo	2.5 (−7.6, 21.1) %		**12 mo**	−15.5 (−24.4, −0.8) %		**12 mo**	−19.8 (−38.0, −1.5) %
			alendronate	70 mg po once week	-			-			**Baseline**		49 (40, 58) μg/L
					%Change	**3 mo**	−33.0 (−41.8, −20.5) %	%Change	**3 mo**	−29.7 (−42.1, −13.6) %	%Change	**3 mo**	−48.3 (−63.7, −34.8) %
						6 mo	−34.4 (−47.9, −24.3) %		**6 mo**	−41.0 (−53.6, −29.2) %		**6 mo**	−59.2 (−70.0, −41.3) %
						9 mo	−29.3 (−41.9, −20.4) %		**9 mo**	−49.9 (−62.8, −39.3) %		**9 mo**	−59.3 (−71.8, −45.8) %
						12 mo	−31.4 (−43.0, −22.7) %		**12 mo**	−49.5 (−59.9, −41.7) %		**12 mo**	−64.2 (−70.3, −44.3) %
			teriparatide	20μg sc once day	-			-			**Baseline**		49 (42, 67) μg/L
					%Change	**3 mo**	21.7 (−4.9, 55.5) %	%Change	**3 mo**	95.5 (38.4, 177.4) %	%Change	**3 mo**	88.8 (43.8, 146.0) %
						6 mo	26.2 (2.7, 70.9) %		**6 mo**	87.6 (27.8, 232.8) %		**6 mo**	120.5 (51.5, 245.3) %
						9 mo	34.8 (5.0, 88.3) %		**9 mo**	69.7 (39.8, 204.4) %		**9 mo**	111.3 (48.4, 233.7) %
						12 mo	43.0 (13.5, 79.5) %		**12 mo**	76.6 (20.1, 193.6) %		**12 mo**	84.2 (48.4, 191.7) %
			placebo	-	-			-			**Baseline**		48 (38, 59) μg/L
					%Change	**1 wk**	0.7 (−4.9, 7.3) %	%Change	**1 wk**	−5.1 (−9.5, 5.4) %	%Change	**1 wk**	−2.2 (−8.4, 5.1) %
						1 mo	−0.5 (−7.6, 10.1) %		**1 mo**	−3.7 (−11.5, 5.7) %		**1 mo**	−4.1 (−12.2, 7.8) %
						2 mo	−3.4 (−13.2, 8.0) %		**2 mo**	−2.5 (−11.2, 16.8) %		**2 mo**	−3.5 (−13.7, 9.5) %
						3 mo	−0.0 (−18.3, 11.1) %		**3 mo**	3.0 (−11.6, 22.7) %		**3 mo**	−6.9 (−17.2, 8.9) %
						6 mo	−2.9 (−16.2, 7.9) %		**6 mo**	−5.9 (−27.9, 15.0) %		**6 mo**	−12.5 (−21.3, 7.1) %
						9 mo	3.9 (−9.9, 16.9) %		**9 mo**	−10.8 (−28.3, 20.0) %		**9 mo**	−11.3 (−20.0, 5.1) %
						12 mo	11.7 (−2.3, 27.0) %		**12 mo**	−12.9 (−26.6, 8.1) %		**12 mo**	−8.5 (−22.3, 15.0) %

