Efgartigimod alfa (chronic inflammatory demyelinating polyneuropathy)

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

EXTRACT

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Efgartigimod alfa, Polyradiculoneuropathy – Chronic Inflammatory Demyelinating, Benefit Assessment

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

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
aINCAT	adjusted Inflammatory Neuropathy Cause and Treatment
CIDP	chronic inflammatory demyelinating polyneuropathy
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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)
SmPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book 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 efgartigimod alfa. 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 24 July 2025.

Research question

The aim of this report is to assess the added benefit of efgartigimod alfa compared with immunoglobulins or corticosteroids as appropriate comparator therapy (ACT) in adults with progressive or recurrent active chronic inflammatory demyelinating polyneuropathy (CIDP) after previous treatment with corticosteroids or immunoglobulins.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of efgartigimod alfa

Therapeutic indication	**ACT**[a]
Adults with progressive or recurrent active chronic inflammatory demyelinating polyneuropathy after previous treatment with corticosteroids or immunoglobulins	Immunoglobulins or corticosteroids[b]

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- Patients in the comparator arm who show an active course of the disease following treatment with immunoglobulins or corticosteroids should be switched to the respective other available treatment option, where indicated.
- The unchanged continuation of an inadequate treatment does not comply with the ACT if the option of treatment optimization is still available.
- Plasmapheresis is not considered to be a regular ACT; however, in individual cases, it may serve as an acute treatment and, where immunoglobulins and corticosteroids have failed, as a treatment option for patients with chronic inflammatory demyelinating polyneuropathy.

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

The company deviated from the G-BA's specification and instead cited an individualized treatment depending on the prior therapy as the ACT.

The company justified the deviation from the G-BA's ACT primarily on the grounds that the disease is characterized by a heterogeneous course and the absence of a uniform standard treatment. Treatment therefore requires a flexible adjustment that takes into account both the individual severity of the disease and any previous therapies and their side effects. Due to

the individual limitations of the drugs, none of the available treatment options – corticosteroids, immunoglobulins or plasmapheresis – was therefore suitable as a sole comparator therapy for the benefit assessment.

For adults in the comparator arm who show an active course of the disease following treatment with immunoglobulins or corticosteroids, the G-BA's ACT provides for a switch to the respective other available treatment option, where indicated. Where this option is available, optimization of treatment is also covered by the G-BA's ACT. In individual cases, plasmapheresis may be used as an acute therapy and when immunoglobulins and corticosteroids have failed. However, the fact that the company deviates from the G-BA's ACT has no consequences, as the therapy in the comparator arm of the study submitted by the company corresponds neither to the G-BA's ACT nor to that specified by the company (see the following section). The present assessment is implemented in comparison with the ACT specified by the G-BA (see Table 2).

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 24 weeks were used to derive the added benefit. This deviates from the company's inclusion criteria, which only included RCTs with a minimum study duration of 48 weeks.

Results

The review of the information retrieval did not identify any relevant studies. The company, in contrast, identified the ADHERE study and used it in its assessment of the added benefit of efgartigimod alfa.

ADHERE study unsuitable for the benefit assessment

ADHERE study

The ADHERE study is a completed study comprising an open-label single-arm phase (Stage A), in which all patients received efgartigimod alfa, followed by a double-blind, randomized and controlled phase (Stage B) for the comparison of efgartigimod alfa with placebo. The study included adults with probable or definite progressive or recurrent CIDP, as defined by the 2010 criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS). The study included both patients who had previously received treatment with corticosteroids or immunoglobulins (intravenously or subcutaneously) for their CIDP, and treatment-naive patients. According to the study protocol, patients who had been treated with corticosteroids and immunoglobulins could also have been included in the ADHERE study and would therefore not have been covered by this research question. However, based on the available data, this does not appear to apply to any of the patients included. Patients who had

not been treated with corticosteroids or immunoglobulins for more than 6 months prior to study enrolment were also considered treatment-naive.

