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Romosozumab (osteoporosis) –

Addendum to Commission A20-24[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OPAQ-SV	Osteoporosis Assessment Questionnaire Short Version
RCT	randomized controlled trial
SAE	serious adverse event

1 Background

On 28 July 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-24 (Romosozumab – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented the randomized controlled trial (RCT) ARCH for the benefit assessment of romosozumab in postmenopausal women with severe osteoporosis at high risk of fracture. This study was used for the benefit assessment for the derivation of the added benefit of romosozumab.

To decide on the added benefit, the G-BA required further analyses. The G-BA's commission comprised the following assessments under consideration of the information provided in the company's dossier and the analyses presented with the comments:

- analysis of the outcome "atypical femoral fractures" (without subdivision into symptomatic/asymptomatic)
- analysis of the measurement instrument Osteoporosis Assessment Questionnaire Short Version (OPAQ-SV) including the assessment regarding the clinical relevance of the differences (e.g. Hedges' g)
- analysis of all patient-relevant outcomes after 12 months (here after 12 months of treatment with romosozumab, before start of the 12-month treatment with alendronate), particularly including the adverse events (AEs)
- AEs: analysis of the vascular (both cardiovascular and cerebrovascular) events regardless of the specified threshold values
- assessment of the sensitivity analyses on the patients with pre-existing vascular disease included in the study

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The ARCH study included in the benefit assessment was a randomized, double-blind multicentre study on the comparison of romosozumab followed by alendronic acid versus alendronic acid. A detailed description of the population, the characteristics of the study and of the interventions, the data cut-offs and the results on the included patient-relevant outcomes can be found in dossier assessment A20-24 [1].

Data used for the benefit assessment

With the present addendum, the data on vascular (both cardiovascular and cerebrovascular) events are taken into account in the benefit assessment, including the sensitivity analyses presented by the company, which were conducted under exclusion of the patients with a history of myocardial infarction or stroke. The assessment of the data can be found in Section 2.1.

Data not used for the benefit assessment

The assessments of all patient-relevant outcomes at month 12 as well as analyses of the outcomes "OPAQ-SV" and "atypical femoral fractures" (at month 12 and month 24) were not used for the derivation of the added benefit of romosozumab and are therefore presented in Appendix B and Appendix C. The reasons why these data were not included in the benefit assessment are described below:

Patient-relevant outcomes at month 12

Dossier assessment A20-24 stipulated a minimum study duration of 24 months [3].

The benefit assessment used the last available dates of analysis relevant for the assessment for each of the included patient-relevant outcomes of the ARCH study (for the available data cut-offs, see Table 11 in [1]). For the intervention arm, the last available period included the administration of romosozumab (12 months) followed by alendronic acid (total study duration of at least 24 months for all patients).

In accordance with the G-BA's commission, the present addendum additionally assesses the results of 12-month romosozumab administration in comparison with 12-month alendronic acid administration for all patient-relevant outcomes. The assessment can be found in Appendix B of the present addendum.

Further outcomes

OPAQ-SV

As described in dossier assessment A20-24, the OPAQ-SV is unsuitable for recording health-related quality of life. Overall, the validity of the OPAQ-SV cannot be assessed. 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. No new information on this aspect has emerged from the commenting procedure. The data on the OPAQ-SV at month 12 and month 24 provided by the company in the dossier are presented in Appendix C.

Atypical femoral fractures

The outcome "symptomatic atypical femoral fractures" was included for the benefit assessment on Commission A20-24. The data on atypical femoral fractures presented by the company were not used for the benefit assessment, as no separate analyses on symptomatic atypical femoral fractures were available. No new information on this aspect has emerged from the commenting procedure. The data on atypical femoral fractures at month 12 and for the total study period provided by the company in the dossier are presented in Appendix C.

2.1 Results on vascular events

The ARCH study predefined the recording of vascular events as adjudicated any cardiovascular serious AEs (SAEs). This outcome is composed of the following individual components: ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization). The total study period was used as date of analysis for the outcome, as this was the last available date of analysis of the ARCH study that was also relevant for the benefit assessment for this outcome.

