Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Rozanolixizumab (myasthenia gravis, AChR antibody+, MuSK antibody+)

of 15 August 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient rozanolixizumab on 1 March 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 29 February 2024.

Rozanolixizumab as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 03 June 2024 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of rozanolixizumab.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Rozanolixizumab (Rystiggo) in accordance with the product information

Rystiggo is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

Therapeutic indication of the resolution (resolution of 15 August 2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In the present therapeutic indication, the patient population was divided according to antibody status. According to the German guideline[2] and the statements of the clinical experts in the written statement procedure, patients with anti-MuSK and anti-AChR antibody-positive gMG differ, among others, in the course of the disease and in their response to various therapy options, such as thymectomy and treatment with complement inhibitors. It is therefore considered appropriate to analyse the patient groups separately.

In summary, the additional benefit of rozanolixizumab is assessed as follows:

For a) adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy, there is a hint for a considerable additional benefit for rozanolixizumab.

For b) adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy, there is a hint for a non-quantifiable additional benefit for rozanolixizumab since the scientific data does not allow quantification.

Justification:

For the benefit assessment, the pharmaceutical company presented the MG0003 study in the dossier. This is a three-arm, double-blind, randomised, multicentre phase III study comparing rozanolixizumab versus placebo in addition to standard therapy in adults with anti-AChR and anti-MuSK antibody-positive gMG over one treatment cycle. Adults with class IIa to IVb gMG according to the Myasthenia Gravis Foundation of America (MGFA) classification at the time of screening were enrolled in the study. Patients in MGFA class I, i.e. with pure ocular MG, and MGFA class V corresponding to gMG requiring intubation (i.e. myasthenic crisis) were not investigated. The study participants had to have disease-specific symptoms at screening and baseline (MG-ADL score ≥ 3 points (with ≥ 3 points from non-ocular symptoms) and QMG score ≥ 11 points).

2 Wiendl H., Meisel A. et al, Diagnostics and Therapy of Myasthenic Syndromes, S2k Guideline, 2022, DGN, in: German Society of Neurology (ed.), Guidelines for Diagnosis and Therapy in Neurology. Online: www.dgn.org/leitlinien (accessed 25.06.2024).

A total of 133 subjects were randomised in a 1:1 ratio into the intervention arm with the on-label dosage (n = 66) and into the placebo arm (n = 67). Randomisation was stratified at baseline according to MuSK antibody status (+/-) and AChR antibody status (+/-).

The treatment was carried out over the course of one treatment cycle of 6 weeks. This was followed by a follow-up phase of 8 weeks (until day 99). The patients enrolled also received concomitant medication with course-modifying, immunosuppressive and symptomatic medicinal therapies.

For the marketing authorisation of rozanolixizumab, the European regulatory authority considered the long-term data available to date from the single-arm MG0004 and MG0007 extension studies in addition to the pivotal MG0003 study. These data were not considered by the pharmaceutical company in the dossier due to the lack of comparison. Furthermore, the data subsequently submitted by the pharmaceutical company in the written statement procedure were not adequately processed.

In accordance with the requirements in the product information, rozanolixizumab is administered in treatment cycles that are administered at patient-individual intervals according to clinical assessment. In view of the fact that this is not a continuous treatment, but a treatment in cycles of frequency different from patient to patient in the therapeutic indication to be assessed, the available data at the end of the treatment cycle on day 43 are used for quantification of the additional benefit.

a) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

For the patient group of adults with anti-AChR antibody-positive gMG analysed here, the pharmaceutical company only submitted the data of the total population of the MG0003 study. This also includes the sub-population with anti-MuSK antibody-positive gMG and subjects without confirmed positive AChR antibody status. Appropriate information regarding a possible effect modification by antibody status was not submitted. Differences between the total population and the sub-population with positive MuSK antibody status can be seen in the baseline values with regard to symptom burden and duration of disease. Since > 90% of the total population had a positive AChR antibody status after IWRS randomisation, the total population is nevertheless shown.

Mortality

The number of deceased patients was recorded as part of the safety assessment. No deaths occurred during the course of the study.

