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Obinutuzumab (follicular lymphoma, rituximab-refractory) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Obinutuzumab (follikuläres Lymphom, Rituximab-refraktär) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 August 2021). 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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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BSA	body surface area
BSC	best supportive care
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone
CVP	cyclophosphamide, vincristine, and prednisolone
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GELF	Groupe d´Etude des Lymphomes Folliculaires (Follicular Lymphoma Study Group)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
Y	yttrium

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug obinutuzumab. 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 12 May 2021.

Research question

The aim of this report is to assess the added benefit of obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance therapy in adult patients with follicular lymphoma who did not respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after treatment. This therapy was compared with the appropriate comparator therapy (ACT) of individualized therapy, selecting from chemotherapies, [^{90}yttrium(^{90}Y)]-labelled ibritumomab tiuxetan, and best supportive care (BSC).

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of obinutuzumab

Indication	ACT[a]
Adult patients with follicular lymphoma[b] who failed to respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after treatment[c]	Individualized therapy, selecting from chemotherapies[d], [^{90}Y]-labelled ibritumomab tiuxetan, and BSC[e], taking into account prior therapies, course of disease, and general condition

a. Presented is the ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. In the present therapeutic indication, the G-BA assumes patients to be indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and therefore assumes a watch & wait strategy not to be an option. Further, it assumes that, at the time of therapy, allogeneic or autologous stem cell transplantation or radiotherapy with curative intent was not an option.
d. As per G-BA, individualized chemotherapy is to involve alternative protocols from the prior, refractory therapy line.
e. The G-BA has defined BSC as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; Y: yttrium

In departure from the G-BA's specification on the ACT, the company specified individualized chemotherapy (e.g. bendamustine) or radioimmunotherapy with [^{90}Y]-labelled ibritumomab tiuxetan as the ACT. Further, in the company's stated view, patients for whom BSC is an option are not indicated for chemoimmunotherapy.

The present benefit assessment is performed in comparison with the ACT specified by the G-BA, individualized therapy selecting from the options listed in Table 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

Study pool and study design

The check for completeness of the study pool revealed no relevant studies comparing obinutuzumab versus individualized therapy as the ACT. The company, in contrast, identified the randomized controlled trial (RCT) GADOLIN and used it in its assessment. The GADOLIN study is unsuitable for the benefit assessment of obinutuzumab versus the ACT. The rationale is provided below.

GADOLIN study

The GADOLIN study is a 2-arm, randomized, actively controlled, open-label, multicentre, phase III study. It included pretreated adult patients with rituximab-refractory, indolent non-Hodgkin lymphoma. Refractoriness was defined as lack of treatment response or progression within 6 months after administration of the last dose of rituximab monotherapy or rituximab in combination with chemotherapy.

A total of 204 patients were randomized to the intervention arm (obinutuzumab + bendamustine) and 209 to the comparator arm (bendamustine). Randomization was stratified by indolent non-Hodgkin lymphoma subtype (follicular versus others), type of refractoriness (rituximab monotherapy versus rituximab in combination with chemotherapy), number of prior therapies (≤ 2 versus < 2), and geographic region. For deriving added benefit, the company used the GADOLIN subpopulation of patients with follicular lymphoma (164 patients in the obinutuzumab + bendamustine arm and 171 patients in the bendamustine arm).

Treatment in the GADOLIN intervention arm was in accordance with the obinutuzumab Summary of Product Characteristics (SPC); treatment in the comparator arm departed from the SPC with regard to treatment duration and cycle length.

The primary outcome of the study was progression-free survival (PFS). Secondary outcomes comprised overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Results

The GADOLIN study is unsuitable for assessing any added benefit of obinutuzumab in comparison with the G-BA'S ACT. All patients in the study's comparator arm received bendamustine. Module 4 B of the company's dossier neither provides a rationale as to why bendamustine represents individualized therapy for patients with follicular lymphoma who were included in the GADOLIN study, nor does it discuss why other, generally available therapy options were not preferable as individualized therapy under clinical aspects. However,

the GADOLIN comparator arm excluded all available therapy options other than bendamustine. Therefore, the study presented by the company does not allow comparing obinutuzumab with the ACT of individualized therapy.

In summary, the company did not submit any suitable data for assessing the added benefit of obinutuzumab versus the ACT in adult patients with follicular lymphoma who failed to respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after this treatment. Consequently, there is no hint of added benefit of obinutuzumab 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]

On the basis of the presented results, the probability and extent of added benefit of the drug obinutuzumab in comparison with the ACT have been assessed as follows:

Table 3 presents a summary of the probability and extent of added benefit of obinutuzumab.