Padhi *et al.* (2014)[41]	48	32 women	46	31 women	Romosozumab	1mg/kg sc every 2 weeks	Baseline 18.00 ± 7.59 μg/L increase similar as P1NP, but data not reported	Baseline: 34.59 ± 24.46 μg/L increase similar as P1NP, but data not reported	Baseline: 66.83 ± 23.54 ng/mL Max. mean increase: 83 ± 22 %
						2mg/kg sc every 4 weeks	Baseline 14.04 ± 3.29 μg/L increase similar as P1NP, but data not reported	Baseline: 25.26 ± 9.94 μg/L increase similar as P1NP, but data not reported	Baseline: 65.00 ± 18.25 ng/mL Max. mean increase: 66 ± 15 %
						2mg/kg sc every 2 weeks	Baseline 15.21 ± 1.71 μg/L increase similar as P1NP, but data not reported	Baseline: 22.73 ± 9.18 μg/L increase similar as P1NP, but data not reported	Baseline: 61.42 ± 14.38 ng/mL Max. mean increase: 140 ± 18 %
						3mg/kg sc every 4 weeks	Baseline 16.40 ± 6.75 μg/L increase similar as P1NP, but data not reported	Baseline: 20.96 ± 8.58 μg/L increase similar as P1NP, but data not reported	Baseline: 59.00 ± 24.45 ng/L Max. mean increase: 129 ± 21 %
					placebo	-	Baseline 14.88 ± 5.02 μg/L decease similar as P1NP, but data not reported	Baseline: 23.09 ± 8.93 μg/L decrease similar as P1NP, but data not reported	Baseline: 54.75 ± 22.77 ng/mL Max. mean increase: 13 ± 6.8 %
		16 men		15 men	Romosozumab	1mg/kg sc every 2 weeks	Baseline 12.83 ± 2.10 μg/L increase similar as P1NP, but data not reported	Baseline: 19.92 ± 0.59 μg/L increase similar as P1NP, but data not reported	Baseline: 39.33 ± 8.11 ng/mL Max. mean increase: 106 ± 15 %
						3mg/kg sc every 4 weeks	Baseline 12.68 ± 1.52 μg/L increase similar as P1NP, but data not reported	Baseline: 20.11 ± 5.90 μg/L increase similar as P1NP, but data not reported	Baseline: 40.08 ± 7.63 ng/mL Max. mean increase: 147 ± 33 %

BSAP -Bone Specific Alkaline Phosphatase ; **P1NP** – Procollagen Type 1 N-terminal Propeptide; **wk** – week; **mo** – month (s); **%Change** – Percent change from Baseline.

Table S14: *Bone Remodeling - Bone Resorption Markers*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	CTX	TRACP-5b
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	-	
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week	-	
					saline vehicle	-	-	
		10 Sham		10 Sham	saline vehicle	-	-	
	45		45		Scl-Ab VI	25mg/kg sc twice week	-	3.52 ± 0.28 U/L
					Scl-Ab VI + DAB	25mg/kg sc + 25mg/kg sc twice week	-	2.5 ± 0.17 U/L
					saline vehicle	-	-	Intact: 3.92 ± 0.24 U/L Extracted: 3.72 ± 0.22 U/L
Wu *et al.* (2018)[55]	40 OVX		40 OVX		Scl-Ab	25mg/kg sc twice week	no significant differences in CTX-1 between all groups.	
					PTH 1-34	60μg/kg sc thrice week		
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week		
					vehicle	-		
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	-	**6 weeks** | no changes vs EP vehicle
						15 μL of 35.6mg/mL solution locally twice week	-	
					EP: vehicle	-	-	
					healthy: PBS	-	-	
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc twice week	-	
					PBS	-	-	
	30		30		Scl-Ab III	25mg/kg	-	no significant differences between both groups at any time.
					PBS	-	-	
McDonald *et al.* (2012)[31]	132	66 Sham	127		Scl-Ab III	25mg/kg sc twice week	-	-
					saline solution	-	-	-
		66 OVX			Scl-Ab III	25mg/kg sc twice week	-	-
					saline solution	-	-	-
Ominsky *et al.* (2011)[54]	35		32		Scl-Ab III	25mg/kg sc twice week	-	-
					vehicle	-	-	-
Tian *et al.* (2011)[32]	67		67		Scl-Ab III	5mg/kg sc twice week	-	-
						25mg/kg sc twice week	-	-
					saline solution	-	-	-
Li *et al.* (2010)[36]	28		26		Scl-Ab III	25mg/kg sc twice week	no significant effects in CTX-1	-
						5mg/kg sc twice week		-
					vehicle	-	-	-
Ominsky *et al.* (2010)[59]	12		12		Scl-Ab IV	3mg/kg sc once month	no significant effects	-
						10mg/kg sc once month		-
						30mg/kg sc once month		-
					vehicle	-	-	-