Morbidity

Disease-specific symptomatology using Myasthenia Gravis – Activities of Daily Living (MG-ADL)

The MG-ADL is an established patient-reported questionnaire used in care to assess the symptomatology of myasthenia gravis and its impact on activities of daily living such as talking, chewing, swallowing, breathing, combing hair or brushing teeth, arise from a chair, incidence of double vision and drooping eyelids.

The *post hoc* responder analysis with a responder threshold of 15% (improvement ≥ 4 points) showed a statistically significant difference in favour of rozanolixizumab compared to placebo at the end of the 6-week treatment cycle.

However, the regression model could not converge with the inclusion of the continuously scaled baseline values, which is why the baseline values could not be fully included in the present evaluation.

Disease-specific symptomatology using Quantitative Myasthenia Gravis (QMG)

In the MG0003 study, the QMG was also surveyed to analyse the disease-specific symptomatology. The QMG is a doctor-reported questionnaire used to quantitatively measure myasthenic symptomatology and assesses the strength of faciopharyngeal, limb and trunk muscles, as well as vital capacity and ocular symptoms. In the present therapeutic indication, the QMG is an established measurement tool in clinical care, which is used together with the MG-ADL and MG-Quality of Life 15 (MG-Qol-15r) questionnaire for the ongoing assessment of disease activity and severity as well as treatment response.

The pharmaceutical company considered the QMG to be irrelevant for the assessment and did not submit any *post hoc* responder analyses with a responder threshold of 15%. Although the available results of the continuous evaluations of the QMG showed a statistically significant difference in favour of rozanolixizumab, the clinical relevance cannot be assessed on the basis of the available data.

Even taking into account that further more significant evaluations on disease-specific symptomatology are available, the endpoint is not used for the present benefit assessment in the overall assessment.

Disease-specific symptomatology using "Myasthenia Gravis Symptoms Patient Reported Outcome" (MG Symptoms PRO)

The MG Symptoms PRO is a self-reported questionnaire developed by the pharmaceutical company itself to collect indication-specific symptoms in the indication of myasthenia gravis. The MG Symptoms PRO with a total of 42 items covers 5 domains: Ocular, bulbar and respiratory symptoms, as well as physical fatigue and muscle weakness/ fatigability. A score between 0 and 100 can be reached, with a higher value indicating more frequent and more severe symptomatology. Since the MG Symptoms PRO surveys the disease symptomatology of gMG in more detail than the "MG-ADL" and "QMG" questionnaires established in clinical practice, the endpoint is used despite the double collection of most disease-specific symptoms.

In the *post hoc* responder analyses - subsequently submitted as part of the written statement procedure - with a responder threshold of 15% (improvement ≥ 15 points for the respective

domain) and inclusion of the baseline values, a statistically significant advantage in favour of rozanolixizumab over placebo was shown in each of the domains "Muscle weakness/ fatigability", "Ocular muscle weakness" and "Bulbar muscle weakness" at the end of the 6-week treatment cycle. There was no statistically significant difference in the "Physical fatigue" domain. In the MG Symptoms PRO domain "Respiratory muscle weakness", the regression model (both dichotomously and continuously scaled) could not converge when including the baseline values as variables.

The regression model for calculating the responder analysis of the "Muscle weakness/ fatigability" domain could not converge using the continuously scaled baseline values, which is why the baseline values were not fully included in the present evaluation.

General health status (EQ-5D VAS)

Health status was collected in the MG0003 study using the Visual Analogue Scale of the European Quality of Life -5-Dimensions (EQ 5D-VAS). In the responder analyses conducted *post hoc* by the pharmaceutical company with a clinical relevance threshold of 15%, there was no statistically significant difference between rozanolixizumab and placebo for this endpoint at the end of 6-week treatment phase.

However, the regression model could not converge with the inclusion of the continuously scaled baseline values, which is why the baseline values could not be fully included in the present evaluation.

Evaluations at the end of the follow-up phase (day 99)

For the study data collected at the end of the follow-up phase (day 99), no evaluations, in which the baseline values of the respective instrument were considered as a variable in the implementation of the (stratified) logistic regression, were submitted as part of the written statement procedure. In addition, the results are of secondary importance for the medical treatment situation in Germany because it was not possible to start a new treatment cycle in accordance with the clinical assessment. Overall, the data was therefore not presented in the resolution.

