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Original article

Risk of falls in postmenopausal women treated with romosozumab: Preliminary indices from a meta-analysis of randomized, controlled trials

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ABSTRACT

Objectives: Falls are the well-known risk factor for osteoporotic fractures and some medications can increase the risk of falls. Therefore, the aim of our study is to evaluate the effect of romosozumab on risk of falls in postmenopausal women.

Methods: Studies were searched on PubMed, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov using the search term "romosozumab." Randomized, clinical trials with romosozumab in postmenopausal women, which met the inclusion criteria and in particular reported on falls in safety or efficacy data, were included into the meta-analysis. Risk ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated using a binary effects model.

Results: A total of four studies with overall 12,128 postmenopausal women with osteoporosis were included into the meta-analysis. Twelve-months treatment with romosozumab reduced the risk of falls nonsignificantly by 16% (RR, 0.84; 95% CI, 0.67−1.04; $P = 0.10$; $n = 11{,}829$). A subgroup analysis with double-blind studies indicated a statistically significant reduction in risk of falls by 20% (RR, 0.80; 95% CI, 0.71−0.92; $P \leq 0.01$; $n = 11{,}211$). A sequential treatment of romosozumab followed by an antiresorptive medication resulted in a 12% (RR, 0.88; 95% CI, 0.80−0.96; $P \leq 0.01$; $n = 11{,}211$) reduction of falls in the romosozumab group compared to the control group.

Conclusions: This analysis indicates that romosozumab has a tendency to reduce risk of falls in postmenopausal women with osteoporosis. Nevertheless, our findings are preliminary results with a low significance and to confirm these findings more data and analyses are needed.

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1. Introduction

The systemic skeletal disease osteoporosis is characterized by low bone mass and defects in bone microarchitecture, resulting in an increased risk for fracture [1]. Currently, most patients are treated with antiresorptive therapies to prevent further disease progression. Romosozumab (210 mg once monthly) is the first approved actively bone forming sclerostin antibody for the 12 months treatment of postmenopausal women at high risk of fracture [2,3].

Romosozumab is targeting and inhibiting sclerostin, which leads to an increased bone formation and decreased bone resorption [4,5]. In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) trial, postmenopausal women treated in sequential approach with romosozumab followed by alendronate showed a significantly lower risk of 48%, 27%, and 19% for vertebral, clinical and non-vertebral fractures compared to women treated with alendronate alone, respectively. In the same study the increase in bone mineral density (BMD) was 8.7% and 3.4% higher among women with romosozumab compared to women with alendronate at lumbar spine and total hip after 12 months, respectively [5]. This data indicate that romosozumab is the first approved treatment for postmenopausal women with osteoporosis, targeting sclerostin and showing superiority over standard of care alendronate.

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Apart from a low BMD, frailty and falls are major risk factors for fractures [6–8]. Patients with falls within the last 12 months reveal a 1.5 to 6.7 higher risk for a fracture compared to nonfallers [6,7]. In addition, frail patients fracture 1.7 times more likely compared to robust patients [8]. Since 90% of all hip fractures in elderly patients result from falls [9], the International Osteoporosis Foundation (IOF) recommends to prevent patients with osteoporosis from falls and to fall-proof their homes [10].

It is well known that some medications such as antidepressants, sleep aids or muscle relaxants can increase the risk of falls and fractures [7]. In contrast, a pooled analysis of placebo-controlled studies with osteoporosis medication denosumab, has shown that denosumab decreases the risk of falls [11].

Due to the fact that falls are an important negative contributor to fracture risk and that various medications can influence the risk of falls, the aim of our study was to evaluate the risk of falls in postmenopausal women treated with romosozumab.

2. Methods

2.1. Study objectives

The main objective was to address the issue whether 12 months of treatment with romosozumab has an effect on the risk of falls in postmenopausal women. A second analysis was performed with studies showing a sequential treatment approach of 12-month romosozumab followed by an antiresorptive treatment.

Besides, the estimation of an overall effect of romosozumab on the risk of falls, a subgroup analysis, including open-label or double-blind studies, was performed. These subgroups were defined, because *open-label* studies tend to show performance and detection biases [12], which might have had an influence on patient-reported outcome, such as falls.

