IQWiG Reports – Commission No. A22-74

# Inebilizumab (neuromyelitis optica spectrum disorders) –

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

**Extract**

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Inebilizumab (Neuromyelitis-optica-Spektrum-Erkrankungen)– Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 18 October 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

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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 |
| AE | adverse event |
| AQP4-IgG | anti-aquaporin-4 immunoglobulin G |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| NMOSD | neuromyelitis optica spectrum disorders |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |

## I 1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug inebilizumab. 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 19 July 2022.

### Research question

The aim of the present report is to assess the added benefit of inebilizumab in comparison with the appropriate comparator therapy (ACT) of treatment of physician's choice in adult patients with neuromyelitis optica spectrum disorders (NMOSD) who are anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive.

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

Table 2: Research questions of the benefit assessment of inebilizumab

| Therapeutic indication | ACT[a] |
|---|---|
| Adult patients with NMOSD who are AQP4-IgG seropositive | Treatment of physician's choice[b] |
| a. Presented is the ACT specified by the G-BA.<br>b. For immunosuppressant long-term therapy, clinical trials are to offer the drugs azathioprine, eculizumab, mycophenolate mofetil, and rituximab.<br>ACT: appropriate comparator therapy; AQP4-IgG: anti-aquaporin-4 immunoglobulin G; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders | |

The company followed the ACT by designating treatment of physician's choice as the ACT. Departing from the G-BA's specification, the company took into account only the 2 drugs approved in the therapeutic indication, satralizumab and eculizumab, as treatment of physician's choice. However, the company neither limited its information retrieval to the treatment options of satralizumab and eculizumab nor did it find any studies with direct comparisons versus satralizumab. Hence, the company's information retrieval is nevertheless of informative value for the present research question as defined by the G-BA.

The assessment is conducted in comparison with the ACT specified by the G-BA 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 for the derivation of added benefit.

### Results

The check of completeness of the study pool identified no studies directly comparing inebilizumab versus the ACT in the present therapeutic indication.

Since no directly comparative data are available, the company has presented an adjusted indirect comparison of inebilizumab versus satralizumab using the common comparator of placebo. For the indirect comparison, the company identified the N-MOmentum study on the intervention side and the SAkuraStar study on the comparator side.

The presented adjusted indirect comparison is unsuitable for assessing the benefit of inebilizumab versus the ACT. This is explained below.

***Evidence provided by the company***

*N-MOmentum study on inebilizumab*

The N-MOmentum study is a double-blind, multicentre, phase II/III RCT comparing inebilizumab versus placebo. The study enrolled adults, the majority with AQP4-IgG seropositive NMOSD, who had at least 1 attack requiring rescue therapy in the previous year or at least 2 attacks requiring rescue therapy in the previous 2 years. A total of 213 patients with AQP4-IgG seropositive NMOSD were randomized in a 3:1 ratio to treatment with either inebilizumab (N = 161) or placebo (N = 52). In line with the Summary of Product Characteristics (SPC), patients received either 300 mg inebilizumab as an intravenous infusion or an appropriate placebo on Days 1 and 15. The planned duration of the randomized treatment phase was 28 weeks. This was followed by an open-label study phase in which inebilizumab treatment was continued (intervention arm) or could be initiated (placebo arm). The study's primary outcome was time to confirmed NMOSD attack.

*SAkuraStar study on satralizumab*

The SAkuraStar study is a double-blind, multicentre, phase III RCT with a subsequent open-label extension phase comparing satralizumab versus placebo. The study enrolled adults with AQP4-IgG seropositive or seronegative NMOSD who had at least 1 attack in the previous year. For the adjusted indirect comparison, the company used the subpopulation of AQP4-IgG seropositive patients. Patients received satralizumab or placebo until the occurrence of an attack or until the end of the study period. The study's primary outcome was time to attack.

*Adjusted indirect comparison*

For assessing the added benefit of inebilizumab, the company submitted an adjusted indirect comparison with satralizumab via the common comparator of placebo for the outcomes of time to confirmed NMOSD attack, annualized attack rate, adverse events (AEs), serious AEs (SAEs), and specific Preferred Terms (PTs) and System Organ Classes (SOCs). No significant differences were found for any of them.

***Failure to implement treatment of physician's choice***

The adjusted indirect comparison presented by the company is unsuitable for assessing any added benefit of inebilizumab in comparison with the ACT specified by the G-BA. In its notes on the ACT, the G-BA states that a single-comparator study is typically an inadequate implementation of treatment of physician's choice and that for the latter, clinical trials are expected to offer a selection from the drugs azathioprine, eculizumab, mycophenate mofetil,

and rituximab (multi-comparator study). Irrespective of the SAkuraStar study failing to offer a selection from various treatment options, satralizumab is not among the ACT options specified by the G-BA.

**Results on added benefit**

Since no usable data are available for the benefit assessment, there is no hint of an added benefit of inebilizumab 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 summarizes the probability and extent of added benefit of inebilizumab.

Table 3: Inebilizumab – probability and extent of added benefit

| Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| Adult patients with NMOSD who are AQP4-IgG seropositive | Treatment of physician's choice[b] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. For immunosuppressant long-term therapy, clinical trials are to offer the drugs azathioprine, eculizumab, mycophenolate mofetil, and rituximab.

ACT: appropriate comparator therapy; AQP4-IgG: anti-aquaporin-4 immunoglobulin G; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders

The G-BA decides on the added benefit.

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

## I 2 Research question

The aim of the present report is to assess the added benefit of inebilizumab in comparison with the ACT of treatment of physician's choice in adult patients with NMOSD who are AQP4-IgG seropositive.

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

Table 4: Research questions of the benefit assessment of inebilizumab

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Adult patients with NMOSD who are AQP4-IgG seropositive | Treatment of physician's choice[b] |

a. Presented is the ACT specified by the G-BA.
b. For immunosuppressant long-term therapy, clinical trials are to offer the drugs azathioprine, eculizumab, mycophenolate mofetil, and rituximab.

ACT: appropriate comparator therapy; AQP4-IgG: anti-aquaporin-4 immunoglobulin G; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders

The company followed the ACT by designating treatment of physician's choice as the ACT. Departing from the G-BA's specification, the company took into account only the 2 drugs approved in the therapeutic indication, satralizumab and eculizumab, as treatment of physician's choice. However, the company neither limited its information retrieval to the treatment options of satralizumab and eculizumab nor did it find any studies with direct comparisons versus satralizumab. Hence, the company's information retrieval is nevertheless of informative value for the present research question as defined by the G-BA.

The assessment is conducted in comparison with the ACT specified by the G-BA and 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 for the derivation of added benefit. This deviates from the company's inclusion criteria, which specified no limitation in terms of minimum duration.

## I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on inebilizumab (status: 12 May 2022)
- bibliographical literature search on inebilizumab (last search on 12 May 2022)
- search in trial registries / trial results databases for studies on inebilizumab (last search on 12 May 2022)
- search on the G-BA website for inebilizumab (last search on 13 May 2022)
- bibliographical literature search on the ACT (last search on 12 May 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 12 May 2022)
- search on the G-BA website for the ACT (last search on 13 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on inebilizumab (last search on 8 August 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no study for the direct comparison of inebilizumab with the ACT in the present therapeutic indication.

Since no directly comparative data are available, the company has presented an adjusted indirect comparison of inebilizumab versus satralizumab using the common comparator of placebo. For the indirect comparison, the company identified the N-MOmentum study [3] on the intervention side and the SAkuraStar study [4] on the comparator side.

The presented adjusted indirect comparison is unsuitable for assessing the benefit of inebilizumab versus the ACT. This is explained below.

**Evidence provided by the company**

***N-MOmentum study on inebilizumab***

The N-MOmentum study is a double-blind, multicentre, phase II/III RCT comparing inebilizumab versus placebo. The study included adults with AQP4-IgG-seropositive NMOSD with at least 1 attack requiring rescue therapy in the previous year or at least 2 attacks requiring rescue therapy within the previous 2 years. Additionally, all patients were to exhibit an Expanded Disability Severity Scale (EDSS) score ≤ 7.5. Patients with AQP4-IgG-seronegative disease were eligible for study enrolment if they (a) met the above inclusion criteria, (b) exhibited no evidence of a brain lesion suggesting multiple sclerosis, and (c) fulfilled the

clinical criteria of NMOSD. Nearly half of all AQP4-IgG-positive patients had received no prior immunosuppressant therapy other than treatment of attacks.

In the N-MOmentum study, a total of 213 patients with AQP4-IgG-seropositive NMOSD were randomized in a 3:1 ratio to either inebilizumab treatment (N = 161) or placebo (N = 52). Based on the inebilizumab marketing authorization, the company disregarded 18 patients from the total population (N = 231) with AQP4-IgG-seronegative NMOSD in its benefit assessment. Randomization was stratified by AQP4-IgG status at screening (seropositive versus seronegative) as well as by region (Japan versus outside Japan).

In line with the SPC [5], patients received 300 mg inebilizumab as an intravenous infusion or a corresponding placebo, both on Day 1 and Day 15, each following prior treatment with methylprednisolone, diphenhydramine, and paracetamol. Additionally, patients were treated with oral corticosteroids in the first 2 weeks, followed by a 1-week tapering phase.

The planned duration of the randomized treatment phase was 28 weeks. This was followed by an open-label study phase in which inebilizumab treatment either could be initiated (placebo arm) or continued while remaining blinded (intervention arm).

The study's primary outcome was time to confirmed NMOSD attack. Furthermore, outcomes on morbidity, health-related quality of life, and side effects were recorded.

***SAkuraStar study on satralizumab***

The SAkuraStar study is a double-blind, multicentre, phase III RCT with a subsequent open-label extension phase comparing satralizumab versus placebo. The study enrolled adults with AQP4-IgG seropositive or seronegative NMOSD who had at least 1 attack in the previous year. Nearly 90% of all patients had received immunosuppressant therapy or other therapies for attack prevention prior to enrolment. However, no information is available on the drugs used for this purpose. For the adjusted indirect comparison, the company used the subpopulation of AQP4-IgG seropositive patients. Participants received satralizumab or placebo until the occurrence of an attack or until the end of the study period. The study's primary outcome was time to attack. Further information on the SAkuraStar study design is available in the G-BA's benefit assessment of satralizumab [6].

***Adjusted indirect comparison***

For assessing the added benefit of inebilizumab, the company submitted an adjusted indirect comparison with satralizumab via the common comparator of placebo for the outcomes of time to confirmed NMOSD attack, annualized attack rate, AEs, SAEs, and specific PTs and SOCs. No significant differences were found for any of them.

**Failure to implement treatment of physician's choice**

The adjusted indirect comparison presented by the company is unsuitable for assessing any added benefit of inebilizumab in comparison with the ACT specified by the G-BA. In its notes on the ACT, the G-BA states that a single-comparator study is typically an inadequate

implementation of treatment of physician's choice and that for the latter, clinical trials are expected to offer a selection from the drugs azathioprine, eculizumab, mycophenate mofetil, and rituximab (multi-comparator study).

The company reports that no multi-comparator studies are available and that, therefore, adjusted indirect comparisons can be conducted only with some of the ACT options. For assessing the added benefit of inebilizumab, the company therefore presented an adjusted indirect comparison with satralizumab via the common comparator of placebo.

Irrespective of the SAkuraStar study failing to offer a selection from various treatment options, satralizumab is not among the ACT options specified by the G-BA. The adjusted indirect comparison presented by the company therefore does not allow any comparison of inebilizumab versus treatment of physician's choice.

## I 4 Results on added benefit

No suitable data are available for assessing the benefit of inebilizumab in adult patients with NMOSD who are AQP4-IgG seropositive. This results in no hint of an added benefit of inebilizumab in comparison with 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 inebilizumab in comparison with the ACT.

Table 5: Inebilizumab – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Adult patients with NMOSD who are AQP4-IgG seropositive | Treatment of physician's choice[b] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. For immunosuppressant long-term therapy, clinical trials are to offer the drugs azathioprine, eculizumab, mycophenolate mofetil, and rituximab.

ACT: appropriate comparator therapy; AQP4-IgG: anti-aquaporin-4 immunoglobulin G; G-BA: Federal Joint Committee; NMOSD: neuromyelitis optica spectrum disorders

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit. The company bases this conclusion on (a) numerical advantages of inebilizumab over satralizumab on the basis of the submitted adjusted indirect comparison and (b)the advantages that – in the opinion of the company – are relevant to the patients due to the action mechanism of inebilizumab and its lower application frequency.

The G-BA decides on the added benefit.

**References for English extract**

Please see full dossier assessment for full reference list.

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

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