The evaluations without including the baseline values as a variable show no significant differences between the treatment arms for the MG-ADL and the various domains of the MG Symptoms PRO at the end of treatment.

In addition, the self-reported Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) questionnaires were collected as patient-relevant endpoints at the end of the follow-up period. These endpoints were not collected at the end of the 6-week treatment phase. There were no statistically significant differences between rozanolixizumab and placebo at the end of the follow-up period for the endpoints "PGI-S response"[3] and "PGI-C response"[4].

[3] defined as reaching category 1 ("no symptoms") or category 2 ("mild symptoms").
[4] defined as reaching category 1 ("very much improved") or category 2 ("much improved").

Quality of life

Health-related quality of life was collected in the MG0003 study using the patient-reported Myasthenia Gravis Quality of Life 15 questionnaire (MG-QoL15r). The MG-QoL15r measures the mental well-being and social activity of patients.

The *post hoc* responder analysis with a responder threshold of 15% (improvement ≥ 5 points) showed a statistically significant difference in favour of rozanolixizumab compared to placebo at the end of the 6-week treatment cycle.

At the end of the follow-up phase (day 99), there was no significant difference between the treatment arms according to the evaluation without inclusion of the baseline values.

Side effects

Adverse events (AEs) that occurred from the first dose of study medication until the end of the observation phase (day 99) were considered for the evaluations of the endpoints in the category "side effects".

There were no statistically significant differences between treatment arms for the overall rates of serious AEs (SAEs), severe AEs and AEs which led to discontinuation of study medication. No AEs of special interest were pre-specified for the study.

Overall assessment

For the benefit assessment of rozanolixizumab for the treatment of adults with gMG who are anti-AChR antibody positive, results on the total population of the randomised controlled trial MG0003 are available for the endpoint categories of mortality, morbidity, quality of life and side effects compared to placebo. In both study arms, most patients received standard therapy consisting of acetylcholinesterase inhibitors, steroids and/or non-steroidal immunosuppressants, which was stable before the start of the study.

There were no deaths in the endpoint category of mortality.

In the morbidity category, there were advantages of rozanolixizumab over placebo in the disease-specific symptomatology, i.e. in the MG-ADL and in the "Muscle weakness/ fatigability", "Ocular muscle weakness" and "Bulbar muscle weakness" domains of the MG Symptoms PRO in the responder analyses on day 43. Neither advantages nor disadvantages of rozanolixizumab compared to placebo at the end of treatment on day 43 can be derived from the "Physical fatigue" domain and the EQ-5D VAS. No assessable data are available for the "Respiratory muscle weakness" domain of the MG Symptoms PRO .

For health-related quality of life, there was an advantage of rozanolixizumab over placebo at the end of the treatment cycle based on MG-QoL15r.

With regard to side effects, neither an advantage nor a disadvantage of rozanolixizumab over placebo can be found, in each case in combination with the standard therapy.

In the overall assessment of the results, an additional benefit of rozanolixizumab can be derived on the basis of the positive effects in the endpoints on morbidity - i.e. on disease-specific symptomatology (MG-ADL, "Muscle weakness/ fatigability", "Ocular muscle weakness" and "Bulbar muscle weakness" domains of the MG Symptoms PRO) - and on health-related quality of life, which is assessed as considerable in its extent.

Significance of the evidence

The risk of bias of the MG0003 study is categorised as low for the total population analysed. However, uncertainties exist due to the fact that no data are available in which only the assessed sub-population of anti-AChR antibody-positive subjects with gMG were included. Patients who are anti-MuSK antibody-positive generally have a higher symptom burden, slightly different symptomatology and are more likely to experience myasthenic crises than subjects with positive AChR antibody status. In addition, it is known that the two patient groups do not respond equally to all therapy options in the therapeutic indication, so that it would have been fundamentally appropriate to examine the presence of an effect modification by the included subjects without anti-AChR antibodies.

Since, in addition to the differences described above, the problems in carrying out the stratified logistic regression including the baseline values indicate that the population is heterogeneous, a high risk of bias can be assumed overall.

Furthermore, it is not possible to draw any conclusions about longer-term effects due to the short duration of treatment and follow-up - even taking into account the fluctuating course of the disease.

