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Romosozumab (osteoporosis) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMD	bone mineral density
DVO	Dachverband Osteologie (Umbrella Association of Osteology)
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
LAD	Limited Activity Days
mBPI-SF	modified Brief Pain Inventory-Short Form
MedDRA	Medical Dictionary for Regulatory Activities
OPAQ-SV	Osteoporosis Assessment Questionnaire Short Version
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug romosozumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 11 March 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of romosozumab in comparison with the appropriate comparator therapy (ACT) in postmenopausal women with severe osteoporosis at high risk of fracture.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of romosozumab

Therapeutic indication	**ACT[a]**
Treatment of postmenopausal women with severe osteoporosis at high risk of fracture	**Alendronic acid** or risedronic acid or zoledronic acid or denosumab or teriparatide

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. Sufficient calcium and vitamin D intake is assumed.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA specified alendronic acid or risedronic acid or zoledronic acid or denosumab or teriparatide as ACT. The company deviated from the G-BA's specification insofar as it did not cite teriparatide as part of the ACT. This had no consequence for the present benefit assessment, as the company chose alendronic acid.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 2 years were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Results

Study pool and study characteristics

The ARCH study was included for the assessment of the added benefit of romosozumab. This was a randomized, double-blind multicentre study on the comparison of romosozumab followed by alendronic acid versus alendronic acid. The study included postmenopausal women (no vaginal bleeding or spotting within 12 months prior to screening) who met at least one of the following bone mineral density (BMD) and fracture criteria:

- BMD T-score ≤ −2.5 at the hip or femoral neck and either at least one moderate or severe vertebral fracture or at least 2 mild vertebral fractures
- BMD T-score ≤ −2.0 at the hip or femoral neck and either at least 2 moderate or severe vertebral fractures or one fracture of the proximal femur that occurred within 3 to 24 months prior to randomization

A total of 4093 patients were included in the study and, stratified by age (< 75 years/≥ 75 years), randomly assigned to either treatment with romosozumab for 12 months (N = 2046) or treatment with alendronic acid (N = 2047). From month 12 on, treatment with alendronic acid was administered in both study arms. The original blinding of the allocation to treatment with romosozumab or alendronic acid in the first 12 months of the study was maintained. The treatment duration for all patients was at least 24 months from the time point of randomization. Treatment with romosozumab and alendronic acid was in compliance with the recommendations of the respective Summaries of Product Characteristics (SPCs).

The patients in the study received at least 500 to 1000 mg daily calcium and 600 to 800 international units (IU) of vitamin D supplements as concomitant medication. Patients with a serum 25 (OH) vitamin D level between 20 and 40 ng/mL at screening received an initial loading dose of 50 000 to 60 000 IU of vitamin D after randomization. If the serum 25 (OH) vitamin D level was above 40 ng/mL at screening, administration of an initial vitamin D loading dose was possible at the investigator's discretion. According to the study protocol, the investigators could increase or reduce the dosages of calcium and vitamin D during the course of the study depending on the patients' needs. Although the mentioned dosages of calcium and vitamin D are below the daily doses of 700 to 1200 mg calcium and 800 to 1000 IU of vitamin D recommended in national and international osteoporosis guidelines, this deviation in the ARCH study did not lead to the exclusion of the study from the benefit assessment.

Primary outcomes of the study were the occurrence of new clinical fractures and new vertebral fractures. Further patient-relevant outcomes were all-cause mortality, as well as outcomes of the outcome categories of morbidity and side effects.

The mean age of the patients included in the study was 74 years, and the patients had been postmenopausal for approximately 27 years; about 96% had a prevalent vertebral fracture at

baseline and about 99% of the patients had an osteoporotic (including vertebral and non-vertebral fractures) fracture at the age of ≥ 55 years.

Risk of bias

The risk of bias for the results of the recorded outcomes with usable data was rated as low. The outcome "non-major non-vertebral fractures" was not analysed separately; the outcome "health-related quality of life" was not recorded. No usable data were available for the following outcomes: worst pain (recorded using Item 3 of the modified Brief Pain Inventory-Short Form [mBPI-SF], health status (measured using the visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D] questionnaire), and symptomatic atypical femoral fractures.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid; an added benefit is therefore not proven.

Morbidity

Clinical vertebral fractures

A statistically significant difference in favour of romosozumab followed by alendronic acid was shown between the treatment arms for the outcome "clinical vertebral fractures". This resulted in an indication of an added benefit of romosozumab in comparison with alendronic acid for this outcome.

Major non-vertebral fractures

A statistically significant difference in favour of romosozumab followed by alendronic acid was shown between the treatment arms for the outcome "major non-vertebral fractures". This resulted in an indication of an added benefit of romosozumab in comparison with alendronic acid for this outcome.

Non-major non-vertebral fractures

The outcome "non-major non-vertebral fractures" was not analysed separately. This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

Worst pain (mBPI-SF)

No usable data were available for the outcome "pain", recorded using Item 3 (worst pain over the last 24 hours) of the mBPI-SF. This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No usable data were available for the outcome "health status" measured with the EQ-5D VAS. This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

Health-related quality of life

In the ARCH study, no suitable instrument was used to reflect health-related quality of life. There was no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs, osteonecrosis of jaw, and gastrointestinal disorders (System Organ Class [SOC], AEs)

No statistically significant differences between the treatment groups were shown for any of the following outcomes: serious adverse events (SAEs), discontinuation due to adverse events (AEs), osteonecrosis of jaw, and gastrointestinal disorders. In each case, this resulted in no hint of greater or lesser harm from romosozumab in comparison with alendronic acid; greater or lesser harm is therefore not proven.