Once the study had commenced, patients who were already being treated with corticosteroids and/or immunoglobulins initially entered a run-in phase during which they had to discontinue their previous treatment. Patients who showed clinical deterioration within a maximum of 12 weeks were able to progress to the single-arm open-label phase (Stage A). According to the study protocol, the purpose of this run-in phase was to ensure that only patients with active CIDP were included in the study (enrichment design), and to ensure that the drug from the previous therapy had been sufficiently degraded/excreted so as not to compromise the study's efficacy analysis. Treatment-naive patients were enrolled directly into Stage A if they had experienced a clinical deterioration within 3 months prior to study enrolment compared with a comparator value recorded within 6 months prior to study enrolment. In Stage A, all patients received efgartigimod alfa once a week for up to 12 weeks. Only patients who showed confirmed clinical improvement in two consecutive weeks during this treatment period were included in Stage B. Patients who did not show clinical improvement until Week 12 were able to extend Stage A by one week to confirm this improvement.

In Stage B, patients were randomized in a 1:1 ratio to receive either a further weekly treatment with efgartigimod alfa or placebo. Patients who experienced clinical deterioration during Stage B – defined as a 1-point increase in the Inflammatory Neuropathy Cause and Treatment (aINCAT) score compared to the baseline value at Stage B – or who attended the Week 48 visit were eligible to switch to the open-label extension study. In this extension study, all patients received efgartigimod alfa. Instead of switching to the extension study, patients could also remain in the ADHERE study for the 28-day follow-up period and were treated at the discretion of the investigator.

Treatment of patients in Stage A and in the intervention arm of Stage B was carried out subject to certain restrictions in accordance with the Summary of Product Characteristics (SmPC) for efgartigimod alfa. According to the SmPC, efgartigimod alfa should be administered at weekly intervals. However, depending on the clinical assessment, it is possible to adjust the dosing interval to every two weeks. This two-week dosing interval was not provided for in the ADHERE study. Furthermore, according to the SmPC, patients who are to be switched from their current CIDP treatment should, where possible, start treatment with efgartigimod alfa before the clinical efficacy of the previous treatment begins to wane. This was not implemented in the previously described run-in phase of the ADHERE study, as a clinical worsening of CIDP following discontinuation of the patient's previous CIDP treatment was explicitly required before treatment with efgartigimod alfa could be initiated in Stage A.

In both treatment arms of the Stage B, no therapies targeting CIDP (such as corticosteroids, immunoglobulins or plasmapheresis) were permitted. During the study treatment, patients in the intervention arm therefore received monotherapy with efgartigimod alfa, whilst those in the control arm received placebo (see also the information below regarding the implementation of the ACT).

Subpopulation of the ADHERE study formed by the company unsuitable

The company used the placebo-controlled Stage B of the ADHERE study for the benefit assessment and, according to its statement, defined a subpopulation relevant to the benefit assessment that reflects the therapeutic indication as set out in the SmPC. The approach of the company is largely comprehensible.

However, the subpopulation formed by the company (as well as the total population) is not suitable for the benefit assessment. The following text describes the underlying problems associated with the chosen study design separately for each phase of the study, starting with the run-in phase:

Run-in phase leads to a transferability problem

Although run-in phases appear to be common in studies in this therapeutic indication due to false diagnoses, this gives rise to a transferability problem, as the SmPC does not provide for a run-in phase. In fact, it is stated there that treatment with efgartigimod alfa should ideally be initiated before the clinical efficacy of the previous therapy begins to wane [1]. Furthermore, a study examining the direct switch to efgartigimod alfa (without a run-in or washout phase) yielded negative results.

In Stage A: Pretreatment of all patients with efgartigimod alfa

As described above, all patients in Stage A had been treated with efgartigimod alfa before they could be included in Stage B. Consequently, the patients assigned to the control arm of Stage B no longer corresponded to the present research question, as they had all been pretreated with efgartigimod alfa. In addition, patients were selected, as only those who showed clinical improvement in Phase A were eligible to proceed to the randomized Phase B. Of the total of 322 patients in Stage A, only 221 progressed to Stage B, meaning that over 30% were excluded from the study. It is striking that a particularly large number of patients who had previously been treated with immunoglobulins discontinued treatment with efgartigimod alfa in Stage A prematurely, in some cases after just a few weeks. After being excluded from Stage A, patients were only examined at a safety follow-up visit 28 days after their last dose; however, at this visit, no outcomes relating to disease activity or health status were recorded.

The comparator therapy in the ADHERE study does not correspond to the ACT

Treatment in the control arm of Stage B in the ADHERE study did not correspond to the ACT. As described before, all patients in the control arm of the ADHERE study only received placebo and no active therapy for their CIDP. In the event of a clinical deterioration, patients could be treated at the investigator's discretion; however, treatment with efgartigimod alfa or placebo had to be discontinued in such cases. Overall, treatment in the comparator arm did thus not correspond to the ACT, so no data were available on the comparison of efgartigimod alfa with the comparator therapy specified by the G-BA.

Conclusion

The ADHERE study is unsuitable for this benefit assessment. This is primarily due to the fact that all patients in the randomized, controlled Stage B had been pretreated with efgartigimod alfa, and that the treatment in the control arm of Stage B did not correspond to the ACT. All patients in the control arm only received placebo in Stage B. This means that no suitable data were available for the comparison of efgartigimod alfa with the G-BA's comparator therapy.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of efgartigimod alfa 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 added benefit of efgartigimod alfa.

[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 [2,3].

Table 3: Efgartigimod alfa – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with progressive or recurrent active chronic inflammatory demyelinating polyneuropathy after previous treatment with corticosteroids or immunoglobulins	Immunoglobulins or corticosteroids[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- Patients in the comparator arm who show an active course of the disease following treatment with immunoglobulins or corticosteroids should be switched to the respective other available treatment option, where indicated.
- The unchanged continuation of an inadequate treatment does not comply with the ACT if the option of treatment optimization is still available.
- Plasmapheresis is not considered to be a regular ACT; however, in individual cases, it may serve as an acute treatment and, where immunoglobulins and corticosteroids have failed, as a treatment option for patients with chronic inflammatory demyelinating polyneuropathy.

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of efgartigimod alfa compared with immunoglobulins or corticosteroids as ACT in adults with progressive or recurrent active CIDP after previous treatment with corticosteroids or immunoglobulins.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4. Research question of the benefit assessment of efgartigimod alfa

Therapeutic indication	**ACT**[a]
Adults with progressive or recurrent active chronic inflammatory demyelinating polyneuropathy after previous treatment with corticosteroids or immunoglobulins	Immunoglobulins or corticosteroids[b]

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- Patients in the comparator arm who show an active course of the disease following treatment with immunoglobulins or corticosteroids should be switched to the respective other available treatment option, where indicated.
- The unchanged continuation of an inadequate treatment does not comply with the ACT if the option of treatment optimization is still available.
- Plasmapheresis is not considered to be a regular ACT; however, in individual cases, it may serve as an acute treatment and, where immunoglobulins and corticosteroids have failed, as a treatment option for patients with chronic inflammatory demyelinating polyneuropathy.

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

The company deviated from the G-BA's specification and instead cited an individualized treatment depending on the prior therapy as the ACT.

The company justified the deviation from the G-BA's ACT primarily on the grounds that the disease is characterized by a heterogeneous course and the absence of a uniform standard treatment. Treatment therefore requires a flexible adjustment that takes into account both the individual severity of the disease and any previous therapies and their side effects. Due to the individual limitations of the drugs, none of the available treatment options – corticosteroids, immunoglobulins or plasmapheresis – was therefore suitable as a sole comparator therapy for the benefit assessment.

For adults in the comparator arm who show an active course of the disease following treatment with immunoglobulins or corticosteroids, the G-BA's ACT provides for a switch to the respective other available treatment option, where indicated. Where this option is available, optimization of treatment is also covered by the G-BA's ACT. In individual cases, plasmapheresis may be used as an acute therapy and when immunoglobulins and

corticosteroids have failed. However, the fact that the company deviates from the G-BA's ACT has no consequences, as the therapy in the comparator arm of the study submitted by the company corresponds neither to the G-BA's ACT nor to that specified by the company (see Chapter I 3). The present assessment is implemented in comparison with the ACT specified by the G-BA (see Table 4).

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 24 weeks were used to derive the added benefit. This deviates from the company's inclusion criteria, which only included RCTs with a minimum study duration of 48 weeks.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on efgartigimod alfa (status: 06 May 2025)
- Bibliographical literature search on efgartigimod alfa (last search on 06 May 2025)
- Search in trial registries/trial results databases for studies on efgartigimod alfa (last search on 06 May 2025)
- Search on the G-BA website for efgartigimod alfa (last search on 06 May 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on efgartigimod alfa (last search on 07 August 2025); for search strategies, see I Appendix A of the full dossier assessment

The review did not identify any relevant studies.

The company, in contrast, identified the ADHERE study [4] and used it for the assessment of the added benefit of efgartigimod alfa.