Overall, the uncertainties mentioned with regard to the significance of the evidence result in a hint for an additional benefit.

b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

For the sub-population of subjects with anti-MuSK antibody-positive gMG who are eligible for an add-on to standard therapy, the pharmaceutical company presented the evaluations in the dossier, in which the past antibody status was taken into account. As part of the written statement procedure, the pharmaceutical company also submitted evaluations with the antibody status at baseline and IWRS (Interactive Web Response System) randomisation. Overall, the procedure or the allocation of individual subjects to the anti-MuSK antibody-positive patient group is considered to be inadequately interpretable. Since the evaluation of the antibody status for IWRS randomisation most closely reflects the ITT population, this is used for the assessment of the additional benefit.

For general information on the various measurement instruments, please refer to the information in patient group a).

Mortality

No deaths occurred.

Morbidity

MG-ADL

At the end of the 6-week treatment cycle, the responder analysis with a responder threshold of 15% (improvement ≥ 4 points) showed no statistically significant difference between the treatment arms for the MG-ADL endpoint.

MG Symptoms PRO

In the *post hoc* responder analyses with a responder threshold of 15% (improvement ≥ 15 points for the respective domain), there was no statistically significant difference between rozanolixizumab and placebo in the various domains of the MG Symptoms PRO at the end of the 6-week treatment cycle.

QMG

For the patient group of anti-MuSK antibody-positive subjects with gMG, the pharmaceutical company also did not conduct any responder analyses *post hoc* with a response threshold of 15% for the QMG. No information is available on the assessment of statistical significance (p value) and clinical relevance (Hedges' g) for the available results of the continuous evaluations of the QMG. An assessment of the effect is therefore not possible on the basis of the present evaluation.

Evaluations at the end of the follow-up phase (day 99)

No evaluations after IWRS randomisation are available for the patient group with anti-MuSK antibody-positive gMG.

Quality of life

At the end of the 6-week treatment cycle, the responder analysis with a responder threshold of 15% (improvement ≥ 4 points) showed no statistically significant difference between the treatment arms for the MG-QoL15r.

Side effects

Severe AEs (CTCAE grade ≥ 3), SAEs or AEs which led to study discontinuation occurred in neither the placebo nor the rozanolixizumab arm.

Overall assessment

For the benefit assessment of rozanolixizumab for the treatment of adults with gMG who are anti-MuSK antibody-positive, results of the randomised controlled trial MG0003 on the sub-population with MuSK-positive antibody status after IWRS randomisation compared to placebo are available. In both study arms, most patients received standard therapy consisting of acetylcholinesterase inhibitors, steroids and/or non-steroidal immunosuppressants, which was stable before the start of the study.

No deaths occurred in the MG0003 study. Likewise, no severe or serious AEs or AEs which led to study discontinuation occurred within the anti-MuSK antibody-positive patient group. Therefore, no conclusions on the extent of the additional benefit can be derived from the data on mortality and side effects.

Both for the endpoints on disease-specific symptomatology (MG-ADL, MG Symptoms PRO) and on health status as well as on health-related quality of life (MG-QoL15r), there were neither advantages nor disadvantages with rozanolixizumab compared to placebo at the end

of the 6-week treatment cycle. It is therefore not possible to quantify the additional benefit on the basis of the data for the endpoint categories of morbidity and quality of life.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of rozanolixizumab for the treatment of adults with gMG who are anti-MuSK antibody-positive on the basis of the criteria in Section 5, paragraph 8 sentences 1, 2 in conjunction with Section 5, paragraph 7, sentence 1, number 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The risk of bias of the MG0003 study is considered high for the sub-population with MuSK-positive antibody status. This assessment is based primarily on the very small sample size. The very small sample size also means that the same evaluations could not be carried out as for the total population and therefore the baseline values were not included in the evaluation of the responder analyses.

In addition, the various evaluation strategies for assigning antibody status are not transparent. Results-driven reporting can therefore not be ruled out overall.

Furthermore, it is not possible to draw any conclusions about longer-term effects due to the short duration of treatment and follow-up - even taking into account the fluctuating course of the disease.

Overall, the uncertainties mentioned with regard to the significance of the evidence result in a hint for an additional benefit.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Rystiggo" with the active ingredient "rozanolixizumab". Rozanolixizumab is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive. Rystiggo was approved as an orphan drug.