The risk of bias for the results of the composite outcome "adjudicated any cardiovascular SAEs" and its individual components (ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event [without revascularization]) was rated as low.

Table 1 summarizes the results of romosozumab followed by alendronic acid in comparison with alendronic acid in postmenopausal women with severe osteoporosis at high risk of fracture on the composite outcome "adjudicated any cardiovascular SAEs" and its individual components.

Table 1: Results (side effects) – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid (total study period)

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)					
Adjudicated any cardiovascular SAEs[b]	2040	144 (7.1)	2014	137 (6.8)	1.04 [0.83; 1.30]; 0.758
Cardiac ischaemic event	2040	32 (1.6)	2014	25 (1.2)	1.26 [0.75; 2.12]; 0.424
Cerebrovascular event	2040	47 (2.3)	2014	27 (1.3)	1.72 [1.07; 2.75]; 0.025
Death[c]	2040	67 (3.3)	2014	68 (3.4)	0.97 [0.70; 1.36]; 0.930
Cardiac failure	2040	14 (0.7)	2014	25 (1.2)	0.55 [0.29; 1.06]; 0.078
Non-coronary revascularization	2040	7 (0.3)	2014	10 (0.5)	0.69 [0.26; 1.81]; 0.477
Peripheral vascular ischaemic event, without revascularization	2040	2 (< 0.1)	2014	5 (0.2)	0.39 [0.08; 2.03]; 0.286

a. Mantel-Haenszel method without adjustment for covariates, Fisher exact test.
b. All deaths as well as all potentially cardiovascular-related SAEs that matched a PT (MedDRA terminology) of a PT list predefined by the company, and all SAEs marked for adjudication by the investigator were evaluated by an adjudication committee for cardiovascular classification. All positively adjudicated cardiovascular SAEs were presented, as well as SAEs of the following individual components: ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization). With regard to the PTs considered, there are isolated inconsistencies between the data in Module 4 A and Module 5, but the respective overall rates do not differ between Module 4 A and Module 5.
c. Besides "cardiovascular-related death", "death due to undetermined cause" was also included in this individual component.

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; vs.: versus

Based on the available data, no more than indications, e.g. of an added benefit, can be determined for the other outcomes.

Side effects

Adjudicated any cardiovascular SAEs and the following individual components: ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization)

No statistically significant difference between the treatment groups was shown for the composite outcome "adjudicated any cardiovascular SAEs". Due to the different directions of effects of the results in the individual components, the result of the composite outcome is not meaningfully interpretable, however. The interpretation of the results was therefore based on the individual components.

No statistically significant difference between the treatment groups was shown for any of the following individual components: cardiac ischaemic event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization).

A statistically significant difference to the disadvantage of romosozumab followed by alendronic acid between the treatment groups was shown for the individual component "cerebrovascular event". The direction of the effect was to the disadvantage of romosozumab already at month 12, but the result was not statistically significant (see Table 9 in Appendix B.2). The majority of events (almost 2 thirds) only occurred in the second half of the study.

In the ARCH study, 6.1% of the patients had a history of myocardial infarction or stroke (contraindications of romosozumab [4]). In Module 5 of the dossier, the company presented sensitivity analyses that did not consider patients with these 2 contraindications. The information on the sensitivity analyses are presented in Table 5 (Appendix A).

These analyses show that, in absolute terms, many of the observed cardiovascular and cerebrovascular events (composite outcome) occurred in patients without a history of myocardial infarction or stroke: Of the 144 events in the intervention arm and 137 in the comparator arm in the total population, 128 events in the intervention arm and 119 in the comparator arm occurred in patients without a history of myocardial infarction or stroke. In relative terms, however, the proportion of patients with events in the smaller population of patients with a history of myocardial infarction or stroke was shown to be comparatively higher. In this population, 12.9% of the patients in the intervention arm and 14.5% of the patients in the comparator arm had cardiovascular or cerebrovascular events, whereas in the population of patients without a history of myocardial infarction or stroke, the figures were 6.7% in the intervention arm and 6.3% in the comparator arm.