2.2. Search strategy and study selection

A systematic search for studies was performed in June 2019 on PubMed, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov using the search term “romosozumab.” The search and subsequent record screening were performed by two authors independently. The following steps were performed to identify studies for inclusion into our analysis, (1) removal of duplicates, (2) abstract and title screening or screening of registry entry to remove records such as systematic reviews and registry entries without results, and (3) screening of full-text publications and registry entries for evaluation of eligibility for inclusion. The search was restricted to publications and registry entries in English or German languages.

Studies identified within the database were screened and only included into the meta-analysis if they met the following criteria: (I) treatment with 210-mg romosozumab once monthly; (II) phase II or phase III randomized, controlled trial; (III) reporting of 12-months data for romosozumab and control; (IV) condition, postmenopausal women with low BMD and/or osteoporosis, and (V) falls reported in the safety and/or efficacy data.

It should be noted here that studies with romosozumab treatment periods exceeding 12 months were only included into the meta-analysis if the 12 months data was available. In addition, data on falls were only included into the meta-analysis if they were available for the treatment period baseline to month 12, to avoid potential influence of other study medications and/or interventions on risk of falls.

2.3. Data extraction

The following data was independently extracted by 2 authors from selected studies: (1) NCT (ClinicalTrials.gov registry) number, (2) number of subjects, (3) mean age of subjects at baseline, (4) BMD at lumbar spine, total hip and femoral neck at baseline, respectively, (5) number and type of fractures at baseline, (6) time of follow-up, (7) comparator therapies, (8) if applicable follow-on therapy after 12 months of romosozumab, and (9) number of falls at month 12 and end of study in terms of a sequential treatment approach. Number of falls were taken from adverse event as well as serious adverse event section of clinicaltrials.gov database and grouped for meta-analysis. If necessary data was not found on clinicaltrials.gov, full-text publications with the respective NCT numbers were taken to extract the data.

2.4. Assessment of study quality

Two authors independently evaluated the risk of bias of studies eligible for the meta-analysis by using the criteria of the Cochrane Collaboration assessment tool [12]: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and researcher (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias), and (7) other biases. Each category was judged using three risk levels: low risk, high risk, and unclear risk.

2.5. Statistical analysis

In studies which compared romosozumab to more than one comparator, the number of falls and patients of comparators were grouped for meta-analysis to increase statistical power. The meta-analysis was performed using the OpenMetaAnalyst software package [13,14] by applying a binary random effects model using the DerSimonian-Laird method. Final outcomes were risk ratios (RRs) and corresponding 95% confidence intervals (CIs) of romosozumab compared to control.

Heterogeneity between studies included into the meta-analysis was statistically assessed by using the I^2. An I^2 below 25% indicates a low, of 25%–50% a moderate and I^2 of >50% a high heterogeneity, respectively [15].

3. Results

3.1. Study identification

A total of 255 records were identified by systematic search on PubMed, CENTRAL and ClinicalTrials.gov (Fig. 1). After removal of duplicates, 215 records were taken for screening of title and abstract and/or registry entry. During this step 194 records were excluded, which were mainly systematic reviews, conference abstracts without any data on falls, nonclinical/nonhuman trials and registry entries without data on falls. Afterwards, remaining records (17 full-text articles and 4 registry entries) were evaluated for eligibility for inclusion into the analysis.

A total of 5 full-text articles and 4 registry entries were included into the qualitative synthesis [4,5,16–22]. Unfortunately, the five full-text publications met inclusion criteria (I) to (IV) [4,5,16–18], but only one of these publications, namely the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) 36-month data: 12-month romosozumab + 24-month denosumab, also met inclusion criterium (V) and reported on falls [18]. None of the identified full-text publications reported number of falls after 12-month treatment with romosozumab. In contrast, all 4 registry