For the benefit assessment, the pharmaceutical company presented the double-blind, randomised phase III MG0003 study, in which rozanolixizumab was compared with placebo in addition to standard therapy in adults with anti-AChR and anti-MuSK antibody-positive gMG over a 6-week treatment cycle and an 8-week follow-up phase.

In the therapeutic indication analysed, two patient groups were differentiated according to their antibody status: a) with anti-AChR antibody-positive and b) with anti-MuSK antibody-positive gMG.

Patient group a) Adults with anti-AChR antibody-positive gMG who are eligible for an add-on to standard therapy

For patient group a), only data for the total population were presented. Evaluations in which only subjects with AChR-positive antibody status were considered were not carried out. There were no deaths in the endpoint category of mortality.

In the morbidity category, there were advantages of rozanolixizumab over placebo in the disease-specific symptomatology, i.e. in the MG-ADL and in the "Muscle weakness/ fatigability", "Ocular muscle weakness" and "Bulbar muscle weakness" domains of the MG Symptoms PRO in the responder analyses on day 43. Neither advantages nor disadvantages of rozanolixizumab compared to placebo at the end of treatment on day 43 can be derived from the "Physical fatigue" domain and the EQ-5D VAS. No assessable data are available for the "Respiratory muscle weakness" domain of the MG Symptoms PRO .

For health-related quality of life, there was an advantage of rozanolixizumab over placebo at the end of the 6-week treatment cycle based on MG-QoL15r.

With regard to side effects, neither an advantage nor a disadvantage of rozanolixizumab over placebo can be found over a period of 14 weeks.

Uncertainties exist in particular due to the absence of data in which only the sub-population to be assessed was included. Furthermore, it is not possible to draw any conclusions about longer-term effects due to the short duration of treatment and follow-up - even taking into account the fluctuating course of the disease.

The overall assessment resulted in a hint for a considerable additional benefit for patient group a).

Patient group b) Adults with MuSK antibody-positive gMG who are eligible for an add-on to standard therapy

No deaths occurred in the MG0003 study. Likewise, no severe or serious AEs or AEs which led to study discontinuation occurred within the anti-MuSK antibody-positive patient group in the course of the study lasting 14 weeks. Both for the endpoints on disease-specific symptomatology (MG-ADL, MG Symptoms PRO) and on health status as well as on health-related quality of life (MG-QoL15r), there were neither advantages nor disadvantages with rozanolixizumab compared to placebo at the end of the 6-week treatment cycle. A quantification of the additional benefit based on the data is thus not possible.

The risk of bias is considered to be high, particularly due to the very small sample size. In addition, the various evaluation strategies regarding the assignment of antibody status are not transparent. Results-driven reporting can therefore not be ruled out overall.

Furthermore, it is not possible to draw any conclusions about longer-term effects due to the short duration of treatment and follow-up - even taking into account the fluctuating course of the disease.

The overall assessment of the available results gives a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

For the anti-AChR antibody-positive gMG (patient population a), the present resolution is based on the information from the dossier of the benefit assessment procedure for the active ingredient efgartigimod alfa, which was ongoing at the time of drafting the resolution. For the anti-MuSK antibody-positive gMG (patient population b), the information provided by the pharmaceutical company in this dossier is used as a basis.

Overall, the stated number of patients with anti-AChR antibody-positive gMG in the SHI target population is subject to uncertainties for the lower limit and overestimated for the upper limit. This results, among other things, from the operationalisation of patients with high disease activity/ severity, which was carried out exclusively taking into account MGFA classes II to IV with reference to the highest degree of severity ever achieved in the course of the disease. Nevertheless, a number at the lower end of the stated range is currently the most plausible estimate of patient numbers in the therapeutic indication of anti-AChR antibody-positive gMG.

In previous procedures in the therapeutic indication of anti-AChR antibody-positive gMG, a significantly higher number of patients (approx. 14,000 - 16,800) was determined for the active ingredient efgartigimod alfa by resolution of 16 February 2023 and a significantly lower number (800 - 1,200) for the active ingredient ravulizumab by resolution of 20 April 2023. The patient numbers in the resolution on the active ingredient efgartigimod alfa refer to all adults with gMG who are anti-AChR antibody-positive, without restriction to patients who are eligible for an add-on to standard therapy. The patient numbers in the resolution on the active ingredient ravulizumab, on the contrary, relate exclusively to refractory patients and therefore only represent part of the current anti-AChR antibody-positive target population. There are no previous procedures on anti-MuSK antibody-positive gMG.