Regardless of the comparatively lower proportion of cardiovascular and cerebrovascular events in the population of patients without a history of myocardial infarction or stroke, the statistically significant effect to the disadvantage of romosozumab followed by alendronic acid described above remains for the individual component "cerebrovascular event" in this population. There is no relevant quantitative difference between this effect and the observed effect in the total

population. Therefore, as for all other outcomes, the analysis of the total population is considered also for the cardiovascular and cerebrovascular events.

Overall, there is an indication of greater harm from romosozumab in comparison with alendronic acid on the basis of cerebrovascular events.

2.2 Extent and probability of added benefit

Table 2 shows probability and extent of the added benefit for the other outcomes.

Table 2: Extent of added benefit at outcome level: romosozumab vs. alendronic acid

Outcome category **Outcome**	**Romosozumab vs. alendronic acid** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
Adjudicated any cardiovascular SAEs	7.1% vs. 6.8% RR: 1.04 [0.83; 1.30] p = 0.758	Greater/lesser harm not proven
Cardiac ischaemic event	1.6% vs. 1.2% RR: 1.26 [0.75; 2.12] p = 0.424	Greater/lesser harm not proven
Cerebrovascular event	2.3% vs. 1.3% RR: 1.72 [1.07; 2.75] RR: 0.58 [0.36; 0.93][c] p = 0.025 probability: “indication”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Death	3.3% vs. 3.4% RR: 0.97 [0.70; 1.36] p = 0.930	Greater/lesser harm not proven
Cardiac failure	0.7% vs. 1.2% RR: 0.55 [0.29; 1.06] p = 0.078	Greater/lesser harm not proven
Non-coronary revascularization	0.3% vs. 0.5% RR: 0.69 [0.26; 1.81] p = 0.477	Greater/lesser harm not proven
Peripheral vascular ischaemic event, without revascularization	< 0.1% vs. 0.2% RR: 0.39 [0.08; 2.03] p = 0.286	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).
c. Institute’s calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

CI: confidence interval; CI_u: upper limit of the confidence interval; RR: relative risk; SAE: serious adverse event; vs.: versus

2.2.1 Overall conclusion on added benefit

Table 3 summarizes the results of the benefit assessment on Commission A20-24 and of the present addendum considered in the overall conclusion on the extent of the added benefit.

Table 3: 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"	**Serious/severe side effects** ▪ **Cerebrovascular event: indication of greater harm – extent: "minor"**
Non-serious/non-severe symptoms/late complications ▪ Clinical vertebral fractures: indication of an added benefit – extent: "considerable"	-
Results printed in **bold** result from the data additionally analysed for this addendum.	

The data additionally analysed for this addendum resulted in one negative effect of romosozumab versus alendronic acid. This effect consisted of an indication of greater harm of minor extent for the outcome "cerebrovascular event".

This was accompanied by 2 positive effects, an indication of minor added benefit for the outcome "major non-vertebral fractures" and an indication of considerable added benefit for the outcome "clinical vertebral fractures".

The negative effect for the outcome "cerebrovascular event" partly called into question the positive effects, and therefore resulted in a downgrading of the extent of the added benefit.

In summary, there is an indication of minor added benefit of romosozumab versus the appropriate comparator therapy (ACT) for postmenopausal women with severe osteoporosis at high risk of fracture.

2.3 Summary

The data additionally analysed for this addendum changed the conclusion on the added benefit of romosozumab from dossier assessment A20-24: There is an indication of minor added benefit of romosozumab versus the ACT for postmenopausal women with severe osteoporosis at high risk of fracture.

The following Table 4 shows the result of the benefit assessment of romosozumab under consideration of dossier assessment A20-24 and the present addendum.