Table 3: Obinutuzumab – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Adult patients with follicular lymphoma[b] who failed to respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after treatment[c]	Individualized therapy, selecting from chemotherapies[d], [^{90}Y]-labelled ibritumomab tiuxetan, and BSC[e], taking into account prior therapies, course of disease, and general condition	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. In the present therapeutic indication, the G-BA assumes patients to be indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and therefore assumes a watch & wait strategy not to be an option. Further, it assumes that at the time of therapy, allogeneic or autologous stem cell transplantation or radiotherapy with curative intent was not an option.
d. As per G-BA, individualized chemotherapy is to involve alternative protocols from the prior, refractory therapy line.
e. The G-BA has defined BSC as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; Y: yttrium

[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].

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2016, wherein the G-BA had found an unquantifiable added benefit of obinutuzumab. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization due to the special status of orphan drugs, regardless of the underlying data.

2.2 Research question

The aim of this report is to assess the added benefit of obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance therapy in adult patients with follicular lymphoma who did not respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after treatment. This therapy was compared against the ACT of individualized therapy, selecting from chemotherapies, [^{90}Y]-labelled ibritumomab tiuxetan, and BSC.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of obinutuzumab

Indication	**ACT**[a]
Adult patients with follicular lymphoma[b] who failed to respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after treatment[c]	Individualized therapy, selecting from chemotherapies[d], [^{90}Y]-labelled ibritumomab tiuxetan, and BSC[e], taking into account prior therapies, course of disease, and general condition
a. Presented is the ACT specified by the G-BA. b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma. c. In the present therapeutic indication, the G-BA assumes patients to be indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and therefore assumes a watch & wait strategy not to be an option. Further, it assumes that at the time of therapy, allogeneic or autologous stem cell transplantation or radiotherapy with curative intent was not an option. d. As per G-BA, individualized chemotherapy is to involve alternative protocols from the prior, refractory therapy line. e. The G-BA has defined BSC as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; Y: yttrium	

In departure from the G-BA's specification on the ACT, the company specified individualized chemotherapy (e.g. bendamustine) or radioimmunotherapy with [^{90}Y]-labelled ibritumomab tiuxetan as the ACT. Further, in the company's stated view, patients for whom BSC is an option are not indicated for chemoimmunotherapy. The company did not provide any rationale for this opinion.

The present benefit assessment, contrary to that submitted by the company, relies on a comparison with individualized therapy as the ACT stipulated by the G-BA and according to the options listed in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on obinutuzumab (as of 16 February 2021)
- Bibliographic literature search on obinutuzumab (most recent search on 16 February 2021)
- Search in trial registries / study results databases on obinutuzumab (most recent search on 18 March 2021)
- Search on the G-BA website on obinutuzumab (most recent search on 11 March 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on obinutuzumab (most recent search on 31 May 2021); see Appendix B of the full dossier assessment for search strategies.

The check for completeness of the study pool revealed no relevant studies comparing obinutuzumab versus individualized therapy as the ACT.

The company, in contrast, identified the RCT GADOLIN [3-11] and used it in its assessment. The GADOLIN study is unsuitable for the benefit assessment of obinutuzumab versus the ACT. The rationale is provided below.

Evidence provided by the company

The GADOLIN study presented by the company compared treatment with obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance therapy versus treatment with bendamustine only. This study is unsuitable for the present benefit assessment because the information submitted by the company fails to demonstrate that, for the included patients, the employed comparator therapy of bendamustine represented individualized therapy, selecting from chemotherapies, [^{90}Y]-labelled ibritumomab tiuxetan, and BSC.

Design of the GADOLIN study

The GADOLIN study is a 2-arm, randomized, actively controlled, open-label, multicentre, phase III study. It included pretreated adult patients with rituximab-refractory, indolent non-Hodgkin lymphoma. Refractoriness was defined as lack of treatment response or progression within 6 months after administration of the last dose of rituximab monotherapy or rituximab in combination with chemotherapy.

A total of 204 patients were randomized to the intervention arm (obinutuzumab + bendamustine) and 209 to the comparator arm (bendamustine). Randomization was stratified by indolent non-Hodgkin lymphoma subtype (follicular versus others), type of refractoriness (rituximab monotherapy versus rituximab in combination with chemotherapy), number of prior therapies (≤ 2 versus < 2), and geographic region. For deriving added benefit, the company used the GADOLIN subpopulation of patients with follicular lymphoma (164 patients in the obinutuzumab + bendamustine arm and 171 patients in the bendamustine arm).

Treatment in the GADOLIN intervention arm was in compliance with the obinutuzumab SPC [12]. First, patients received induction therapy, in which obinutuzumab in combination with bendamustine was administered for a maximum of 6 (28-day) cycles, unless they exhibited progression or unacceptable toxicity. The drugs were each administered intravenously: obinutuzumab at a dose of 1000 mg and bendamustine at 90 mg/m^2 body surface area (BSA). Patients who fully or partially responded to induction therapy or whose disease had not further progressed received the subsequent maintenance therapy of obinutuzumab monotherapy at a dose of 1000 mg every 2 months for a maximum of 2 years or until progression.

In the study's comparator arm, bendamustine monotherapy was administered intravenously at a dose of 120 mg/m^2 BSA for a maximum of 6 (28-day) cycles or until progression or unacceptable toxicity. This means that bendamustine administration departed from the SPC, which specifies a minimum treatment duration of 6 cycles rather than a maximum of 6 cycles. In the pivotal study of bendamustine, treatment duration depended on patient response. In addition, the SPC specifies a shorter cycle length (21 days) [13].

The primary outcome of the study was PFS. Secondary outcomes comprised overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

Further information on the GADOLIN study and on the characterization of the subpopulation analysed by the company is found in Appendix A of the full dossier assessment.

Failure to implement individualized therapy in the GADOLIN study

The GADOLIN study is unsuitable for assessing any added benefit of obinutuzumab in comparison with the G-BA's ACT. All patients in the study's comparator arm received bendamustine. However, Module 4 B of the company's dossier neglects to demonstrate that this treatment option represents the ACT of individualized therapy as specified by the G-BA for the patients included in the study:

For patients with follicular lymphoma who failed to respond to treatment with rituximab or a rituximab-containing regimen or who experienced progression during or up to 6 months after treatment, the ACT is individualized therapy, selecting from chemotherapies, [^{90}Y]-labelled ibritumomab tiuxetan, and BSC. This therapy was to be chosen in view of prior therapies, the course of disease, and the patient's general condition.

For relapsed patients, the S3 Guideline on the Diagnostics, Therapy, and Follow-up of patients with follicular lymphoma states that therapy should be selected based on the following factors: type of prior therapy and maintenance therapy, quality of response, time to relapse and timing of relapse, clinical symptoms at relapse, patient age and comorbidities, patient wishes, and specific side effects of the various treatment options [14]. In Module 4 B, the company fails to disclose the extent to which these aspects were taken into account when including patients in the GADOLIN study, whose comparator arm provided only bendamustine as a treatment option.

According to the S3 Guideline, qualifying prior therapies administered to relapsed follicular lymphoma patients as part of chemoimmunotherapy include, besides bendamustine, also the following chemotherapies: cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and cyclophosphamide, vincristine, and prednisolone (CVP). Unless alternative approaches are available, patients experiencing relapse within less than 2 years after chemoimmunotherapy should receive at least one alternative chemotherapy regimen in the relapsed situation [14]. Module 4 B of the dossier fails to show to what extent the study complied with this recommendation.

In the GADOLIN comparator arm, 22% of patients with follicular lymphoma were refractory to rituximab monotherapy (see Table 11 in Appendix A of the full dossier assessment). As approved, rituximab monotherapy is to be offered to patients refractory to chemotherapy or who suffered a second or subsequent relapse after chemotherapy [15]. The information provided by the company does not show to what extent chemotherapy was nevertheless indicated for GADOLIN participants even if they were refractory to rituximab monotherapy. Chemotherapy regimens other than bendamustine, such as CHOP or CVP, might technically be an option for relapse therapy.

One alternative treatment option for patients with relapsed or refractory follicular lymphoma after rituximab treatment is radioimmunotherapy with [^{90}Y]-labelled ibritumomab tiuxetan. As per S3 Guideline, an important prerequisite for this therapy is that patients exhibit < 20% bone marrow infiltration [14]. Module 4 B of the company's dossier shows that, in the comparator arm, 64% of patients with follicular lymphoma had no bone marrow involvement at the time of study inclusion (see Table 11 in Appendix A of the full dossier assessment). The company did not submit any information on the reason why therapy with [^{90}Y]-labelled ibritumomab tiuxetan was not an individualized therapy option for these patients.

In summary, the company neither provided a rationale as to why bendamustine represented individualized therapy for GADOLIN participants with follicular lymphoma, nor did it discuss the extent to which other, generally available therapy options were not preferable individualized therapy under clinical aspects. However, the GADOLIN comparator arm excluded all available therapy options other than bendamustine. Therefore, the study presented by the company does not allow comparing obinutuzumab with the ACT of individualized therapy.

Irrespective of the GADOLIN study being unsuitable for the benefit assessment for the reasons discussed above, the following further points of criticism arise regarding the data presented by the company:

- In the GADOLIN comparator arm, bendamustine was administered for 28 days, a cycle length departing from that stated in the SPC (21 days). Additionally, the study specified a maximum of 6 cycles of bendamustine treatment, which also departs from the specifications of the SPC (a minimum of 6 cycles [depending on response]) [13]. The company's Module 3 B discusses these deviations and even mentions that the G-BA

recommended substantiating in the dossier both the longer cycles and the greater number of cycles. However, Module 4 B of the company's dossier does not provide any evidence justifying the deviations from the specifications of the SPC.

In the G-BA's assessment procedure conducted as part of the marketing authorization in 2016, departures from the SPC in the administration of bendamustine were a topic of discussion as well [16]. Regarding the GADOLIN study's restriction to a maximum of 6 treatment cycles in consideration of the various prior therapies, the justification paper of the G-BA's decision noted that some of the patients would conceivably have benefited from longer bendamustine treatment [17]. The company's dossier did not address this topic.

- The majority of participants included and treated in the GADOLIN study were adult patients with rituximab-refractory, follicular lymphoma. According to national and international guidelines, a mandatory prerequisite for starting therapy in both first-line therapy and in relapsed follicular lymphoma is need for therapy [14,18,19]. This is determined using, e.g., the Groupe d´Etude des Lymphomes Folliculaires (GELF) criteria, which include the presence of B symptoms and very large masses or conglomerates (bulky disease) as well as haematopoietic dysfunction, lymphoma-related compression syndrome, or pleural effusion / ascites [14]. Similarly, the G-BA believes that systemic antineoplastic therapy is indicated in this scenario, especially if the course is symptomatic.

  The presence of a need for therapy – e.g. based on the GELF criteria – was not an inclusion criterion of the GADOLIN study. For the subpopulation of patients with follicular lymphoma, data were available only on the presence of B symptoms and bulky disease at baseline (see Table 11 in Appendix A of the full dossier assessment); these data showed that 15% of patients had B symptoms and 34% bulky disease. The company's dossier provided neither information on the other criteria for need for therapy (e.g., as per GELF) nor aggregated data on need for therapy for the included patients with follicular lymphoma.

- The results of the GADOLIN study as presented in the company's dossier are incomplete. For the final data cut-off of 30 November 2018, the company's Module 4 B provides analyses only on the outcome categories of mortality and side effects. For patient-reported outcomes of the morbidity and health-related quality of life categories, the company presented analyses from 1 of the earlier data cut-offs (1 September 2014) only. For the G-BA's assessment procedure conducted as part of the approval procedure in 2016, the company had already submitted analyses of patient-reported outcomes from a more current data cut-off (1 May 2015), which was carried out upon request by the Food and Drug Administration (FDA) [20,21]. This data situation is similar to that of dossier assessment A21-66 (benefit assessment of obinutuzumab in follicular lymphoma, first-line therapy [22]). Dossier assessment A21-66 includes an in-depth discussion not only on

this problem but also on further deficiencies in the compilation of the results presented by the company, which are comparable between the two dossiers as well.

2.4 Results on added benefit

The company did not submit any suitable data for assessing the added benefit of obinutuzumab versus the ACT in adult patients with follicular lymphoma who did not respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after this treatment. Consequently, there is no hint of added benefit of obinutuzumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results of the benefit assessment of obinutuzumab in comparison with the ACT.

Table 5: Obinutuzumab – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with follicular lymphoma[b] who failed to respond to treatment with rituximab or a rituximab-containing regimen or experienced progression during or up to 6 months after treatment[c]	Individualized therapy, selecting from chemotherapies[d], [^{90}Y]-labelled ibritumomab tiuxetan, and BSC[e], taking into account prior therapies, course of disease, and general condition	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The G-BA understands the present therapeutic indication to exclude follicular lymphoma grade 3b since this subentity is typically classified as aggressive non-Hodgkin lymphoma.
c. In the present therapeutic indication, the G-BA assumes patients to be indicated for systemic antineoplastic therapy due to advanced stage of disease, particularly with regard to a symptomatic course (e.g. as per GELF criteria), and therefore assumes a watch & wait strategy not to be an option. Further, it assumes that at the time of therapy, allogeneic or autologous stem cell transplantation or radiotherapy with curative intent was not an option.
d. As per G-BA, individualized chemotherapy is to involve alternative protocols from the prior, refractory therapy line.
e. The G-BA has defined BSC as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; GELF: Groupe d´Etude des Lymphomes Folliculaires; Y: yttrium

The above-described assessment departs from that by the company, which derived proof of minor added benefit on the basis of the GADOLIN study's subpopulation of patients with follicular lymphoma.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2016, wherein the G-BA had found an

unquantifiable added benefit of obinutuzumab. However, in that assessment, the added benefit was viewed as being backed by the marketing authorization due to the special status of orphan drugs, regardless of the underlying data.

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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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