Symptomatic atypical femoral fractures

No usable data were available for the outcome "symptomatic atypical femoral fractures". This resulted in no hint of greater or lesser harm from romosozumab in comparison with alendronic acid; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug romosozumab in comparison with the ACT are assessed as follows:

In the overall consideration, there are exclusively positive effects for romosozumab in comparison with alendronic acid. These consist of an indication of considerable added benefit for the outcome "clinical vertebral fractures" and in an indication of a minor added benefit for the outcome "major non-vertebral fractures".

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

In summary, there is an indication of considerable added benefit of romosozumab versus the ACT alendronic acid for postmenopausal women with severe osteoporosis at high risk of fracture.

Table 3 shows a summary of probability and extent of the added benefit of romosozumab.

Table 3: Romosozumab[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Treatment of postmenopausal women with severe osteoporosis at high risk of fracture[c]	**Alendronic acid** or risedronic acid or zoledronic acid or denosumab or teriparatide	Indication of considerable added benefit

a. In the ARCH study, romosozumab was investigated only followed by alendronic acid.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. Sufficient calcium and vitamin D intake is assumed.
c. Refers to patients with severe osteoporosis at high risk of fracture as defined in the ARCH study.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of romosozumab in comparison with the ACT in postmenopausal women with severe osteoporosis at high risk of fracture.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of romosozumab

Therapeutic indication	**ACT**[a]
Treatment of postmenopausal women with severe osteoporosis at high risk of fracture	**Alendronic acid** or risedronic acid or zoledronic acid or denosumab or teriparatide
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. Sufficient calcium and vitamin D intake is assumed. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The G-BA specified alendronic acid or risedronic acid or zoledronic acid or denosumab or teriparatide as ACT. The company deviated from the G-BA's specification insofar as it did not cite teriparatide as part of the ACT. This had no consequence for the present benefit assessment, as the company chose alendronic acid.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 2 years were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on romosozumab (status: 16 January 2020)
- bibliographical literature search on romosozumab (last search on 16 January 2020)
- search in trial registries/trial results databases for studies on romosozumab (last search on 16 January 2020)
- search on the G-BA website for romosozumab (last search on 16 January 2020)

To check the completeness of the study pool:

- search in trial registries for studies on romosozumab (last search on 18 March 2020)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no)	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
20110142 (ARCH[d])	Yes	Yes	No	No[e]	Yes [3-9]	Yes [10,11]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: EPAR.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; EPAR: European Public Assessment Report; RCT: randomized controlled trial; vs.: versus

The study pool for the benefit assessment of romosozumab in comparison with the ACT consisted of the ARCH study. The study pool concurs with that of the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ARCH	RCT, double-blind, parallel[b]	Postmenopausal[c] women (≥ 55 to ≤ 90 years) with at least one of the following BMD and fracture criteria: ▪ BMD T-score[d] ≤ −2.50 at the hip or femoral neck and either at least one moderate or severe [12] vertebral fracture or at least 2 mild [12] vertebral fractures or ▪ BMD T-score[d] ≤ −2.00 at the hip or femoral neck and either at least 2 moderate or severe [12] vertebral fractures or one fracture of the proximal femur (occurred within 3 to 24 months prior to randomization)	▪ Romosozumab followed by alendronic acid (N = 2046) ▪ alendronic acid (N = 2047)	▪ Screening: 35 days before start of treatment ▪ Treatment: romosozumab for 12 months followed by alendronic acid, or continuous treatment with alendronic acid until end of study ▪ Observation: at least 24 months, at most until end of study[e]	270 study centres in Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, Denmark, Dominican Republic, Estonia, Finland, France, Germany, Great Britain, Greece, Guatemala, Hong Kong, Hungary, Israel, Italy, Latvia, Lithuania, Mexico, Netherlands, New Zealand, Norway, Peru, Poland, Republic of Korea, Romania, Russia, Slovakia, South Africa, Spain, Sweden, Taiwan, Turkey, USA 5/2012–6/2017 Primary analysis: planned for when clinical fractures[f] have been confirmed in ≥ 330 patients and study visit at month 24 completed (27 February 2017) End of study[e]: 29 June 2017	▪ Primary: occurrence of new clinical fractures[f], new vertebral fractures ▪ Secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. From month 12 on, treatment with alendronic acid was administered in both study arms; the original blinding, i.e. blinded allocation to prior treatment with romosozumab or alendronic acid, was maintained.
c. Defined as no vaginal bleeding or spotting within 12 consecutive months prior to screening.
d. BMD T-score and vertebral fractures were assessed at the time of screening based on radiological examinations, a proximal femur fracture based on discharge summary, radiology report, or comparable documentation of type and date of fracture.
e. According to the study protocol, a final analysis after the primary analysis was to be conducted when at least 440 patients have experienced non-vertebral fractures, unless the primary analysis already showed the superiority of romosozumab for non-vertebral fractures. The primary analysis (data cut-off on 27 February 2017) showed the required superiority of romosozumab for non-vertebral fractures. Thus, the study ended on 29 June 2017, and, in compliance with the protocol, no final analysis was conducted.
f. Clinical fractures include clinicial (symptomatic) vertebral fractures and non-vertebral fractures.

AE: adverse event; BMD: bone mineral density; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid (multipage table)