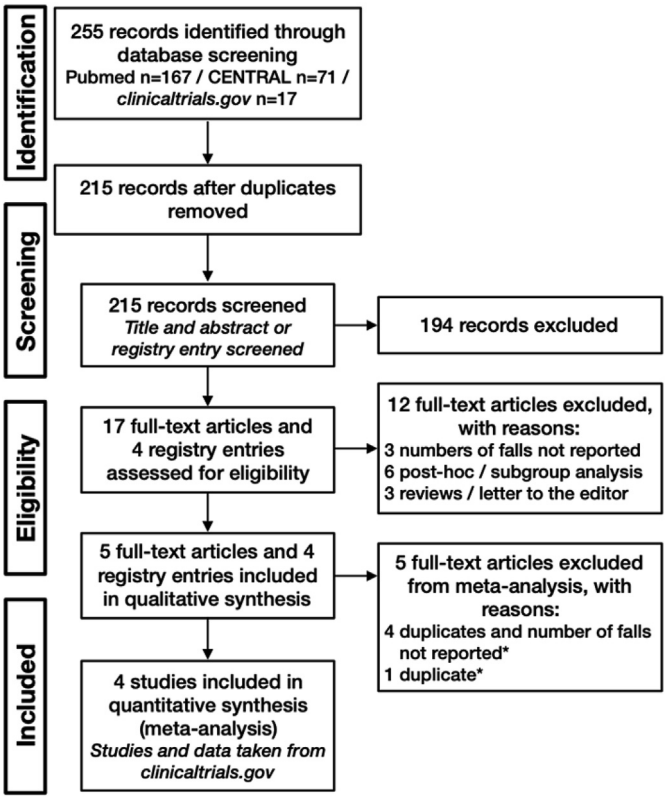

Fig. 1. Systematic study search. *Studies were included into meta-analysis by taking data on falls from corresponding entries on ClinicalTrials.gov study registry. Full-text publications were used for qualitative analysis of the respective studies.

entries identified during search reported on 12-month data [19–22] and 2 even on 33- to 36-month data on falls [21,22]. Due to the fact that the registry entries [19–22] were the same studies like the full-text publications mentioned above [4,5,16–18], we included the full-text publications into the qualitative analysis for evaluation of risk of bias and study/patient characteristics.

To be mentioned here, full-text publication with FRAME 36-month data only reported falls after 36 months [18], but corresponds to registry entry NCT01575834 on clinicaltrials.gov [21]. Therefore, 36-month data on falls for FRAME study was taken from clinicaltrials.gov [21] to have the same data source like for the 12-month data and the other 3 studies taken from clinicaltrials.gov [19,20,22] and included into the meta-analysis.

3.2. Characteristics of studies and patients included into the meta-analysis

Studies eligible for meta-analysis contained a total of 12,128 postmenopausal women with low BMD or osteoporosis [4,5,16,17,19–22]. Study NCT00896532 included five romosozumab treatment arms of which only the treatment arm of 210-mg romosozumab once monthly was used for this meta-analysis.

Baseline characteristics (Table 1) reveal that 3 studies compared romosozumab with active comparators, whereas one study was a placebo comparison. Mean age in the included studies was between 66.3 and 74.4 years and 2 studies, the Open-label Study to Evaluate the Effect of Treatment with Romosozumab or Teriparatide in Postmenopausal Women (STRUCTURE) and ARCH, contained nearly 100% patients with a prevalent fracture at baseline. To be mentioned here is, that based on the baseline BMD values, patients in NCT00896532 had osteopenia, whereas patients in the other three studies showed BMD values for osteoporosis.

Three studies ARCH, FRAME, and NCT00896532 were designed as trials with sequential treatment approach, in which romosozumab was followed by an antiresorptive treatment (Table 1). Important to mention here, are the 2 studies ARCH and FRAME, in which 12-month romosozumab followed by alendronate was compared to alendronate only and 12-month romosozumab followed by denosumab was compared to 12-month placebo followed by denosmumab, respectively.