Tian *et al.* (2010)[57]	32	32	Scl-Ab III	5mg/kg sc twice week	-				-
				25mg/kg sc twice week	-				-
			saline solution	-	-				-
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → alendronate	210mg sc once month → 70mg po once week	**12 mo**	βCTX levels decreased vs control			-
					36 mo	βCTX levels decreased and were maintained below baseline			
			alendronate → alendronate	70mg po once week → 70mg po once week	βCTX levels decreased since the 1st month, remaining below baseline at 36 months				
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc every 3 months	**βCTX**	**Baseline**		525 (358, 714) ng/L	
						%Change	**1 wk**	−34.5 (−45.0, −27.6) %	
							1 mo	−22.7 (−40.1, 0.7) %	
							2 mo	−8.4 (−24.9, 5.8) %	
							3 mo	−5.3 (−27.0, 5.4) %	
							6 mo	−13.1 (−25.3, 2.7) %	
							9 mo	−1.0 (−22.6, 18.8) %	
							12 mo	6.2 (−9.8, 32.8) %	
				210mg sc every 3 months	**βCTX**	**Baseline**		478 (362, 695) ng/L	
						%Change	**1 wk**	−42.0 (−53.3, −27.4) %	
							1 mo	−33.6 (−45.0, −21.0) %	
							2 mo	−10.4 (−27.6, 12.5) %	
							3 mo	−11.5 (−28.9, 6.2) %	
							6 mo	−12.6 (−27.1, 18.1) %	
							9 mo	−2.3 (−29.9, 12.1) %	
							12 mo	−7.1 (−16.9, 18.8) %	
				70mg sc once month	**βCTX**	**Baseline**		486 (374, 627) ng/L	
						%Change	**1 wk**	−33.7 (−42.2, −22.4) %	
							1 mo	−22.3 (−31.8, −5.7) %	
							2 mo	−14.5 (−28.7, 4.1) %	
							3 mo	−17.1 (−29.7, −5.7) %	
							6 mo	−10.6 (−34.5, 13.4) %	
							9 mo	−17.7 (−33.1, 18.7) %	
							12 mo	−18.7 (−37.9, 3.7) %	
				140mg sc once month	**βCTX**	**Baseline**		532 (363, 622) ng/L	
						%Change	**1 wk**	−36.8 (−46.2, −29.2) %	
							1 mo	−35.9 (−44.8, −16.3) %	
							2 mo	−26.9 (−37.7, −0.0) %	
							3 mo	−27.4 (−36.8, −13.3) %	
							6 mo	−24.5 (−46.6, 4.1) %	
							9 mo	−29.2 (−48.1, −1.5) %	
							12 mo	−29.3 (−55.1, −14.5) %	
				210mg sc once month	**β**		**Baseline**	519 (405, 642) ng/L	