Study	Intervention	Comparison
ARCH	Until month 12: romosozumab 210 mg, once a month (3 SC injections of 70 mg each) + placebo tablets, orally, once a week From month 13: alendronic acid 70 mg, orally, once a week	Until month 12: alendronic acid 70 mg, orally, once a week + placebo injection, once a month (3 SC injections) From month 13: alendronic acid 70 mg, orally, once a week
	Dose adjustments: ▪ no dose adjustments for romosozumab, alendronic acid and placebo allowed	
	Required concomitant treatment ▪ daily intake of at least calcium (500 mg to 1000 mg) and vitamin D supplements (600 to 800 IU)[a] **Non-permitted pretreatment** ▪ strontium ranelate or fluoride (for osteoporosis) ≤ 5 years prior to randomization[b] ▪ zoledronic acid (IV) of any dose ≤ 3 years and more than 1 dose ≤ 5 years prior to randomization ▪ ibandronic acid or pamidronic acid (IV) ≤ 1 year prior to randomization[c] ▪ oral bisphosphonates[c, d] ▪ denosumab or any cathepsin K inhibitor ≤ 18 months prior to randomization ▪ teriparatide or any PTH analogues[d] ▪ systemic oral or transdermal oestrogens or SERMs ≤ 6 months prior to randomization[b] ▪ hormone replacement therapy ≤ 6 months prior to randomization[b] ▪ tibolone, cinacalcet or calcitonin, any dose ≤ 3 months prior to randomization ▪ systemic glucocorticoids: ≥ 5 mg prednisone equivalent/day for more than 14 days ≤ 3 months prior to randomization **Non-permitted concomitant treatment** ▪ strontium ranelate ▪ fluoride, vitamin K and vitamin K analogues (for treatment of osteoporosis) ▪ IV and oral bisphosphonates[e] ▪ denosumab ▪ teriparatide or any PTH analogues ▪ oral glucocorticoids ≥ 5 mg prednisone equivalent/day > 3 months (exception: tapering of glucocorticoids of < 1 month duration regardless of dose) ▪ oestrogens[e] (except vaginal and cutaneous use) ▪ SERMs[e], tibolone[e], calcitonin[e] ▪ cinacalcet ▪ hormone replacement therapy ▪ activated vitamin D	

Table 7: Characteristics of the intervention – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid (multipage table)

Study	Intervention	Comparison
a. Patients with a serum 25 (OH) vitamin D level of ≥ 20 and ≤ 40 ng/mL at screening received an initial loading dose of 50 000 to 60 000 IU of vitamin D after randomization. If the serum 25 (OH) vitamin D level was > 40 ng/mL at screening, administration of an initial vitamin D loading dose was possible at the investigator's discretion. b. Cumulative use over a period of > 1 month. c. Cumulative use for > 3 years prior to randomization (exception: last dose ≥ 5 years prior to randomization). d. Any dose ≤ 3 months prior to randomization, cumulative use for > 1 month between 3 and 12 months prior to randomization. e. Cumulative use for ≤ 1 month allowed as concomitant treatment. 25 (OH) vitamin D: 25-hydroxy vitamin D; IU: international units; IV: intravenous; PTH: parathyroid hormone; RCT: randomized controlled trial; SC: subcutaneous; SERM: selective oestrogen receptor modulator; vs.: versus		

Study design

The ARCH study was a randomized, double-blind multicentre study on the comparison of romosozumab followed by alendronic acid versus alendronic acid. The study included postmenopausal women (no vaginal bleeding or spotting within 12 months prior to screening) who met at least one of the following BMD and fracture criteria:

- BMD T-score[4] ≤ −2.5 at the hip or femoral neck and either at least one moderate or severe vertebral fracture or at least 2 mild vertebral fractures
- BMD T-score[4] ≤ −2.0 at the hip or femoral neck and either at least 2 moderate or severe vertebral fractures or one fracture of the proximal femur that occurred within 3 to 24 months prior to randomization

In the ARCH study, vertebral fractures were graded using the semiquantitative method according to Genant 1993 [12], in which fractures are divided into different severity grades ranging from mild to severe (grade 1 to grade 3) depending on the degree of height reduction of the affected vertebra.

A total of 4093 patients were included in the study and randomly assigned in a 1:1 ratio stratified by age (< 75 years/≥ 75 years) to either treatment with romosozumab for 12 months (N = 2046) or treatment with alendronic acid (N = 2047). From month 13 after screening, treatment with alendronic acid was administered in both study arms. The original blinding of the allocation to treatment with romosozumab or alendronic acid in the first 12 months of the study was maintained. The treatment duration for all patients was at least 24 months from the time point of randomization.

[4] The T-score is the deviation from the bone density of a young woman given in standard deviations [13]. The ARCH study used the data of white women from the National Health and Nutritional Examination Survey (1998) of the National Center for Health Statistics as a basis.

Treatment with romosozumab and alendronic acid was in accordance with the regimen described in Table 7 and was in compliance with the recommendations provided in the SPCs [14,15]. In contrast to the SPC, romosozumab was not administered in 2 subcutaneous injections (105 mg each), but in 3 subcutaneous injections (70 mg each). The European Medicines Agency (EMA) considered the pharmacological equivalence and the non-inferiority of this dosage regimen as given [11]. Hence, the deviation of the dosage regimen had no consequence for the benefit assessment.

The patients in the study received at least 500 to 1000 mg daily calcium and 600 to 800 IU of vitamin D supplements as concomitant medication. Within these requirements, the investigators could increase or reduce the dosages of calcium and vitamin D depending on the patients' needs. Patients with a serum 25 (OH) vitamin D level between 20 and 40 ng/mL at screening received an initial loading dose of 50 000 to 60 000 IU of vitamin D after randomization. If the serum 25 (OH) vitamin D level was above 40 ng/mL at screening, administration of an initial vitamin D loading dose was possible at the investigator's discretion.

The mentioned dosages of calcium and vitamin D are below the daily doses of 700 to 1200 mg calcium [13,16,17] and 800 to 1000 IU of vitamin D [13,18] recommended in national and international osteoporosis guidelines. However, the deviation of the allowed limits from possible dosages of calcium and vitamin D in the ARCH study did not lead to the exclusion of the study from the benefit assessment.

Primary outcomes of the study were the occurrence of new clinical fractures and new vertebral fractures. Further patient-relevant outcomes were all-cause mortality, as well as outcomes of the outcome categories of morbidity and side effects.

Patients with severe osteoporosis at high risk of fracture in the ARCH study

According to the guideline for the prophylaxis, diagnosis and therapy of osteoporosis in postmenopausal women produced by the DVO, the German Umbrella Association of Osteology, osteoporosis is defined as severe if osteoporosis-related fractures have occurred [13]. The patients in the ARCH study fulfilled this criterion.

The inclusion criteria for the study showed that all patients had to have existing fractures before baseline, depending on BMD. It can be inferred from the information on patient characteristics (Table 8) that about 99% of the patients included had osteoporotic fractures (after the age of 55 years).

The criteria defined in the ARCH study for the presence of a high risk of fracture cover the criteria in the DVO guideline [13], but are slightly narrower in the ARCH study. The DVO guideline cites several characteristics in postmenopausal women that increase the risk of fracture, including advanced age and a history of osteoporosis-related fractures. These risk factors were present in the included patient population (see Table 8).

The DVO guideline recommends drug therapy for postmenopausal women with a T-score < −2.0 at the lumbar spine, the femoral neck or the proximal femur, individually also with a T-score > −2.0 if any of the following events have additionally occurred:

- a single low-trauma vertebral fracture of grade 2 or 3 according to Genant 1993 [12], or
- multiple low-trauma vertebral fractures of grade 1 to 3 according to Genant 1993 [12], or
- low-trauma fractures of the proximal femur

It must be excluded that other, non-osteoporotic causes of a fracture are not more likely. In the inclusion criteria of the ARCH study, the T-score is recorded at the hip and the femoral neck. According to international guidelines, these are suitable sites for obtaining the T-score besides the spine [17,19].

In contrast to the company's assessment, a comparison with the inclusion criteria of the ARCH study (see section above on the study design) shows that the included study population of the ARCH study does not cover all patients who have a high risk of fracture according to the DVO guideline, and for whom therefore drug therapy is indicated. For example, patients with a T-score < −2.0 and ≥ −2.5 and single moderate (grade 2) or severe (grade 3) or multiple mild (grade 1) vertebral fractures are not comprised by the inclusion criteria of the ARCH study.

Patients with cardiovascular risk in the ARCH study

According to the SPC, romosozumab is contraindicated in patients with previous myocardial infarction or stroke. In addition, consideration should be given to the patient's fracture risk over the next year and her cardiovascular risk in the treatment decision regarding romosozumab. Romosozumab should only be used after appropriate evaluation of the risk [14].

According to the information provided by the company in Module 4 A, the proportion of patients with myocardial infarction or stroke included in the ARCH study was very low (6.1%). Due to the small proportion, this had no consequence for the benefit assessment.

Data cut-offs

Analyses with potential relevance for the present assessment were planned a priori in the ARCH study for different documentation periods:

- Months 0 to 24: Data from the observation of individual patients from months 0 to 24 were included in the analysis.
- Primary analysis (primary analysis period): The primary analysis was planned to be performed when clinical fractures (clinical vertebral fractures and non-vertebral fractures) have occurred in ≥ 330 patients, and all patients have completed the month 24 study visit; this was the case on 27 February 2017 (data cut-off date).
- Month 0 until final analysis: The final analysis was planned to be performed when non-vertebral fractures have occurred in 440 patients; the final analysis was to be omitted if

the primary analysis already demonstrated superiority of romosozumab for non-vertebral fractures.

The primary analysis was performed on the basis of the cut-off on 27 February 2017 and, according to the company, showed superiority of romosozumab for non-vertebral fractures. In accordance with the protocol, the final analysis was therefore omitted and the study ended on 29 June 2017 (referred to as "total study period"). The analysis of AE outcomes was based on this total study period.

In accordance with the study protocol, not all outcomes were recorded at all documentation times. In the present benefit assessment, the last available time of analysis relevant for the benefit assessment was used in each case for the patient-relevant outcomes included (see Table 11).

The approach largely corresponds to that of the company, which for various outcomes also considered the results at month 12 in addition to the analyses at month 24 or the primary analysis.

Table 8 shows the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid (multipage table)

Study Characteristics Category	**Romosozumab followed by alendronic acid N[a] = 2046**	**Alendronic acid N[a] = 2047**
ARCH		
Age [years], mean (SD)	74 (8)	74 (8)
Family origin, n (%)		
Asian	137 (6.7)	149 (7.3)
Black or African American	19 (0.9)	23 (1.1)
White	1447 (70.7)	1415 (69.1)
Other[b]	443 (21.7)	459 (22.4)
Missing	0 (0)	1 (< 0.1)
Geographical region, n (%)		
Asia-Pacific and South Africa	213 (10.4)	216 (10.6)
Western Europe and New Zealand/Australia	269 (13.1)	264 (12.9)
Central and Eastern Europe and Middle East	835 (40.8)	798 (39.0)
Central and South America	674 (32.9)	727 (35.5)
North America	55 (2.7)	42 (2.1)
BMI [kg/m²], mean (SD)	25.5 (4.4)	25.4 (4.4)
Time since menopause [years], mean (SD)	26.9 (9.4)	26.9 (9.2)
10-year fracture risk[c] of major osteoporotic fractures[d] [%], mean (SD)	20.2 (10.2)	20.0 (10.1)
10-year fracture risk[c] of hip fractures [%], mean (SD)	9.9 (7.9)	9.8 (7.8)

Table 8: Characteristics of the study population – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid (multipage table)

Study Characteristics Category	**Romosozumab followed by alendronic acid N[a] = 2046**	**Alendronic acid N[a] = 2047**
History of fracture, n (%)		
Prevalent vertebral fracture	1969 (96.2)	1964 (95.9)
Severe [12] vertebral fracture[e]	1369 (66.9)	1321 (64.5)
Fracture at the age of ≥ 55 years		
Osteoporotic fracture	2021 (98.8)	2029 (99.1)
Non-vertebral (osteoporotic) fracture	705 (34.5)	692 (33.8)
Thereof major non-vertebral fractures	554 (27.1)	564 (27.6)
BMD T-score[f] of the lumbar spine, n (%)		
≤ −3	997 (48.7)	1024 (50.0)
> −3 and ≤ −2.5	304 (14.9)	305 (14.9)
> −2.5	649 (31.7)	617 (30.1)
Missing	96 (4.7)	101 (4.9)
BMD T-score[f] of the hip, n (%)		
≤ −2.5	1356 (66.3)	1384 (67.6)
> −2.5	690 (33.7)	662 (32.3)
Missing	0 (0)	1 (< 0.1)
BMD T-score[f] of the femoral neck, n (%)		
≤ −2.5	1712 (83.7)	1691 (82.6)
> −2.5	334 (16.3)	355 (17.3)
Missing	0 (0)	1 (< 0.1)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	471 (23.0[b])	472 (23.1[b])

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. Based on the FRAX components, calculated with BMD; FRAX is a calculation model by the WHO to estimate the country-specific 10-year fracture risk for hip fractures and major osteoporotic fractures.
d. Consisting of fractures of hip, humerus, forearm and clinical vertebral fractures.
e. Based on radiography of the spine at screening.
f. Ratio of individual BMD – BMD mean value of adult young women and SD in the population to determine the mean value.

BMD: bone mineral density; BMI: body mass index; F: female; FRAX: Fracture Risk Assessment Tool; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus; WHO: World Health Organization

The characteristics of the included study population were largely comparable between both treatment arms. The mean age of the patients was 74 years; most of them were of white family origin and had been postmenopausal for about 27 years.

About 96% of the patients had a prevalent vertebral fracture at baseline, and about 99% of the patients had an osteoporotic (including vertebral and non-vertebral fractures) fracture at the age of ≥ 55 years.

Transferability of the study results to the German health care context

In Module 4 A (Section 4.3.1.2.1), the company rated the results of the ARCH study as transferable to the German health care context.

The company explained that the patients included in the ARCH study were postmenopausal women who had an increased risk of fracture according to the criteria of the DVO guideline [13] and that, in addition, the fracture outcomes had been recorded in compliance with the guidelines.

The company pointed out that the study had also been conducted in study centres in Germany, and that, besides, there were no relevant indications of biodynamic or kinetic differences between individual population groups.

The company stated that in the ARCH study, romosozumab was administered in 3 subcutaneous injections of 70 mg each per month for 1 year, but that, according to the SPC [14], romosozumab is to be administered in 2 subcutaneous injections of 105 mg each per month for 1 year. In this context, the company pointed out that the pharmacological equivalence and non-inferiority of the dosage regimen used in the ARCH study had been demonstrated in clinical studies [11].

The company did not provide any further information on the transferability of the study results to the German health care context.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ARCH	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the ARCH study. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - clinical vertebral fractures
  - major non-vertebral fractures
  - non-major non-vertebral fractures
  - worst pain (mBPI-SF, measured with the scale “worst pain over the last 24 hours” [Item 3])
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - osteonecrosis of jaw
  - symptomatic atypical femoral fractures
  - gastrointestinal disorders (SOC, AEs)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study	Outcomes											
	All-cause mortality	**Clinical vertebral fractures**	**Major non-vertebral fractures[a]**	**Non-major non-vertebral fractures**	**Worst pain (mBPI-SF)[b]**	**Health status (EQ-5D VAS)**	**Health-related quality of life**	**SAEs[c]**	**Discontinuation due to AEs[c]**	**Osteonecrosis of jaw**	**Symptomatic atypical femoral fracture**	**Gastrointestinal disorders (SOC, AEs)**
ARCH	Y	Y	Y	No[d]	No[e]	No[e]	No[e]	Y	Y	Y	No[f]	Y

a. Composite outcome consisting of fractures at the following sites: hip, pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm.
b. Measured with the scale "worst pain over the last 24 hours" (Item 3).
c. Without recording of osteoporotic events.
d. Outcome was not analysed separately.
e. No usable data.
f. No usable data; the company presented data on atypical femoral fractures, but not separately on symptomatic atypical femoral fractures.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; mBPI-SF: modified Brief Pain Inventory-Short Form; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; Y: yes

Morbidity

mBPI-SF

No usable data were available, as > 30% of the patients were not considered in the analysis.

EQ-5D VAS

No usable data were available, as > 30% of the patients were not considered in the relevant analysis of the change in EQ-5D VAS in comparison with baseline.

The company referred to the work of Pickard 2007 [20] to prove the validity of a response criterion of 10 points. This work is unsuitable for showing the validity of a response criterion of the EQ-5D VAS, however [21]. The response criterion used by the company was therefore not used (the results are presented in Appendix A of the full dossier assessment as supplementary information).

Health-related quality of life

Osteoporosis Assessment Questionnaire Short Version (OPAQ-SV)

The company presented data on the basis of the OPAQ-SV for the outcome "health-related quality of life". Contrary to the company's assessment, this instrument is unsuitable for recording health-related quality of life. Overall, the validity of the OPAQ-SV cannot be assessed on the basis of the sources presented [22-25]. In particular, it is not clear whether the reduction of the original version with 102 items to the short version with 34 items still reflects all patient-relevant aspects. For this reason, the data on the OPAQ-SV presented by the company were not considered in the present benefit assessment.

Limited Activity Days (LAD)

The company presented data on the LAD for the outcome "health-related quality of life". According to the references provided by the company [26,27], this cannot be regarded as an instrument, but consists of 3 individual questions on hospitalization, bed rest, and limited activity. The LAD is therefore unsuitable for reflecting the construct of health-related quality of life, addressing aspects of morbidity at best. Irrespective of the fact that the exact formulation of the individual questions is unknown, it remains unclear how they were analysed. It can be inferred from the available documents that these were 2-step questions. For the events of hospitalization, bed rest, and limited activity, it was asked in a second step whether these had occurred for health-related reasons or due to a fracture, and for how many days this limitation had existed in the last 30 days. However, overall it remains unclear which method was used to analyse the data recorded in this way. Overall, the data on the LAD presented by the company were not considered in the present benefit assessment.

Table 11 shows which dates of analysis were used for the respective outcomes.

Table 11: Overview of the date of analysis used per outcome

Outcome category **Outcome**	**Analysis date used**
Mortality	
All-cause mortality	Total study period
Morbidity	
Clinical vertebral fractures	Month 24
Major non-vertebral fractures, non-major non-vertebral fractures	Primary analysis
Worst pain (mBPI-SF), health status (EQ-5D VAS)	Month 24
Health-related quality of life	Month 24
Side effects	Total study period

2.4.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study	Study level	Outcomes											
		All-cause mortality	Clinical vertebral fractures	Major non-vertebral fractures[a]	Non-major non-vertebral fractures	Worst pain (mBPI-SF)[b]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs[c]	Discontinuation due to AEs[c]	Osteonecrosis of jaw	Symptomatic atypical femoral fracture	Gastrointestinal disorders (SOC, AEs)
ARCH	L	L	L	L	–[d]	–[e]	–[e]	–[e]	L	L	L	–[f]	L

a. Composite outcome consisting of fractures of the following sites: hip, pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm.
b. Measured with the scale "worst pain over the last 24 hours" (Item 3).
c. Without recording of osteoporotic events.
d. Outcome was not analysed separately.
e. No usable data.
f. No usable data; the company presented data on atypical femoral fractures, but not separately on symptomatic atypical femoral fractures.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; L: low; mBPI-SF: modified Brief Pain Inventory-Short Form; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias for the results of the recorded outcomes with usable data was rated as low. This concurs with the company's assessment.

The outcome "non-major non-vertebral fractures" was not analysed separately; the outcome "health-related quality of life" was not recorded; hence the risk of bias was not assessed.

No usable data were available for the outcomes "worst pain" (recorded using Item 3 of the mBPI-SF), "health status" (measured using the EQ-5D VAS), and "symptomatic atypical femoral fractures". The risk of bias for the results on these outcomes was therefore not assessed.

2.4.3 Results

Table 13, Table 14 and Table 15 summarize the results of romosozumab followed by alendronic acid in comparison with alendronic acid in postmenopausal women with severe osteoporosis at high risk of fracture. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The available Kaplan-Meier curves on the event time analyses used are presented in Appendix B, the results on common AEs, SAEs and discontinuation due to AEs in Appendix C of the full dossier assessment. The data cut-off underlying the Kaplan-Meier curves is unknown. Due to the presentation of common AEs and SAEs in Module 4 A, SOCs and Preferred Terms (PTs) are presented separately.

Table 13: Results (mortality, morbidity, time to event) – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study Outcome category Outcome	Romosozumab followed by alendronic acid		Alendronic acid		Romosozumab followed by alendronic acid vs. alendronic acid
	N	Median time to event [95% CI] Patients with event n (%)	N	Median time to event [95% CI] Patients with event n (%)	HR [95% CI]; p-value
ARCH					
Mortality (total study period)					
All-cause mortality[a]	2040	ND 101 (5.0)	2014	ND 103 (5.1)	0.98 [0.74; 1.29]; 0.87
Morbidity (primary analysis period, unless stated otherwise)					
Clinical vertebral fractures (month 24)[b]	2046	– 18 (0.9)	2047	– 44 (2.1)	RR: 0.41 [0.24; 0.71]; < 0.001[c]
Major non-vertebral fractures	2046	ND 146 (7.1)	2047	ND 196 (9.6)	0.73 [0.59; 0.90]; 0.004
Fractures of the hip	2046	ND 41 (2.0)	2047	ND 66 (3.2)	0.62 [0.42; 0.92]; 0.015
Fractures of the pelvis	2046	ND 5 (0.2)	2047	ND 17 (0.8)	0.29 [0.11; 0.78]; 0.009
Fractures of the distal femur	2046	ND 11 (0.5)	2047	ND 7 (0.3)	1.56 [0.60; 4.01]; 0.36
Fractures of the proximal tibia	2046	ND 4 (0.2)	2047	ND 6 (0.3)	0.65 [0.18; 2.29]; 0.49
Fractures of the ribs	2046	ND 13 (0.6)	2047	ND 23 (1.1)	0.56 [0.29; 1.11]; 0.094
Fractures of the proximal humerus	2046	ND 17 (0.8)	2047	ND 28 (1.4)	0.60 [0.33; 1.09]; 0.091
Fractures of the forearm	2046	ND 65 (3.2)	2047	ND 73 (3.6)	0.89 [0.63; 1.24]; 0.47
Non-major non-vertebral fractures	Outcome not analysed separately				

a. Data of the safety population; in Module 4 A, the company presented AEs leading to death for the outcome "all-cause mortality". The available sources show that, based on the randomized patients, 106 patients in the intervention arm and 113 patients in the comparator arm died, but no HR is available for these data.
b. These are the data for the period for which the values for all women for the individual observation period from baseline to month 24 are included; no data are available for the primary analysis period (median observation period of 33 months).
c. Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [28]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 14: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study **Outcome category** **Outcome**	**Romosozumab followed by alendronic acid**			**Alendronic acid**			**Romosozumab followed by alendronic acid vs. alendronic acid**
	N	**Values at baseline mean (SD)**	**Change at month 24 mean (SE)**	**N**	**Values at baseline mean (SD)**	**Change at month 24 mean (SE)**	**MD [95% CI]; p-value**
ARCH							
Morbidity							
Worst pain (mBPI-SF)[a]	No usable data[b]						
Health status (EQ-5D VAS)	No usable data[b]						
Health-related quality of life							
	No usable data[c]						

a. Measured with the scale "worst pain over the last 24 hours" (Item 3).
b. No usable data, as > 30% of the patients were not considered in the analysis. The available analyses showed no statistically significant results.
c. No usable data; the OPAQ-SV and the individual questions of the LAD are unsuitable for recording health-related quality of life.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LAD: Limited Activity Days; mBPI-SF: modified Brief Pain Inventory-Short Form; MD: mean difference; N: number of analysed patients; OPAQ-SV: Osteoporosis Assessment Questionnaire Short Version; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 15: Results (side effects) – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid

Study Outcome category Outcome	Romosozumab followed by alendronic acid		Alendronic acid		Romosozumab followed by alendronic acid vs. alendronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ARCH					
Side effects (total study period)					
AEs (supplementary information)[b]	2040	1761 (86.3)	2014	1776 (88.2)	–
SAEs[b]	2040	568 (27.8)	2014	553 (27.5)	1.01 [0.92; 1.12]; 0.806
Discontinuation due to AEs[b, c]	2040	142 (7.0)	2014	152 (7.5)	0.92 [0.74; 1.15]; 0.505
Osteonecrosis of jaw[d]	2040	2 (< 0.1)	2014	1 (< 0.1)	1.97 [0.18; 21.76]; > 0.999
Symptomatic atypical femoral fracture	No usable data[e]				
Gastrointestinal disorders (SOC, AEs)	2040	777 (38.1)	2014	796 (39.5)	0.96 [0.89; 1.04]; 0.350

a. Mantel-Haenszel method without adjustment for covariates, Fisher exact test.
b. Based on the analyses presented by the company without recording of osteoporotic events. The company did not deduct the PTs “bone pain”, “spinal pain” and “foot fracture”, although these events are also most likely related to the underlying disease. Since these events occurred in fewer than 3% of the patients, however, this has no consequence for the benefit assessment.
c. These are treatment discontinuations due to AEs; besides, 43 patients (2.1%) in the intervention arm and 44 patients (2.2%) in the comparator arm discontinued the study due to AEs.
d. Events of a MedDRA query predefined by the company according to PT list; the occurred PTs were assessed by an adjudication committee. In addition, the company stated in Module 4 A that events identified after review of the case report forms and allocated by an adjudication committee were also recorded. There are discrepant data between the registry entry and Module 4 A. The registry entry shows that there was one patient for each event of the PTs “osteonecrosis”, “osteonecrosis of jaw”, “pain in jaw” and “osteomyelitis” in the comparator arm. According to the registry entry, no events occurred in the intervention arm. Due to the small number of events, this is not relevant for the benefit assessment.
e. The company presented data on atypical femoral fractures, but not separately on symptomatic atypical femoral fractures.

AE: adverse event; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

Operationalization

The outcome “all-cause mortality” was recorded by means of the deaths noted in the individual case report forms and in the framework of AEs leading to death. This operationalization may

not cover all deaths; the data on patient flow show that the number of deceased patients differed only slightly.

Result

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid; an added benefit is therefore not proven.

This concurs with the assessment of the company, which derived no added benefit for the outcome "all-cause mortality".

Morbidity

Clinical vertebral fractures

Operationalization

The outcome "clinical vertebral fractures" comprised fractures regardless of trauma severity or cause of fracture. The outcome was defined a priori as new or worsened vertebral fractures associated with back pain. Back pain that occurred with temporal delay and thus not immediately with detection of the fracture was also recorded. As a result, back pain from other causes could have been mistakenly rated as a symptom of a vertebral fracture. However, since back pain is the key symptom of a vertebral fracture, it is assumed that symptomatic vertebral fractures were adequately recorded with this operationalization.

Result

A statistically significant difference in favour of romosozumab followed by alendronic acid was shown between the treatment arms for the outcome "clinical vertebral fractures". This resulted in an indication of an added benefit of romosozumab in comparison with alendronic acid for this outcome.

This concurs with the company's assessment.

Major non-vertebral fractures

Operationalization

The outcome did not comprise fractures associated with high trauma severity or pathologic fractures (defined as fractures due to a disease other than osteoporosis).

Result

A statistically significant difference in favour of romosozumab followed by alendronic acid was shown between the treatment arms for the outcome "major non-vertebral fractures". The effect of the composite outcome was particularly determined by the component "hip fractures". There was an indication of an added benefit of romosozumab in comparison with alendronic acid for the outcome "major non-vertebral fractures".

This concurs with the company's assessment.

Non-major non-vertebral fractures

The outcome "non-major non-vertebral fractures" was not analysed separately. This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

This deviates from the company's approach insofar as the company did not use the outcome "non-major non-vertebral fractures" as separate outcome.

Worst pain (mBPI-SF)

No usable data were available for the outcome "pain", recorded using Item 3 (worst pain over the last 24 hours) of the mBPI-SF. This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company, which presented the results of the outcome "worst pain" (mBPI-SF), but did not draw a conclusion on the added benefit for the outcome.

Health status (EQ-5D VAS)

No usable data were available for the outcome "health status" measured with the EQ-5D VAS. This resulted in no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

This deviates from the approach of the company, which presented the results of the outcome "health status", but did not draw a conclusion on the added benefit for the outcome.

Health-related quality of life

In the ARCH study, no suitable instrument was used to reflect health-related quality of life. There was no hint of an added benefit of romosozumab in comparison with alendronic acid for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which presented the results of the OPAQ-SV and of the LAD in the outcome category of health-related quality of life. Based on the OPAQ-SV results of post hoc defined responder analyses for the clinically relevant change in the dimension of physical function at month 24, the company derived an indication of an added benefit of romosozumab in comparison with alendronic acid. The company additionally presented the results of the prespecified mean differences of the OPAQ-SV and the LAD, based on which no statistically significant difference was shown in each case; however, the company did not use these results for the derivation of the added benefit.

Side effects

SAEs and discontinuation due to AEs

Operationalization

For the assessment of the outcomes "SAEs" and "discontinuation due to AEs", the company presented analyses that did not consider osteoporotic events determined by the company. These analyses were used for the present benefit assessment.

Result

There was no statistically significant difference between the treatment groups for each of the outcomes "SAEs" and "discontinuation due to AEs". In each case, this resulted in no hint of greater or lesser harm from romosozumab in comparison with alendronic acid; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Osteonecrosis of jaw

Operationalization

For the outcome "osteonecrosis of jaw", the company presented analyses that, on the one hand, included events from a query of predefined PTs using the Medical Dictionary for Regulatory Activities (MedDRA) and, on the other, events that were identified after reviewing the individual patients' case report forms. The analysis only included those events that had been confirmed by a blinded adjudication committee.

Result

No statistically significant difference between the treatment groups was shown for the outcome "osteonecrosis of jaw". This resulted in no hint of greater or lesser harm from romosozumab in comparison with alendronic acid; greater or lesser harm is therefore not proven.

This deviates from the approach of the company, which presented the results of the outcome "osteonecrosis of jaw", but did not draw a conclusion on the added benefit for the outcome.

Symptomatic atypical femoral fractures

No usable data were available for the outcome "symptomatic atypical femoral fractures". This resulted in no hint of greater or lesser harm from romosozumab in comparison with alendronic acid; greater or lesser harm is therefore not proven.

This deviates from the approach of the company, which used the results of the outcome "atypical femoral fractures" without considering symptomatic atypical femoral fractures separately. The company did not draw a conclusion on the added benefit for the outcome "atypical femoral fractures".

Gastrointestinal disorders (SOC, AEs)

There was no statistically significant difference between the treatment groups for the outcome "gastrointestinal disorders". This resulted in no hint of greater or lesser harm from romosozumab in comparison with alendronic acid; greater or lesser harm is therefore not proven.

This deviates from the approach of the company, which presented the results of the outcome "gastrointestinal disorders", but did not draw a conclusion on the added benefit for the outcome.

2.4.4 Subgroups and other effect modifiers

The subgroup characteristic "age" (< 75 years versus ≥ 75 years) was relevant for the present assessment.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The complete subgroup analyses for the recorded outcomes of the categories of mortality and morbidity were available for the benefit assessment. For the outcomes of the category of side effects, subgroup analyses were available for the outcomes "SAEs", "discontinuation due to AEs" and "osteonecrosis of jaw".

Using the methods described above, the available subgroup results did not show any effect modifications.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.5 (see Table 16).

Determination of the outcome category for the outcomes on morbidity

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Clinical vertebral fractures

No sufficient information for the assessment of the severity grade was available for the outcome "clinical vertebral fractures". For example, information on the patients' assessment regarding severity of back pain recorded to detect a clinical vertebral fracture could provide information on the severity of clinical vertebral fractures. No such data were available, however. Therefore, the outcome "clinical vertebral fractures" was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Major non-vertebral fractures

The composite outcome "major non-vertebral fractures" was assigned to the outcome category "severe/serious", as the effect of the outcome was mainly due to the effects in hip and pelvic fractures. These fractures are serious events associated with hospitalization of the patients.

Table 16: Extent of added benefit at outcome level: romosozumab vs. alendronic acid (multipage table)

Outcome category **Outcome**	**Romosozumab vs. alendronic acid** **Proportion of events (%) or MD at month 24** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	5.0% vs. 5.1% HR: 0.98 [0.74; 1.29]; p = 0.87	Lesser benefit/added benefit not proven
Morbidity		
Clinical vertebral fractures	0.9% vs. 2.1% RR: 0.41 [0.24; 0.71]; p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Major non-vertebral fractures	7.1% vs. 9.6% HR: 0.73 [0.59; 0.90]; p = 0.004 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Non-major non-vertebral fractures	Outcome not recorded	
Worst pain (mBPI-SF)	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: romosozumab vs. alendronic acid (multipage table)

Outcome category **Outcome**	**Romosozumab vs. alendronic acid** **Proportion of events (%) or MD at month 24** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
No usable data		
Side effects		
SAEs	27.8% vs. 27.5% RR: 1.01 [0.92; 1.12]; p = 0.806	Greater/lesser harm not proven
Discontinuation due to AEs	7.0% vs. 7.5% RR: 0.92 [0.74; 1.15]; p = 0.505	Greater/lesser harm not proven
Osteonecrosis of jaw	< 0.1% vs. < 0.1% RR: 1.97 [0.18; 21.76]; p > 0.999	Greater/lesser harm not proven
Symptomatic atypical femoral fractures	No usable data	Greater/lesser harm not proven
Gastrointestinal disorders (SOC, AEs)	38.1% vs. 39.5% RR: 0.96 [0.89; 1.04]; p = 0.350	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; MD: mean difference; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 17: Positive and negative effects from the assessment of romosozumab in comparison with alendronic acid

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Major non-vertebral fractures: indication of an added benefit – extent: “minor”	-
Non-serious/non-severe symptoms/late complications ▪ Clinical vertebral fractures: indication of an added benefit – extent: “considerable”	-

In the overall consideration, there are exclusively positive effects for romosozumab in comparison with alendronic acid. These consist of an indication of considerable added benefit for the outcome “clinical vertebral fractures” and in an indication of a minor added benefit for the outcome “major non-vertebral fractures”.

In summary, there is an indication of considerable added benefit of romosozumab versus the ACT for postmenopausal women with severe osteoporosis at high risk of fracture.

The result of the assessment of the added benefit of romosozumab in comparison with the ACT is summarized in Table 18.

Table 18: Romosozumab[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Treatment of postmenopausal women with severe osteoporosis at high risk of fracture[c]	**Alendronic acid** or risedronic acid or zoledronic acid or denosumab or teriparatide	Indication of considerable added benefit

a. In the ARCH study, romosozumab was investigated only followed by alendronic acid.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA’s specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. Sufficient calcium and vitamin D intake is assumed.
c. Refers to patients with severe osteoporosis at high risk of fracture as defined in the ARCH study.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above concurs with that of the company, which derived an indication of considerable added benefit.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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