For anti-MuSK antibody-positive gMG, the derivation of patient numbers is subject to uncertainties overall.

These result, among other things, from the routine data, on which the prevalence rate of myasthenia gravis is based and which come from only two federal states, from a lack of demarcation between generalised and ocular myasthenia gravis, as well as uncertainties regarding the percentage of patients who are not treated exclusively symptomatically. A further uncertainty arises from the operationalisation of patients with high disease activity/ disease severity, which was not carried out in accordance with the criteria of the S2k guideline "Diagnosis and treatment of myasthenic syndromes". In addition, there are uncertainties regarding the percentage of anti-MuSK antibody-positive subjects with gMG based on the myasthenia registry.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Rystiggo (active ingredient: rozanolixizumab) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 23 May 2024):

https://www.ema.europa.eu/en/documents/product-information/rystiggo-epar-product-information_en.pdf

Treatment with rozanolixizumab should only be initiated and monitored by doctors experienced in treating neuromuscular or neuroinflammatory diseases.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 July 2024).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

Treatment period:

The dosage recommended in the product information was used as the calculation basis. One treatment cycle of rozanolixizumab lasts 6 weeks. A new treatment cycle is initiated patient-individually according to the clinical assessment. According to the requirements in the product information, most study participants in the clinical development programme had treatment-free intervals of 4 – 13 weeks. This range is used for the cost calculation.

The acetylcholinesterase inhibitor neostigmine is applied several times daily different from patient to patient.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Rozanolixizumab	1 x every 7 days per 6-week cycle	5.2	6	31.2
	1 x every 7 days per 6-week cycle	2.7	6	16.2
Patient-individual standard therapy				
Azathioprine	Continuously, 1 x daily	365	1	365
Prednisolone	Continuously, 1 x daily	365	1	365
Prednisone	Continuously, 1 x daily	365	1	365
Pyridostigmine	Continuously, 2 – 4 x daily	365	1	365
Neostigmine	Different from patient to patient			
Distigmine	Continuously, 1 x daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Mycophenolate mofetil[5]	Continuously, 0.5 – 2.5 g daily	365	1	365

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population"[6] were used as a basis (average body weight: 77.7 kg).

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Rozanolixizumab	560 mg for ≥ 70 to < 100 kg BW	560 mg	2 x 280 mg	31.2	62.4 x 280 mg
	560 mg for ≥ 70 to < 100 kg BW	560 mg	2 x 280 mg	16.2	32.4 x 280 mg
Patient-individual standard therapy					
Azathioprine	2 mg/ kg BW = 155 mg –	155 mg –	1 x 100 mg + 1 x 50 mg –	365	365 x 100 mg + 365 x 50 mg
	3 mg/kg BW = 233 mg	233 mg	2 x 100 mg + 0.5 x 75 mg		730 x 100 mg + 182.5 x 75 mg
Prednisolone	5 mg –	5 mg –	1 x 5 mg	365	365 x 5 mg
	15 mg	15 mg	1 x 5 mg 1 x 10 mg		365 x 5 mg + 365 x 10 mg
Prednisone	5 mg –	5 mg –	1 x 5 mg	365	365 x 5 mg

[5] Mycophenolate mofetil is not approved in the therapeutic indication under consideration, but is reimbursable within the framework of off-label use (Pharmaceuticals Directive Annex VI) in the case of resistance to treatment with the approved substances or in the case of azathioprine intolerance.