							%Change	**1 wk**	−41.4 (−52.5, −32.1) %	
								1 mo	−29.5 (−40.6, −12.6) %	
								2 mo	−4.9 (−28.7, 15.0) %	
								3 mo	1.2 (−21.7, 19.9) %	
								6 mo	−9.6 (−26.8, 11.0) %	
								9 mo	−20.4 (−31.9, −1.1) %	
								12 mo	−26.3 (−42.1, −8.8) %	
				alendronate	70 mg po once week	βCTX	**Baseline**		494 (373, 614) ng/L	
							%Change	**3 mo**	−65.8 (−84.0, −51.5) %	
								6 mo	−65.0 (−76.7, −45.9) %	
								9 mo	−66.8 (−75.0, −47.9) %	
								12 mo	−65.5 (−82.3, −49.7) %	
				teriparatide	20μg sc once day	βCTX	**Baseline**		506 (410, 690) ng/L	
							%Change	**3 mo**	58.6 (23.8, 135.2) %	
								6 mo	80.4 (39.7, 167.8) %	
								9 mo	79.7 (15.3, 169.3) %	
								12 mo	79.7 (15.7, 140.5) %	
				placebo	-	βCTX	**Baseline**		481 (373, 673) ng/L	
							%Change	**1 wk**	−0.6 (−13.7, 14.4) %	
								1 mo	−3.1 (−12.8, 8.8) %	
								2 mo	2.2 (−15.7, 13.6) %	
								3 mo	−3.5 (−19.3, 18.0) %	
								6 mo	0.3 (−12.8, 24.4) %	
								9 mo	1.0 (−17.0, 32.5) %	
								12 mo	4.6 (−13.3, 41.5) %	
Padhi *et al.* (2014)[41]	48	32 women	46	31 women	Romosozumab	1mg/kg sc every 2 weeks	sCTX	Baseline: 5771.58 ± 2304.36 pmol/L		
								Max. mean decrease: 15 ± 11 %		
						2mg/kg sc every 4 weeks		Baseline: 4516.42 ± 1154.62 pmol/L		
								Max. mean decrease: 35 ± 8.7 %		
						2mg/kg sc every 2 weeks		Baseline: 4808.58 ± 616.58 pmol/L		
								Max. mean decrease: 38 ± 2.2 %		
						3mg/kg sc every 4 weeks		Baseline: 4733.00 ± 1686.35 pmol/L		
								Max. mean decrease: 37 ± 5.4 %		
					placebo	-		Baseline: 5651.00 ± 1686.53 pmol/L		
								Max. mean decrease: 13 ± 6.8 %		
		16 men		15 men	Romosozumab	1mg/kg sc every 2 weeks		Baseline: 3451.00 ± 638.09 pmol/L		
								Max. mean decrease: 42 ± 4.1 %		
						3mg/kg sc every 4 weeks		Baseline: 4027.08 ± 1413.24 pmol/L		
								Max. mean decrease: 50 ± 4.8 %		

CTX/ sCTX– serum C-Telopeptide ; **CTX-1**–; **βCTX -** ;**wk** – week; **mo** – month (s); **%Change** – Percent change from Baseline.

Table S 15: *Bone Strength Endpoints*

	Sample Size (Initial)		Sample Size (Final)		Drug/Control	Dosage & Administration Route	Maximum Load	Stiffness	Energy to Failure	Peak Load
Liu *et al.* (2018)[52]	50	40 OVX	50	40 OVX	Scl-Ab VI	18.2mg/kg sc twice week	-	-	-	-
					Scl-Ab VI + DAB	18.1mg/kg sc + 18.1mg/kg sc twice week	-	-	-	-
					saline vehicle	-	-	-	-	-
		10 Sham		10 Sham	saline vehicle	-	-	-	-	-
	45		45		Scl-Ab VI	25mg/kg sc twice week	-	-	-	-
					Scl-Ab VI + DAB	25mg/kg sc + 25mg/kg sc twice week	-	-	-	-
					saline vehicle	-	-	-	-	-
Wu *et al.* (2018)[55]	40 OVX		40 OVX		Scl-Ab	25mg/kg sc twice week	**12 wks** higher increase vs vehicle no difference vs PTH	**12 wks** higher increase vs vehicle no difference vs PTH	**12 wks** higher increase vs vehicle no difference vs Scl-Ab	-
					PTH 1-34	60μg/kg sc thrice week	**12 wks** sig. increase vs vehicle; no difference vs Scl-Ab	**12 wks** significant increase vs vehicle no difference vs Scl-Ab	**12 wks** higher increase vs vehicle no difference vs Scl-Ab	-
					Scl-Ab + PTH 1-34	25mg/kg sc twice week + 60μg/kg sc thrice week	**12 wks** sig. increase vs vehicle no difference vs other 2 groups	**12 wks** significant increase vs all groups	**12 wks** significant increase vs all groups	-
					vehicle	-	-	-	-	-
Taut *et al.* (2013)[60]	69		69		EP: Scl-Ab III	25 mg/kg sc twice week	-	-	-	-
						15 μL of 35.6mg/mL solution locally twice week	-	-	-	-
					EP: vehicle	-	-	-	-	-
					healthy: PBS	-	-	-	-	-
Virk *et al.* (2013)[53]	72		72		Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					PBS	-	-	-	-	-
	30		30		Scl-Ab III	25mg/kg	-	6 weeks: significantly greater than control	12 weeks: significantly greater than control	-
					PBS	-	-	-	-	-
McDonald *et al.* (2012)[31]	132	66 Sham	127		Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					saline solution	-	-	-	-	-
		66 OVX			Scl-Ab III	25mg/kg sc twice week	-	-	-	-
					saline solution	-	-	-	-	-
Ominsky *et al.* (2011)[54]	35		32		Scl-Ab III	25mg/kg sc twice week	-	**Fractured Femur:** 48% increase in torsional stiffness compared to vehicle **Intact Femur:** FD: 637 ± 37 N/mm	-	**Intact Femur:** FD: 223 ± 10 N
					vehicle	-	-	FD: 570 ± 22 N/mm	-	FD: 191 ± 8 N
Tian *et al.* (2011)[32]	67		67		Scl-Ab III	5mg/kg sc twice week	-	-	-	-
						25mg/kg sc twice week	-	-	-	-
					saline solution	-	-	-	-	-