However, the data of the ADHERE study presented by the company are unsuitable for drawing conclusions on the added benefit of efgartigimod alfa in comparison with the ACT. The ADHERE study and the reasons why it is not suitable for the present benefit assessment are described in more detail below.

Evidence presented by the company – ADHERE study

ADHERE study

The ADHERE study is a completed study comprising an open-label single-arm phase (Stage A), in which all patients received efgartigimod alfa, followed by a double-blind, randomized and controlled phase (Stage B) for the comparison of efgartigimod alfa with placebo. The study included adults with probable or definite progressive or recurrent CIDP, as defined by the 2010 criteria of the EFNS/PNS [5]. The CIDP diagnosis also had to be confirmed by an independent committee of experts (CIDP Confirmation Committee). Patients had to have a CIDP Disease Activity Status (CDAS) score of ≥ 2 at the time of study enrolment. The study included both patients who had previously received treatment with corticosteroids or immunoglobulins (intravenously or subcutaneously) for their CIDP, and treatment-naive patients. According to the study protocol, patients who had been treated with corticosteroids and immunoglobulins could also have been included in the ADHERE study and would therefore not have been covered by this research question. However, based on the available data, this does not appear

to apply to any of the patients included. Patients who had not been treated with corticosteroids or immunoglobulins for more than 6 months prior to study enrolment were also considered treatment-naive.

Once the study had commenced, patients who were already being treated with corticosteroids and/or immunoglobulins initially entered a run-in phase during which they had to discontinue their previous treatment. Patients who showed clinical deterioration within a maximum of 12 weeks were able to progress to the single-arm open-label phase (Stage A). According to the study protocol, the purpose of this run-in phase was to ensure that only patients with active CIDP were included in the study (enrichment design), and to ensure that the drug from the previous therapy had been sufficiently degraded/excreted so as not to compromise the study's efficacy analysis. Treatment-naive patients were enrolled directly into Stage A if they had experienced a clinical deterioration within 3 months prior to study enrolment compared with a comparator value recorded within 6 months prior to study enrolment. In Stage A, all patients received efgartigimod alfa once a week for up to 12 weeks. Only patients who showed confirmed clinical improvement in two consecutive weeks during this treatment period were included in Stage B. Patients who did not show clinical improvement until Week 12 were able to extend Stage A by one week to confirm this improvement. The assessment of clinical deterioration (referred to by the company as Evidence of Clinically Meaningful Deterioration [ECMD]) or improvement (referred to by the company as Evidence of Clinical Improvement [ECI]) was based on prespecified criteria using the adjusted aINCAT, the Inflammatory Rasch-built Overall Disability Scale (I-RODS) and/or grip strength.

In Stage B, patients were randomized in a 1:1 ratio to receive either a further weekly treatment with efgartigimod alfa or placebo. Randomization was stratified according to the change in patients' aINCAT during Stage A (no change vs. decrease by ≥ 1 point) and according to prior treatment (treatment-naive vs. corticosteroids vs. immunoglobulins). Patients who experienced clinical deterioration during Stage B – defined as a 1-point increase in the aINCAT compared to the Stage B baseline value – or who attended the visit at Week 48 were eligible to switch to the open-label extension study [6-8]. In this extension study, all patients received efgartigimod alfa. The ADHERE study was terminated once 88 events had occurred in the primary outcome in Stage B. Patients who were still participating in the study at that point in time (regardless of the study phase) were also able to transfer to the extension study. Instead of switching to the extension study, patients could also remain in the ADHERE study for the 28-day follow-up period and were treated at the discretion of the investigator.

The run-in phase included 306 patients. Of these, 286 patients progressed to Stage A. Over 90% of patients therefore showed clinical deterioration during the run-in phase. 36 treatment-naive patients who had already experienced a clinical deterioration of CIDP prior to enrolment

in the study were directly included in Stage A. Thus, a total of 322 patients were included in Stage A. Of these 322 patients, 63 (20%) had received corticosteroids and 165 (51%) had received immunoglobulins (intravenously or subcutaneously) as prior treatment, whilst 94 (29%) were considered treatment-naive (according to the study report, 18 [19%] of them had never received treatment for CIDP prior to study inclusion, whilst 76 [81%] had not received treatment for CIDP within the last six months prior to study inclusion). Of the 322 patients in Stage A, a total of 221 (69%) progressed to Stage B (efgartigimod alfa: N = 111; control arm: N = 110). The majority of patients in Stage B switched to the open-label extension study following the relevant event (see above) (of the 111 patients in the intervention arm, a total of 98 patients, and of the 110 patients in the control arm, a total of 99 switched to the extension study).

Treatment of patients in Stage A and in the intervention arm of Stage B was carried out subject to certain restrictions in accordance with the SmPC for efgartigimod alfa [1]. According to the SmPC, efgartigimod alfa should be administered at weekly intervals. However, depending on the clinical assessment, it is possible to adjust the dosing interval to every two weeks. This two-week dosing interval was not provided for in the ADHERE study. Furthermore, according to the SmPC, patients who are to be switched from their current CIDP treatment should, where possible, start treatment with efgartigimod alfa before the clinical efficacy of the previous treatment begins to wane. This was not implemented in the previously described run-in phase of the ADHERE study, as a clinical deterioration of CIDP following discontinuation of the patient's previous CIDP therapy was explicitly required before treatment with efgartigimod alfa could be initiated in Stage A (see also 'Conclusion').

In both treatment arms of the Stage B, no therapies targeting CIDP (such as corticosteroids, immunoglobulins or plasmapheresis) were permitted. During the study treatment, patients in the intervention arm therefore received monotherapy with efgartigimod alfa, whilst those in the control arm received placebo (see also the information below regarding the implementation of the ACT).

Primary outcome of the ADHERE study was the proportion of patients with confirmed clinical improvement in Stage A, or the time to the first aINCAT deterioration in Stage B. Further outcomes were surveyed in the categories of morbidity and side effects.

Subpopulation of the ADHERE study formed by the company

The company used the placebo-controlled Stage B of the ADHERE study for the benefit assessment and, according to its statement, defined a subpopulation relevant to the benefit assessment that reflects the therapeutic indication as set out in the SmPC. According to the company, treatment-naive patients were excluded from this subpopulation. Patients who had not received treatment with corticosteroids or immunoglobulins within the 6 months prior to

study enrolment and who were considered treatment-naive according to the study design were considered in the formation of the subpopulation. However, patients who were considered cured following treatment (no longer under treatment for ≥ 5 years) or who were in remission and showed no active disease (no longer undergoing treatment for ≥ 1 to < 5 years) were excluded. Patients who showed a stable health status whilst undergoing treatment were also excluded from the subpopulation. The approach of the company is largely comprehensible.

Subpopulation of the ADHERE study unsuitable

The subpopulation formed by the company (as well as the total population) is not suitable for the benefit assessment. The following text describes the underlying problems associated with the chosen study design separately for each phase of the study, starting with the run-in phase:

Run-in phase leads to a transferability problem

Although run-in phases appear to be common in studies in this therapeutic indication due to false diagnoses, this gives rise to a transferability problem, as the SmPC does not provide for a run-in phase. In fact, it is stated there that treatment with efgartigimod alfa should ideally be initiated before the clinical efficacy of the previous therapy begins to wane [1]. Furthermore, a study examining the direct switch to efgartigimod alfa (without a run-in or washout phase) yielded negative results [9]. The health status of 4 out of a total of 9 CIDP patients who had switched from intravenous immunoglobulins to efgartigimod deteriorated rapidly. This is particularly serious because it is not certain that CIDP patients who experience a relapse will return to their original condition. A relapse is therefore always a cause for concern, as some patients may experience permanent deterioration, as has been observed in previous studies on CIDP [10].

In Stage A: Pretreatment of all patients with efgartigimod alfa

As described above, all patients in Stage A had been treated with efgartigimod alfa before they could be included in Stage B. Consequently, the patients assigned to the control arm of Stage B no longer corresponded to the present research question, as they had all been pretreated with efgartigimod alfa. In addition, patients were selected, as only those who showed clinical improvement in Phase A were eligible to proceed to the randomized Phase B. Of the total of 322 patients in Stage A, only 221 progressed to Stage B, meaning that over 30% were excluded from the study. It is striking that a particularly large number of patients who had previously been treated with immunoglobulins discontinued treatment with efgartigimod alfa in Stage A prematurely, in some cases after just a few weeks. Of the 165 patients who had received prior treatment with immunoglobulin, 55 (33%) discontinued treatment with efgartigimod alfa prematurely, whereas of the 63 patients who had received prior treatment with corticosteroids, only 8 (13%) discontinued treatment with efgartigimod alfa prematurely. The most common reasons for premature treatment discontinuation in both groups were lack

of efficacy (immunoglobulins and corticosteroids: 21 [13%] and 3 [5%] respectively) and adverse events (AEs) (immunoglobulins and corticosteroids: 18 [11%] and 2 [3%] respectively). After being excluded from Stage A, patients were only examined at a safety follow-up visit 28 days after their last dose; however, at this visit, no outcomes relating to disease activity or health status were recorded.