Table 4: Romosozumab[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit[c]**
Treatment of postmenopausal women with severe osteoporosis at high risk of fracture[d]	**Alendronic acid** or risedronic acid or zoledronic acid or denosumab or teriparatide	Indication of **minor** 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. Changes in comparison with dossier assessment A20-24 are printed in **bold**.
d. 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 G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Romosozumab (Osteoporose): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-24 [online]. 10.06.2020 [Accessed: 17.06.2020]. (IQWiG-Berichte; Volume 925). URL: https://www.iqwig.de/download/A20-24_Romosozumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

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Appendix A – Sensitivity analyses under exclusion of the patients with a history of myocardial infarction or stroke for the outcome "adjudicated any cardiovascular SAEs" (total study period)

Table 5: Results (side effects) – RCT, direct comparison: romosozumab followed by alendronic acid vs. alendronic acid (sensitivity analysis: under exclusion of the patients with a history of myocardial infarction or stroke, total study period)

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 (total study period)					
Side effects					
Adjudicated any cardiovascular SAEs[b]	1916	128 (6.7)	1890	119 (6.3)	1.06 [0.83; 1.35]; 0.646
Cardiac ischaemic event	1916	28 (1.5)	1890	23 (1.2)	1.20 [0.69; 2.08]; 0.574
Cerebrovascular event	1916	41 (2.1)	1890	23 (1.2)	1.76 [1.06; 2.92]; 0.032
Death[c]	1916	63 (3.3)	1890	61 (3.2)	1.02 [0.72; 1.44]; 0.928
Cardiac failure	1916	12 (0.6)	1890	21 (1.1)	0.56 [0.28; 1.14]; 0.118
Non-coronary revascularization	1916	3 (0.2)	1890	8 (0.4)	0.37 [0.10; 1.39]; 0.143
Peripheral vascular ischaemic event, without revascularization	1916	2 (0.1)	1890	4 (0.2)	0.49 [0.09; 2.69]; 0.450

a. Mantel-Haenszel method without adjustment for covariates, Fisher exact test.
b. All deaths as well as all potentially cardiovascular-related SAEs that matched a PT (MedDRA terminology) of a PT list predefined by the company, and all SAEs marked for adjudication by the investigator were evaluated by an adjudication committee for cardiovascular classification. All positively adjudicated cardiovascular SAEs were presented, as well as SAEs of the following individual components: ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization). With regard to the PTs considered, there are isolated inconsistencies between the data in Module 4 A and Module 5, but the respective overall rates do not differ between Module 4 A and Module 5.
c. Besides "cardiovascular-related death", "death due to undetermined cause" was also included in this individual component.

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; vs.: versus

Appendix B – Analysis of patient-relevant outcomes at month 12

B.1 – Risk of bias

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: romosozumab vs. alendronic acid (month 12)

Study		Outcomes												
	Study level	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 fractures	Gastrointestinal disorders (SOC, AEs)	Adjudicated any cardiovascular SAEs[d]
ARCH (month 12)	L	L	L	L	–[e]	H[f]	H[f]	–[g]	L	L	L	–[h]	L	L[i]

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. See Table 9 for operationalization.
e. Outcome was not analysed separately.
f. > 10% missing values.
g. No usable data; see dossier assessment A20-24 [1] for reasons; the data on the OPAQ-SV are shown in Appendix C of the present addendum.
h. No usable data; the company presented data on atypical femoral fractures, but not separately on symptomatic atypical femoral fractures. The data presented by the company are shown in Appendix C of the present addendum.
i. The assessment of the risk of bias as low refers also to the following individual components: ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization).