Li *et al.* (2010)[36]	28	26	Scl-Ab III	25mg/kg sc twice week	LV: 693 ± 37 N FD: 249 ± 13 N FN: 247 ± 12 N	LV: 4623 ± 549 N/mm FD: 781 ± 53 N/mm FN: 689 ± 56 N/mm	LV: 82.6 ± 10.0 mJ FD: 172 ± 22 mJ FN: 68.6 ± 9.5 mJ	-
				5mg/kg sc twice week	LV: 467 ± 42 N FD: 254 ± 13 N FN: 241 ± 12 N	LV: 3292 ± 379 N/mm FD: 770 ± 61 N/mm FN: 805 ± 70 N/mm	LV: 59.9 ± 5.7 mJ FD: 148 ± 16 mJ FN: 35.7 ± 5.8 mJ	-
			vehicle	-	LV: 349 ± 28 N FD: 190 ± 12 N FN: 201 ± 8 N	LV: 2710 ± 299 N/mm FD: 680 ± 35 N/mm FN: 611 ± 20 N/mm	LV: 38.9 ± 4.9 mJ FD: 139 ± 13 mJ FN: 46.2 ± 5.6 mJ	-
Ominsky *et al.* (2010)[59]	12	12	Scl-Ab IV	3mg/kg sc once month	-	FD: 838 ± 106 N/mm	FD: 2523 N×mm	FD: 917 ± 121 N
				10mg/kg sc once month	-	FD: 873 ± 84 N/mm	FD: 3190 ± 743 N×mm	FD: 1005 ± 81 N
				30mg/kg sc once month	-	FD: 1040 ± 192 N/mm	FD: 4994 ± 904 N×mm	FD: 1285 ± 241 N
			vehicle	-	-	FD: 888 ± 106 N/mm	FD: 3600 ± 282 N×mm	FD: 1008 ± 102 N
Tian *et al.* (2011)[32]	32	32	Scl-Ab III	5mg/kg sc twice week	-	-	-	-
				25mg/kg sc twice week	-	-	-	-
			saline solution	-	-	-	-	-
Saag *et al.* (2017)[62]	4093	3150	Romosozumab → Alendronate	210mg sc once month → 70mg po once week	-	-	-	-
			Alendronate → Alendronate	70mg po once week → 70mg po once week	-	-	-	-
McClung *et al.* (2014)[39]	419	383	Romosozumab	140mg sc every 3 months	-	-	-	-
				210mg sc every 3 months	-	-	-	-
				70mg sc once month	-	-	-	-
				140mg sc once month	-	-	-	-
				210mg sc once month	-	-	-	-
			Alendronate	70 mg po once week	-	-	-	-
			Teriparatide	20μg sc once day	-	-	-	-
			placebo	-	-	-	-	-
Padhi *et al.* (2014)[41]	48	32 women / 16 men	46	31 women / 15 men	Romosozumab	1mg/kg sc every 2 weeks		
						2mg/kg sc every 4 weeks		
						2mg/kg sc every 2 weeks		
						3mg/kg sc every 4 weeks		
					placebo	-		
					Romosozumab	1mg/kg sc every 2 weeks		
						3mg/kg sc every 4 weeks		

FD – Femoral Diaphysis; **LV** - 5th Lumbar Vertebra; **FN** – Femoral Neck.