[6] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
	15 mg	15 mg	1 x 5 mg + 1 x 10 mg		365 x 5 mg + 365 x 10 mg
Pyridostigmine	10 mg –	30 mg –	3 x 10 mg –	365	1,095 x 10 mg
	540 mg	1,080 mg	6 x 180 mg		2,190 x 180 mg
Neostigmine	Different from patient to patient				
Distigmine	10 mg	10 mg	2 x 5 mg	365	730 x 5 mg
Mycophenolate mofetil	500 mg –	500 mg –	1 x 500 mg –	365	365 x 500 mg –
	2,500 g	2,500 g	5 x 500 mg		1825 x 500 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Rozanolixizumab 280 mg	1 SFI	€ 10,415.62	€ 2.00	€ 591.55	€ 9,822.07
Patient-individual standard therapy					
Azathioprine[7] 100 mg	100 FCT	€ 58.01	€ 2.00	€ 3.69	€ 52.32
Azathioprine[7] 75 mg	100 FCT	€ 49.83	€ 2.00	€ 3.05	€ 44.78
Azathioprine[7] 50 mg	100 FCT	€ 40.67	€ 2.00	€ 2.32	€ 36.35
Prednisolone[7] 5 mg	100 TAB	€ 15.43	€ 2.00	€ 0.33	€ 13.10

[7] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Prednisolone[7] 10 mg	100 TAB	€ 17.81	€ 2.00	€ 0.51	€ 15.30
Prednisone[7] 5 mg	100 TAB	€ 16.74	€ 2.00	€ 0.43	€ 14.31
Prednisone[7] 10 mg	100 TAB	€ 21.23	€ 2.00	€ 0.78	€ 18.45
Pyridostigmine bromide 10 mg	100 FCT	€ 23.23	€ 2.00	€ 1.51	€ 19.72
Pyridostigmine bromide 180 mg	100 SRT	€ 264.12	€ 2.00	€ 32.00	€ 230.12
Neostigmine	Different from patient to patient				
Distigmine bromide 5 mg	50 TAB	€ 108.59	€ 2.00	€ 5.39	€ 101.20
Mycophenolate mofetil[7] 500 mg	250 FCT	€ 409.94	€ 2.00	€ 31.53	€ 376.41
Abbreviations: FCT = film-coated tablets; SFI = solution for injection; SRT = sustained release tablets; TAB = tablets					

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b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Rozanolixizumab 280 mg	1 SFI	€ 10,415.62	€ 2.00	€ 591.55	€ 9,822.07
Patient-individual standard therapy					
Azathioprine[7] 100 mg	100 FCT	€ 58.01	€ 2.00	€ 3.69	€ 52.32
Azathioprine[7] 75 mg	100 FCT	€ 49.83	€ 2.00	€ 3.05	€ 44.78
Azathioprine[7] 50 mg	100 FCT	€ 40.67	€ 2.00	€ 2.32	€ 36.35
Prednisolone[7] 5 mg	100 TAB	€ 15.43	€ 2.00	€ 0.33	€ 13.10
Prednisolone[7] 10 mg	100 TAB	€ 17.81	€ 2.00	€ 0.51	€ 15.30
Prednisone[7] 5 mg	100 TAB	€ 16.74	€ 2.00	€ 0.43	€ 14.31
Prednisone[7] 10 mg	100 TAB	€ 21.23	€ 2.00	€ 0.78	€ 18.45
Pyridostigmine bromide 10 mg	100 FCT	€ 23.23	€ 2.00	€ 1.51	€ 19.72
Pyridostigmine bromide 180 mg	100 SRT	€ 264.12	€ 2.00	€ 32.00	€ 230.12
Neostigmine	Different from patient to patient				
Distigmine bromide 5 mg	50 TAB	€ 108.59	€ 2.00	€ 5.39	€ 101.20
Mycophenolate mofetil[7] 500 mg	250 FCT	€ 409.94	€ 2.00	€ 31.53	€ 376.41

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Abbreviations: FCT = film-coated tablets; SFI = solution for injection; SRT = sustained release tablets; TAB = tablets					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for rozanolixizumab (Rystiggo); Rystiggo® 140 mg/ml solution for injection; last revised: March 2024

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 29 February 2024, the pharmaceutical company submitted a dossier for the benefit assessment of rozanolixizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 3 June 2024 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 24 June 2024.

The oral hearing was held on 8 July 2024.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 25 July 2024.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 6 August 2024, and the proposed draft resolution was approved.

At its session on 15 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 May 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	3 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 July 2024	Conduct of the oral hearing
Working group Section 35a	17 July 2024 31 July 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	6 August 2024	Concluding discussion of the draft resolution
Plenum	15 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 August 2024

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken