Abaloparatide (osteoporosis)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCP	good clinical practice
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug abaloparatide. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 15 April 2024.

Research question

The aim of the present report is the assessment of the added benefit of abaloparatide in comparison with the appropriate comparator therapy (ACT) in postmenopausal women with osteoporosis and increased risk of fracture.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of abaloparatide

Therapeutic indication	**ACT**[a]
Postmenopausal women with osteoporosis and increased risk of fracture[b]	▪ Alendronic acid or ▪ risedronic acid or ▪ zoledronic acid or ▪ denosumab or ▪ romosozumab (women with a significantly increased risk of fracture) or ▪ teriparatide
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, sufficient calcium and vitamin D intake is assumed. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company designated only romosozumab and teriparatide as the ACT, thus deviating from the G-BA's specification. This is of no further relevance for the present benefit assessment, as the company considered all options specified by the G-BA in its information retrieval.

The assessment is 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 24 months were used for the derivation of the added benefit.

Results

Evidence presented by the company – ACTIVE study

The ACTIVE study is a completed, triple-arm, randomized, partially blinded, multicentre phase 3 study comparing abaloparatide with either teriparatide or placebo in postmenopausal women with osteoporosis and increased risk of fracture. The abaloparatide arm and the placebo arm were blinded, while the teriparatide arm was unblinded. The study included postmenopausal women aged between 50 and 85 with osteoporosis.

A total of 2463 women were included in the study and assigned by unstratified randomization in a 1:1:1 ratio to treatment with abaloparatide (N = 824), teriparatide (N = 818) or placebo (N = 821). During regulatory audits, deviations from the principles of good clinical practice (GCP) were identified in 2 study centres. As part of the European authorization procedure, the EMA therefore stipulated that these 2 study centres should be excluded from the evaluation of the study. This led to a reduction in the analysis population to 2070 participants (abaloparatide arm N = 696, teriparatide arm N = 686, placebo arm N = 688). In Module 4 A of its dossier, the company presented both the results of the analysis population excluding these 2 study centres and the results of the overall study population.

After completing 18 months of treatment in the ACTIVE study, patients in the abaloparatide arm and the placebo arm, but not the teriparatide arm, could be included in the subsequent extension study ACTIVExtend. This is a completed, non-randomised, open-label study in which patients could be treated with alendronic acid for up to 24 months. Patients in the teriparatide arm of the ACTIVE study could not be included in the ACTIVExtend study and were not monitored further.

Study unsuitable for the benefit assessment

The ACTIVE study presented by the company is unsuitable for assessing the added benefit of abaloparatide in comparison with the ACT. The reason for this is that the minimum duration of 24 months has not been achieved. Deviating from this, the company considered studies with a minimum duration of 18 months to be relevant and justified this by stating that this fully reflects the maximum total treatment duration of abaloparatide according to the Summary of Product Characteristics (SPC). The approach of the company is not appropriate. An appropriate minimum duration of 24 months could have been achieved regardless of the maximum total treatment duration of abaloparatide if the observation within the study had been continued with adequate subsequent therapy. In addition, the comparator therapy teriparatide can be used for a maximum total treatment duration of 24 months in accordance with the SPC. However, patients in the teriparatide arm of the ACTIVE study were no longer treated with teriparatide after 18 months and were not monitored further. The maximum total treatment duration with teriparatide could therefore not be fully achieved in the ACTIVE study. Therefore, the ACTIVE study is not relevant for the present benefit assessment.

Patients in the teriparatide arm could not be included in the ACTIVExtend extension study that succeeded the ACTIVE study. In addition, switching from teriparatide to alendronic acid after 18 months, as specified in the study protocol, would mean that the maximum possible treatment duration with teriparatide of 2 years, as specified in the SPC, could not be achieved. Therefore, even taking the ACTIVExtend study into account, no suitable data are available for the benefit assessment.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of abaloparatide in comparison with the ACT; an added benefit is therefore not proven.

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

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

Table 3: Probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Postmeno-pausal women with osteoporosis and increased risk of fracture[b]	▪ Alendronic acid or ▪ risedronic acid or ▪ zoledronic acid or ▪ denosumab or ▪ romosozumab (women with a significantly increased risk of fracture) or ▪ teriparatide	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, sufficient calcium and vitamin D intake is assumed. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is the assessment of the added benefit of abaloparatide in comparison with the ACT in postmenopausal women with osteoporosis and increased risk of fracture.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of abaloparatide

Therapeutic indication	**ACT**[a]
Postmenopausal women with osteoporosis and increased risk of fracture[b]	▪ Alendronic acid or ▪ risedronic acid or ▪ zoledronic acid or ▪ denosumab or ▪ romosozumab (women with a significantly increased risk of fracture) or ▪ teriparatide
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, sufficient calcium and vitamin D intake is assumed. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company designated only romosozumab and teriparatide as the ACT, thus deviating from the G-BA's specification. This is of no further relevance for the present benefit assessment, as the company considered all options specified by the G-BA in its information retrieval.

The assessment is 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 24 months were used for the derivation of the added benefit. This is in line with the guidelines of the European Medicines Agency in the present therapeutic indication (EMA) [3]. However, the company included RCTs with a minimum duration of 18 months.

I 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 abaloparatide (status: 16 February 2024)
- bibliographical literature search on abaloparatide (last search on 16 February 2024)
- search in trial registries/trial results databases for studies on abaloparatide (last search on 16 February 2024)
- search on the G-BA website for abaloparatide (last search on 16 February 2024)

To check the completeness of the study pool:

- search in trial registries for studies on abaloparatide (last search on 26 April 2024); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check of the completeness of the study pool. This departs from the approach of the company, which included the ACTIVE RCT [4] in its study pool and used it for the assessment.

Evidence presented by the company – ACTIVE study

The ACTIVE study is a completed, triple-arm, randomized, partially blinded, multicentre phase 3 study comparing abaloparatide with either teriparatide or placebo in postmenopausal women with osteoporosis and increased risk of fracture. The abaloparatide arm and the placebo arm were blinded, while the teriparatide arm was unblinded. The study included postmenopausal women aged between 50 and 85 with osteoporosis. Postmenopausal status was defined as amenorrhoea for at least 5 years and a serum follicle-stimulating hormone (FSH) level of ≥ 30 international units (IU)/L. The bone mineral density had to have a T-score between -5.0 and -2.5 inclusive. In addition, there had to be radiological evidence of ≥ 2 mild or ≥ 1 moderate lumbar or thoracic vertebral fractures or a history of forearm, humerus, sacrum, pelvis, hip, femur, or tibia fractures with minor trauma within the last 5 years. Women over 65 years of age could be included in the study with a T-score between -5.0 and -3.0 inclusive, regardless of the above fracture criteria, or with a T-score between -5.0 and -2.0 inclusive if the above fracture criteria were met. Women with more than 4 mild or moderate vertebral fractures or any severe vertebral fractures or bilateral hip replacement were excluded from the study.

A total of 2463 women were included in the study and assigned by unstratified randomization in a 1:1:1 ratio to treatment with abaloparatide (N = 824), teriparatide (N = 818) or placebo (N = 821). During regulatory audits, deviations from the principles of GCP were identified in

2 study centres. As part of the European authorization procedure, the EMA therefore stipulated that these 2 study centres should be excluded from the evaluation of the study. This led to a reduction in the analysis population to 2070 participants (abaloparatide arm N = 696, teriparatide arm N = 686, placebo arm N = 688). In Module 4 A of its dossier, the company presented both the results of the analysis population excluding these 2 study centres and the results of the overall study population.

The primary outcome of the study was the occurrence of one or more new vertebral fractures. Further patient-relevant outcomes were surveyed in the categories of morbidity and side effects.

After completing 18 months of treatment in the ACTIVE study, patients in the abaloparatide arm and the placebo arm, but not the teriparatide arm, could be included in the subsequent extension study ACTIVExtend [5]. This is a completed, non-randomised, open-label study in which patients could be treated with alendronic acid for up to 24 months. The ACTIVExtend study is not discussed in Module 4 A of the company's dossier. Patients in the teriparatide arm of the ACTIVE study could not be included in the ACTIVExtend study and were not monitored further.

Study unsuitable for the benefit assessment

The ACTIVE study presented by the company is unsuitable for assessing the added benefit of abaloparatide in comparison with the ACT. The reason for this is that the minimum duration of 24 months has not been achieved. This minimum duration corresponds to the EMA's guidelines for the investigation of drug interventions for osteoporosis in postmenopausal women in order to collect data on fractures and safety [3].

Deviating from this, the company considered studies with a minimum duration of 18 months to be relevant and justified this by stating that this fully reflects the maximum total treatment duration of abaloparatide according to the SPC [6].

The approach of the company is not appropriate. According to the current S3 guideline, osteoporosis requires long-term treatment in the vast majority of cases, which is why treatment sequences should be taken into account from the first initiation of treatment [7]. The SPC for abaloparatide also refers to a follow-up therapy with bisphosphonates [6]. Against this background, an appropriate minimum duration of 24 months could have been achieved regardless of the maximum total treatment duration of abaloparatide if the observation in the randomized study had been continued with adequate subsequent therapy (such as alendronic acid). In addition, the comparator therapy teriparatide can be used for a maximum total treatment duration of 24 months in accordance with the SPC [8]. However, patients in the teriparatide arm of the ACTIVE study were no longer treated with teriparatide after 18 months and were not monitored further. The maximum total treatment duration with teriparatide

could therefore not be fully achieved in the ACTIVE study. Therefore, the ACTIVE study is not relevant for the present benefit assessment.

Patients in the teriparatide arm could not be included in the ACTIVExtend extension study that succeeded the ACTIVE study. In addition, switching from teriparatide to alendronic acid after 18 months, as specified in the study protocol, would mean that the maximum possible treatment duration with teriparatide of 2 years, as specified in the SPC, could not be achieved. Therefore, even taking the ACTIVExtend study into account, no suitable data are available for the benefit assessment.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of abaloparatide in comparison with the ACT in postmenopausal women with osteoporosis and increased risk of fracture. There is no hint of an added benefit of abaloparatide in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of abaloparatide in comparison with the ACT is summarized in Table 5.

Table 5: Probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Postmenopausal women with osteoporosis and increased risk of fracture[b]	▪ Alendronic acid or ▪ risedronic acid or ▪ zoledronic acid or ▪ denosumab or ▪ romosozumab (women with a significantly increased risk of fracture) or ▪ teriparatide	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, sufficient calcium and vitamin D intake is assumed. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

I 6 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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