3.3. Risk of bias evaluation of studies included into the meta-analysis

All studies indicated a low risk of bias in terms of random sequence generation and allocation concealment. Two studies NCT00896532 and STRUCTURE showed a high risk of bias for "blinding of participants and personnel," because in both studies active comparators were administered open-label. In terms of blinding of outcomes assessment, high risk of bias was defined for NCT00896532 and STRUCTURE, since falls are patient-reported outcomes and as mentioned before, knowledge on specific treatment might influence patients behavior and reporting. All 4 included studies were rated with high risk in terms of other bias, since all studies were sponsored by pharmaceutical industry. Full evaluation on risk of bias is shown in Table 2.

3.4. Risk of falls assessment

Data of placebo, alendronate and teriparatide arms from NCT00896532 were clustered into one control group for analysis.

Meta-analysis using 12-month data (Fig. 2A) indicated a nonsignificant reduction in risk of falls by romosozumab of 16% vs. control group (RR, 0.84; 95% CI, 0.67–1.04; $P = 0.10$; $n = 11{,}829$). In the subgroup analysis with open-label studies risk of falls was nonsignificantly higher among patients receiving romoszumab (RR, 1.19; 95% CI, 0.21–6.74; $P = 0.85$; $n = 618$). In contrast, subgroup analysis with double-blind studies indicated a statistically significant 20% reduction in risk of falls by romosozumab compared to control (RR, 0.80; 95% CI, 0.71–0.92; $P \leq 0.01$; $n = 11{,}211$). Heterogeneity among included studies was moderate for the overall analysis ($I^2 = 36.61\%$; $P = 0.19$), high for open-label subgroup analysis ($I^2 = 58.47\%$, $P = 0.19$) and low for double-blind subgroup analysis ($I^2 = 0\%$, $P = 0.82$), respectively.

Two studies were included into the risk of fall assessment of 12-month romosozumab followed by an antiresorptive treatment, covering a treatment period of 33-36 months (Fig. 2B). In this analysis patients treated with romosozumab showed a statistically significant 12% lower risk of falls (RR, 0.88; 95% CI, 0.80–0.96; $P \leq 0.01$; $n = 11{,}211$). The study heterogeneity with an $I^2 = 0$ ($P = 0.45$) was considered low. NCT00896532 was not included into this analysis, because romosozumab was administered from baseline to month 24 before switching to an antiresorptive therapy.

4. Discussion

Our meta-analysis indicates that romosozumab has the tendency to reduce the risk of falls in postmenopausal women with osteoporosis. The evaluation and reduction in risk of falls is an essential piece in the management and treatment of patients with osteoporosis. The IOF explicitly recommends to avoid and prevent patients with osteoporosis from falls [10] and previous studies have shown, that frailty and falls in the history are strongly associated with fractures [6–8].

This meta-analysis shows that 12-month treatment with romosozumab decreases the risk of falls overall nonsignificantly by

Table 1
Characteristics of studies and patients included into the meta-analysis.

Study	NCT00896532 [4,19]	NCT01796301 STRUCTURE [16,20]	NCT01575834 FRAME [17,21]	NCT01631214 ARCH [5,22]
Treatments	210-mg Romosozumab[a] QM Placebo[b] 70-mg Alendronate QW[b] 20-μg Teriparatide QD[b]	210-mg Romosozumab QM 20-μg Teriparatide QD	210-mg Romosozumab QM Placebo	210-mg Romosozumab QM 70-mg Alendronate QW
No. of patients	Romosozumab: 52 Placebo: 52 Alendronate: 51 Teriparatide: 55	Romosozumab: 218 Teriparatide: 218	Romosozumab: 3589 Placebo: 3591	Romosozumab: 2046 Alendronate: 2047
Age, yr	Romosozumab: 66.3 ± 6.5 Placebo: 67.0 ± 6.5 Alendronate: 67.1 ± 5.8 Teriparatide: 66.8 ± 5.7	Romosozumab: 71.8 ± 7.4 Teriparatide: 71.2 ± 7.7	Romosozumab: 70.9 ± 7.0 Placebo: 70.8 ± 6.9	Romosozumab: 74.4 ± 7.5 Alendronate: 74.2 ± 7.5
BMD T-score	Romosozumab: LS: -2.33 ± 0.57 TH: -1.45 ± 0.65 FN: -1.87 ± 0.58 Placebo: LS: -2.29 ± 0.66 TH: -1.35 ± 0.67 FN: -1.76 ± 0.56 Alendronate: LS: -2.08 ± 0.69 TH: -1.55 ± 0.68 FN: -1.91 ± 0.61 Teriparatide: LS: -2.29 ± 0.57 TH: -1.32 ± 0.78 FN: -1.79 ± 0.67	Romosozumab: LS: -2.83 ± 1.10 TH: -2.27 ± 0.75 FN: -2.49 ± 0.67 Teriparatide: LS: -2.87 ± 1.04 TH: -2.21 ± 0.72 FN: -2.43 ± 0.66	Romosozumab: LS: -2.72 ± 1.04 TH: -2.48 ± 0.47 FN: -2.76 ± 0.28 Placebo: LS: -2.71 ± 1.04 TH: -2.46 ± 0.47 FN: -2.74 ± 0.29	Romosozumab: LS: -2.94 ± 1.25 TH: -2.78 ± 0.68 FN: -2.89 ± 0.49 Alendronate: LS: -2.99 ± 1.24 TH: -2.81 ± 0.67 FN: -2.90 ± 0.50
Patients with fractures	–	Romosozumab: 100% (n = 218) Teriparatide: <100% (n = 217)	Romosozumab: -Vertebral: 18.7% -Nonvertebral: 21.7% Placebo: -Vertebral: 18.0% -Nonvertebral: 21.8%	Romosozumab: 99.1% -Vertebral: 96.2% -Nonvertebral: 37.5% Alendronate: 99.1% -Vertebral: 95.9% -Nonvertebral: 37.6%
Follow-up time	72 Months	12 Months	36 Months	33 Months[d]
Sequential treatment	24-month romosozumab → 12-month denosumab or placebo → 12-month romosozumab → 24-month zoldronate[c]	–	12-month romosozumab → 24-month denosumab 12-month placebo → 24-month denosumab	12-month romosozumab → 21-month alendronate 12-month alendronate → 21-month alendronate

Values are presented as mean ± standard deviation.
STRUCTURE, Study to Evaluate the Effect of Treatment with Romosozumab or Teriparatide in Postmenopausal Women; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk; QD, once daily; QW, once weekly; QM, once monthly; BMD, bone mineral density; LS, lumbar spine; TH, total hip; FN, femoral neck.
[a] Other romosozumab doses (70 mg QM, 140 Q3M, 140 QM, 210 Q3M) were not included into the meta-analysis.
[b] Comparators were grouped for meta-analysis.
[c] Only one sequence with romosozumab shown, study also included other sequences.
[d] Median follow-up at time of primary analysis.

16%, but statistically significant by 20% in double-blind studies and 12% in a sequential treatment approach with romosozumab followed by an antiresorptive treatment, respectively. But important to mention here is that the number of studies included into the meta-analysis was low. Therefore, the results of the meta-analysis indicate a low significance and more studies are needed.

Nevertheless, based on the magnitude of risk reduction a similar effect like for romosozumab on risk of falls was seen for denosumab in a pooled analysis of 5 trials including more than 10,000 patients. In this analysis, a 22% reduction in incidence of falls by denosumab

Table 2
Risk of bias assessment of studies included into the meta-analysis.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcomes assessment	Incomplete outcome data	Selective reporting	Other bias
NCT00896532 [4,19]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
NCT01796301 STRUCTURE [16,20]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk
NCT01575834 FRAME [17,21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
NCT01631214 ARCH [5,22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk

FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; ARCH, Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk.

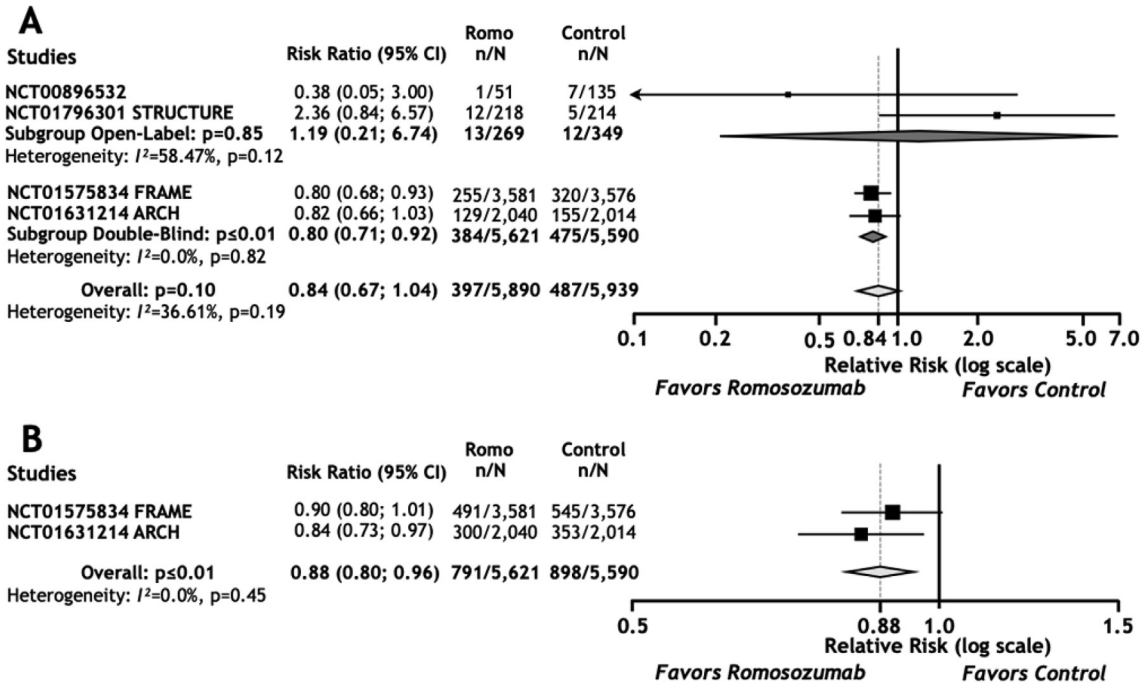

Fig. 2. Meta-analysis of risk of falls in postmenopausal women treated with romosozumab (the grey dashed line indicates the overall effect estimate). (A) 12-month data stratified by study design. (B) 33- to 36-month data – romosozumab followed by an antiresorptive treatment. CI, confidence interval; I^2, heterogeneity assessment; Romo, romosozumab; n/N, number of events/total number of patients.

compared to placebo was reported [11]. Thus, the results for denosumab were comparable to our findings for romosozumab in the present study.

In contrast to that, in one small study with 181 frail women treated either with zoledronate or placebo, number of falls was nonsignificantly increased in the zoledronate group (proportion of single fallers: odds ratio [OR], 1.24; P = 0.52). In addition, more subjects experienced multiple falls in the zoledronate group (OR, 1.83; P = 0.047), however, this effect was not significant anymore after adjusting for baseline frailty (OR, 1.60; P = 0.142) [23]. The results of our study and the data reported in literature indicate that for frail patients with high risk of falls romosozumab, similar to denosmuab, could be an appropriate treatment option.

To be mentioned here is that in our subgroup analysis of *open-label* studies the risk of falls was nonsignificantly lower in the control group. Reasons might be that the number of included patients (n = 618) and consequently, number of falls (n = 25) in the open-label studies alone was too small to get an appropriate effect estimate. Especially, since the heterogeneity was high between studies in the *open-label* subgroup analysis. In addition, the potential knowledge of patients on their treatment might have changed their behavior and therefore, their risk of falls. Due to the fact that *open-label* studies always have a high risk of bias [12], the effect of the double-blind subgroup analysis should have a higher impact for the evaluation of the effect of romosozumab on the risk of falls over 12 months.

Open remains the question how romosozumab influences the risk of falls in posmenopausal women with low BMD. Since frail patients typically have weak muscles [24], the hypothesis for less falls could be that romosozumab somehow increases muscle mass.

It is known that there is a correlation between thigh muscle volume and BMD. Obese, frail patients performing exercise showed a significant increase in thigh muscle volume and BMD, respectively. Patients in the same study, fulfilling a diet without exercise, experienced decreases in BMD and muscle volume. The authors concluded that changes in thigh muscle volume is predictive for hip BMD changes [25]. In addition, 2 other studies made the conclusion that BMD is predictive for frailty as well as prefrailty in women [26] and that sarcopenia is a risk factor for hip fractures [27]. Romosozumab has shown to increase BMD at lumbar spine and total hip by 13.7% and 6.2% from baseline [5], respectively. If there is a relationship between muscle mass and BMD, muscle mass might has increased comparable to BMD in patients treated with romosozumab.

A study by Krause et al. [28] revealed that sclerostin-deficient mice had increased trabecular bone volumes, but decreased muscle mass. Based on this data, a blockage of sclerostin would lead to a decrease in muscle mass and theoretically to an increase in frailty and risk of falls. However, a second study with sclerostin-deficient older mice, showed an increased bone mass, normal body weight and a trend towards an increase in lean body mass fraction (P = 0.06) [29].

Another potential link between increase in muscle mass and bone formation might be osteocalcin, which is produced by osteoblasts. A study has shown that osteocalcin is necessary to avoid the age-related muscle loss in mice and exogenous osteocalcin increased muscle mass in older mice [30]. The inhibition of sclerostin by romosozumab leads to a higher activity of osteoblasts and the formation of new osteoblasts from osteoprogenitor cells and bone lining cells [31]. A hypothesis could be that the higher activity and increased number of osteoblasts lead to an increased level of osteocalcin and thus to an increase in muscle mass. This increase in muscle mass could have a positive impact on frailty and risk of falls in patients treated with romosozumab.

Nevertheless, to answer the question how romosozumab influences the risk of falls and frailty, more data is needed to support our findings and to identify the potential mechanism.

This study has specific limitations which are caused by statistical evaluation as well as data availability and which are thus inevitable.

First, study search was restricted to 3 databases. Nevertheless, we included the ClinicalTrials.gov database into the search, which contained the major well-known studies of romosozumab and pharmaceutical companies often index their studies in this database. In addition, romosozumab recently received market authorizations and therefore, we do not expect that smaller, investigator-initiated studies are finished or even published elsewhere.

Second, incidence of falls was not defined as primary, secondary or any other endpoint in any of the studies included into this meta-analysis. Number of falls were collected as safety data in each study and not as a predefined outcome. Therefore, the number of falls for the conduction of this meta-analysis were taken from (severe) adverse event section of the ClinicalTrials.gov database.

Third, we included open-label studies, which always show a higher risk of bias. In addition, the heterogeneity of these studies was high in the performed subgroup analysis.

Fourth, falls are patient-reported outcomes. Therefore, it is likely that not all falls which occurred during the studies were reported by patients.

Fifth, the number of studies included into the meta-analysis, especially for the analysis of risk of falls in a sequential treatment approach, is low.

Sixth, our study brings no evidence on the effect by which romosozumab decreases the risk of falls and more studies on this topic are needed.

5. Conclusions

Our analysis indicates, based on the currently available, very limited amount of data, a positive trend for romosozumab on the reduction of risk for falls in postmenopausal women. However, the effect is only statistically significant when analyzing double-blind studies only or studies showing 12-month treatment with romosozumab followed by an antiresorptive medication for additional 21–24 months. It is very important to consider, that these findings are only preliminary results with a low significance, due to the fact that the number of studies included into the meta-analysis was very low and the overall effect after 12 months of treatment was nonsignificantly favoring romosozumab. To draw meaningful conclusions on the real effect of romosozumab on risk of falls, more data and analysis are needed to confirm and support our findings.

Conflicts of interest

CM and MB declare to have no conflict of interest. LM is a former employee of UCB Pharma and received fees for consultancy and presentations from UCB Pharma GmbH.

CRediT authorship contribution statement

Luis Möckel: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Matthias Bartneck:** Formal analysis, Investigation, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing. **Christina Möckel:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing - review & editing.

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