The comparator therapy in the ADHERE study does not correspond to the ACT

Treatment in the control arm of Stage B in the ADHERE study did not correspond to the ACT. As described before, all patients in the control arm of the ADHERE study only received placebo and no active therapy for their CIDP. In the event of a clinical deterioration, patients could be treated at the investigator's discretion; however, treatment with efgartigimod alfa or placebo had to be discontinued in such cases. Overall, treatment in the comparator arm did thus not correspond to the ACT, so no data were available on the comparison of efgartigimod alfa with the comparator therapy specified by the G-BA. On the one hand (at the start of the study) this foresees a treatment optimization and, on the other hand, an examination of whether a switch from immunoglobulins (51% of patients in Stage A had previously been treated with immunoglobulins) or corticosteroids (20% of patients in Stage A had previously been treated with corticosteroids) to the other available treatment option is indicated. Regardless of this, a total of 99 patients (including those who had experienced clinical deterioration) out of the 110 patients in the control arm of Stage B had progressed to the open-label extension study, where they all received efgartigimod alfa.

Conclusion

The ADHERE study is unsuitable for this benefit assessment. This is primarily due to the fact that all patients in the randomized, controlled Stage B had been pretreated with efgartigimod alfa, and that the treatment in the control arm of Stage B did not correspond to the ACT. All patients in the control arm only received placebo in Stage B. This means that no suitable data were available for the comparison of efgartigimod alfa with the G-BA's comparator therapy.

If a run-in phase is at all useful and necessary, a study design in which patients are randomly assigned directly to treatment with efgartigimod alfa or to treatment with corticosteroids or immunoglobulins following this run-in phase would generally have been appropriate.

Regardless of whether the ADHERE study is suitable for this benefit assessment, the study design requires critical discussion. During the run-in phase, a clinical deterioration of CIDP is anticipated, followed by an improvement under treatment with efgartigimod alfa in the open-label, single-arm Stage A. In the subsequent Stage B, patients in the control arm will once again be withdrawn from active treatment until clinical deterioration occurs. It is striking that a particularly high number of patients who had previously been treated with immunoglobulins discontinued treatment with efgartigimod alfa prematurely in Stage A (33% of patients who

had previously been treated with immunoglobulins vs. 13% of patients who had previously been treated with corticosteroids). The further course of the patients after leaving the run-in phase or Stage A is (largely) unclear and raises further questions (see also [11]).

Regardless of this, it is worth noting that the approval of the European Medicines Agency (EMA) appears to be largely based on a historical comparison of data from Stage A on efgartigimod alfa with historical placebo controls (the study design, including Stage B, is also discussed quite critically in the European Public Assessment Report (EPAR)) [12]. However, the company did not provide data on a historical comparison with corticosteroids or immunoglobulins for the benefit assessment.

I 4 Results on added benefit

There are no suitable data available to assess the added benefit of efgartigimod alfa in adults with progressive or recurrent active CIDP after previous treatment with corticosteroids or immunoglobulins. There is no hint of an added benefit of efgartigimod alfa over the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of efgartigimod alfa in comparison with the ACT.

Table 5: Efgartigimod alfa – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with progressive or recurrent active chronic inflammatory demyelinating polyneuropathy after previous treatment with corticosteroids or immunoglobulins	Immunoglobulins or corticosteroids[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- Patients in the comparator arm who show an active course of the disease following treatment with immunoglobulins or corticosteroids should be switched to the respective other available treatment option, where indicated.
- The unchanged continuation of an inadequate treatment does not comply with the ACT if the option of treatment optimization is still available.
- Plasmapheresis is not considered to be a regular ACT; however, in individual cases, it may serve as an acute treatment and, where immunoglobulins and corticosteroids have failed, as a treatment option for patients with chronic inflammatory demyelinating polyneuropathy.

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

The assessment described above deviates from that of the company, which derived an indication of 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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