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

B.2 – Results

Table 7: Results (mortality, morbidity, time to event) – RCT, direct comparison: romosozumab vs. alendronic acid (month 12)

Study Outcome category Outcome	Romosozumab N	Romosozumab Median time to event [95% CI] Patients with event n (%)	Alendronic acid N	Alendronic acid Median time to event [95% CI] Patients with event n (%)	Romosozumab vs. alendronic acid HR [95% CI]; p-value
ARCH (month 12)					
Mortality					
All-cause mortality[a]	2040	ND 30 (1.5)	2014	ND 22 (1.1)	1.37 [0.79; 2.37]; 0.26
Morbidity					
Clinical vertebral fractures	2046	– 10 (0.5)	2047	– 18 (0.9)	RR: 0.56 [0.26; 1.20]; 0.135[b]
Major non-vertebral fractures	2046	NA 59 (2.9)	2047	NA 88 (4.3)	0.67 [0.48; 0.94]; 0.019
Fractures of the hip	2046	NA 14 (0.7)	2047	NA 22 (1.1)	0.64 [0.33; 1.26]; 0.19
Fractures of the pelvis	2046	NA 1 (< 0.1)	2047	NA 8 (0.4)	0.13 [0.02; 1.03]; 0.022
Fractures of the distal femur	2046	NA 1 (< 0.1)	2047	NA 1 (< 0.1)	1.01 [0.06; 16.10]; > 0.999
Fractures of the proximal tibia	2046	NA 2 (< 0.1)	2047	NA 4 (0.2)	0.48 [0.09; 2.63]; 0.39
Fractures of the ribs	2046	NA 5 (0.2)	2047	NA 10 (0.5)	0.49 [0.17; 1.44]; 0.19
Fractures of the proximal humerus	2046	NA 5 (0.2)	2047	NA 10 (0.5)	0.51 [0.17; 1.50]; 0.21
Fractures of the forearm	2046	NA 33 (1.6)	2047	NA 42 (2.1)	0.80 [0.50; 1.25]; 0.32
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".
b. Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [5]).

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; NA: not achieved; ND: no data; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 8: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: romosozumab vs. alendronic acid (month 12)

Study Outcome category Outcome	Romosozumab			Alendronic acid			Romosozumab vs. alendronic acid
	N	Values at baseline mean (SD)	Change at month 12 mean (SE)	N	Values at baseline mean (SD)	Change at month 12 mean (SE)	MD [95% CI]; p-value
ARCH (month 12)							
Morbidity							
Worst pain (mBPI-SF)[a, b]	1547	3.9 (2.8)	−0.7 (0.1)	1532	4.0 (2.9)	−0.5 (0.1)	−0.1 [−0.29; 0.05]; 0.18
Health status (EQ-5D VAS)[c]	1557	67.7 (20.5)	3.6 (0.4)	1540	67.8 (20.6)	3.0 (0.4)	0.5 [−0.63; 1.67]; 0.37
Health-related quality of life							
No usable data[d]							

a. Measured with the scale "worst pain over the last 24 hours" (Item 3).
b. Lower (decreasing) values indicate better symptoms; negative effects (intervention minus control) indicate an advantage for romosozumab.
c. Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for romosozumab.
d. No usable data; the OPAQ-SV and the individual questions of the LAD are unsuitable for recording health-related quality of life; see dossier assessment A20-24 [1] for reasons; the data on the OPAQ-SV are shown in Appendix C of the present addendum.

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 9: Results (side effects) – RCT, direct comparison: romosozumab vs. alendronic acid (month 12) (multipage table)

Study Outcome category Outcome	Romosozumab		Alendronic acid		Romosozumab vs. alendronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ARCH (month 12)					
Side effects					
AEs (supplementary information)[b]	2040	1528 (74.9)	2014	1560 (77.5)	–
SAEs[b]	2040	238 (11.7)	2014	239 (11.9)	0.98 [0.83; 1.16]; 0.846
Discontinuation due to AEs[b, c]	2040	68 (3.3)	2014	64 (3.2)	1.05 [0.75; 1.47]; 0.791
Osteonecrosis of jaw[d]	2040	0 (0)	2014	0 (0)	–
Symptomatic atypical femoral fractures	No usable data[e]				
Gastrointestinal disorders (SOC, AEs)	2040	494 (24.2)	2014	541 (26.9)	0.90 [0.81; 1.00]; 0.056

Table 9: Results (side effects) – RCT, direct comparison: romosozumab vs. alendronic acid (month 12) (multipage table)

Study Outcome category Outcome	Romosozumab		Alendronic acid		Romosozumab vs. alendronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Adjudicated any cardiovascular SAEs[f]	2040	50 (2.5)	2014	38 (1.9)	1.30 [0.86; 1.97]; 0.237
Cardiac ischaemic event	2040	16 (0.8)	2014	6 (0.3)	2.63 [1.03; 6.71]; 0.052
Cerebrovascular event	2040	16 (0.8)	2014	7 (0.3)	2.26 [0.93; 5.47]; 0.092
Death[g]	2040	17 (0.8)	2014	12 (0.6)	1.40 [0.67; 2.92]; 0.457
Cardiac failure	2040	4 (0.2)	2014	8 (0.4)	0.49 [0.15; 1.64]; 0.263
Non-coronary revascularization	2040	3 (0.1)	2014	5 (0.2)	0.59 [0.14; 2.48]; 0.505
Peripheral vascular ischaemic event, without revascularization	2040	0 (0)	2014	2 (< 0.1)	0.20 [0.01; 4.11][h]; 0.247

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, 30 patients (1.5%) in the intervention arm and 27 patients (1.3%) 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”, “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. The data presented by the company on atypical femoral fractures are shown in Appendix C of the present addendum.
f. All deaths as well as all potentially cardiovascular-related SAEs that matched a PT (MedDRA terminology) of a PT list predefined by the company, and all SAEs marked for adjudication by the investigator were evaluated by an adjudication committee for cardiovascular classification. All positively adjudicated cardiovascular SAEs were presented, as well as SAEs of the following individual components: ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization). With regard to the PTs considered, there are isolated inconsistencies between the data in Module 4 A and Module 5, but the respective overall rates do not differ between Module 4 A and Module 5.
g. Besides “cardiovascular-related death”, “death due to undetermined cause” was also included in this individual component.
h. Institute’s calculation of RR (with correction factor 0.5 in both study arms) and CI (asymptotic).

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

Table 10: Results (side effects) – RCT, direct comparison: romosozumab vs. alendronic acid (sensitivity analysis: under exclusion of the patients with a history of myocardial infarction or stroke, month 12)

Study Outcome category Outcome	Romosozumab		Alendronic acid		Romosozumab vs. alendronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ARCH (month 12)					
Side effects					
Adjudicated any cardiovascular SAEs[b]	1916	44 (2.3)	1890	30 (1.6)	1.45 [0.91; 2.29]; 0.127
Cardiac ischaemic event	1916	15 (0.8)	1890	5 (0.3)	2.96 [1.08; 8.13]; 0.041
Cerebrovascular event	1916	15 (0.8)	1890	4 (0.2)	3.70 [1.23; 11.12]; 0.019
Death[c]	1916	14 (0.7)	1890	11 (0.6)	1.26 [0.57; 2.76]; 0.689
Cardiac failure	1916	4 (0.2)	1890	6 (0.3)	0.66 [0.19; 2.33]; 0.546
Non-coronary revascularization	1916	1 (< 0.1)	1890	5 (0.3)	0.20 [0.02; 1.69]; 0.122
Peripheral vascular ischaemic event, without revascularization	1916	0 (0)	1890	1 (< 0.1)	0.33 [0.01; 8.07][d]; 0.497

a. Mantel-Haenszel method without adjustment for covariates, Fisher exact test.
b. All deaths as well as all potentially cardiovascular-related SAEs that matched a PT (MedDRA terminology) of a PT list predefined by the company, and all SAEs marked for adjudication by the investigator were evaluated by an adjudication committee for cardiovascular classification. All positively adjudicated cardiovascular SAEs were presented, as well as SAEs of the following individual components: ischaemic event, cerebrovascular event, death, cardiac failure, non-coronary revascularization, and peripheral vascular ischaemic event (without revascularization). With regard to the PTs considered, there are isolated inconsistencies between the data in Module 4 A and Module 5, but the respective overall rates do not differ between Module 4 A and Module 5.
c. Besides "cardiovascular-related death", "death due to undetermined cause" was also included in this individual component.
d. Institute's calculation of RR (with correction factor 0.5 in both study arms) and CI (asymptotic).

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; vs.: versus

Table 11: Supplementary presentation: results (health status) – RCT, direct comparison: romosozumab vs. alendronic acid (month 12)

Study **Outcome category**	**Romosozumab**		**Alendronic acid**		**Romosozumab vs. alendronic acid**
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR[a] [95% CI]; p-value**
ARCH					
Morbidity (month 12)					
Health status (EQ-5D VAS)					
≥ 10 points[b]	1658	590 (35.6)	1676	571 (34.1)	1.05 [0.95; 1.15]; 0.421

a. Based on the Mantel-Haenszel method, adjusted for age strata, BMD T-score of the hip at baseline, and presence of severe vertebral fractures at baseline.
b. Patients with clinically relevant deterioration; defined as decrease of the score by ≥ 10 points from baseline.

BMD: bone mineral density; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; VAS: visual analogue scale; vs.: versus

Appendix C – Analyses on the OPAQ-SV and on atypical femoral fractures

Results on the OPAQ-SV

Table 12: Results on the OPAQ-SV – RCT, direct comparison: romosozumab vs. alendronic acid (month 12) or romosozumab followed by alendronic acid vs. alendronic acid (month 24)

Study Outcome Time point	Romosozumab (month 12) or romosozumab followed by alendronic acid (month 24)			Alendronic acid			Romosozumab (month 12) or romosozumab followed by alendronic acid (month 24) vs. alendronic acid
	N[a]	Values at baseline mean (SD)	Change at month 12 or 24 mean (SE)[b]	N[a]	Values at baseline mean (SD)	Change at month 12 or 24 mean (SE)[b]	MD [95% CI]; p-value[b]
ARCH							
OPAQ-SV[c]							
Month 12							
Physical functioning	1562	67.6 (23.4)	2.7 (0.4)	1550	67.1 (23.0)	1.6 (0.4)	1.1 [0.06; 2.15]; 0.038 Hedges' g[d]: 0.07 [0.004; 0.14]
Emotional status	1560	53.7 (22.9)	1.7 (0.4)	1544	52.8 (22.8)	1.7 (0.4)	0.0 [−1.05; 1.13]; 0.94
Back pain	1561	51.3 (26.9)	7.1 (0.5)	1546	51.6 (26.9)	6.1 (0.5)	1.0 [−0.44; 2.44]; 0.17
Month 24							
No usable data[e]							

a. Number of patients considered in the analysis for the calculation of the effect estimation; baseline values may be based on other patient numbers.
b. Based on a repeated measures model adjusted for treatment, age strata, presence of severe vertebral fractures at baseline, visit, baseline value, and *treatment by visit* interaction.
c. Higher (increasing) values indicate better health status; positive effects (intervention minus control) indicate an advantage for the intervention.
d. Institute's calculation.
e. At month 24, > 30% of the patients were not considered in the analysis.

CI: confidence interval; 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; vs.: versus

Results on atypical femoral fractures

Table 13: Results on atypical femoral fractures – RCT, direct comparison: romosozumab vs. alendronic acid (month 12) or romosozumab followed by alendronic acid vs. alendronic acid (total study period)

Study Outcome category Outcome	Romosozumab (month 12) or romosozumab followed by alendronic acid (total study period)		Alendronic acid		Romosozumab (month 12) or romosozumab followed by alendronic acid (total study period) vs. alendronic acid
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
ARCH					
Atypical femoral fractures[b]					
Month 12	2040	0 (0.0)	2014	0 (0.0)	NC
Total study period	2040	3 (0.1)	2014	4 (0.2)	0.74 [0.17; 3.30]; 0.725

a. Mantel-Haenszel method without adjustment for covariates, Fisher exact test.
b. Events of a MedDRA query predefined by the company according to PT list; the occurred PTs were assessed by an adjudication committee.

CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; vs.: versus