IQWiG Reports – Commission No. A20-82

Ibalizumab (HIV infection) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ibalizumab (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 22 January 2021). Please note: This translation 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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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

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

IQWiG employees involved in the dossier assessment

- Selver Altin
- Gertrud Egger
- Christopher Kunigkeit
- Ana Liberman
- Katrin Nink
- Dominik Schierbaum
- Dorothea Sow
- Sibylle Sturtz

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ART	antiretroviral therapy
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
OBT	optimized background treatment
PI	protease inhibitor
RCT	randomized controlled trial
RNA	ribonucleic acid
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 ibalizumab. 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 1 September 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of ibalizumab in combination with other antiretroviral drugs in comparison with the appropriate comparator therapy (ACT) in adult patients with multidrug-resistant human immunodeficiency virus type 1 (HIV-1) infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of ibalizumab

Therapeutic indication	**ACT[a]**
Adults with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1	

The company followed the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 48 weeks were used for the derivation of the added benefit.

Results

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of ibalizumab versus the ACT.

As there were no data on ibalizumab from comparative studies, the company searched for further investigations that would allow a comparison of individual arms of different studies. The company's search produced the non-comparative studies TMB-301 and TMB-311 for the intervention, and the RCT TNX-355.03 for the comparator therapy. The comparison presented by the company is unsuitable for the assessment of the added benefit of ibalizumab. This is justified below.

Study pool of the company

Studies with the intervention

Study TMB-301

The TMB-301 study is a 25-week, single-arm study of ibalizumab in combination with individually optimized background treatment (OBT). This study included patients with multidrug-resistant HIV-1 infection who had received antiretroviral therapy (ART) for at least 6 months and a stable active ART for at least 8 weeks before screening. Multidrug-resistant HIV-1 infection was defined as a viral load > 1000 copies/mL and documented resistance to at least one drug from each of 3 ART classes (3-class resistance). A total of 40 patients were included in the study. Patients who completed study TMB-301 could continue their treatment with ibalizumab + OBT in the extension study TMB-311 (cohort 1).

The dosage of ibalizumab used in the study is in compliance with the Summary of Product Characteristics (SPC). The OBT was a regimen selected by the investigator based on treatment history and the results of viral resistance testing.

The primary outcome of the TMB-301 study was the ≥ 0.5 log10 reduction in viral load from day 7 to day 14.

Study TMB-311

The TMB-311 study is a 2-arm parallel-group study of ibalizumab + OBT. Both study cohorts included patients with multidrug-resistant HIV-1 infection who had been pretreated with antiretroviral drugs. The definition of multidrug-resistant disease was the same as in the TMB-301 study. Cohort 1 included a total of 41 patients who had already received ibalizumab, e.g. in other studies. In this cohort, treatment was continued with the pre-existing dosage of ibalizumab and individual OBT. Cohort 2 included 38 patients who had not been pretreated with ibalizumab. These patients received ibalizumab together with the individual OBT in compliance with the specifications of the SPC.

The primary outcomes of the TMB-311 study were the ≥ 0.5 log10 reduction in viral load on day 7 (only cohort 2) and adverse events.

Study with the comparator therapy

Study TNX-355.03

The TNX-355.03 study is a double-blind, 3-arm RCT comparing 2 dosages of ibalizumab + OBT with placebo + OBT. It included patients who had been treated with highly active ART for at least 6 months cumulatively. Documented resistance to certain antiretroviral drug classes was not necessary for inclusion in the TNX-355.03 study. A total of 82 patients were included and randomly allocated in a 1:1:1 ratio to the following study arms after selection of the individual OBTs:

- arm A: alternating ibalizumab 15 mg/kg and placebo weekly for the first 9 doses; then ibalizumab 15 mg/kg every 2 weeks + OBT (N = 28)
- arm B: ibalizumab 10 mg/kg weekly for the first 9 doses; then ibalizumab 10 mg/kg every 2 weeks + OBT (N = 27)
- placebo arm: placebo weekly for the first 9 doses; then placebo every 2 weeks + OBT (N = 27)

The therapy regimens used in the ibalizumab arms (arms A and B) do not comply with the specifications in the SPC. Therefore, the company only used the placebo arm on the side of the comparator therapy for the comparison of individual arms. The blinded treatment duration was a minimum of 16 to a maximum of 48 weeks or until treatment failure. In case of documented treatment failure, patients from all study arms could switch to unblinded treatment with a new OBT and ibalizumab (15 mg/kg; every 2 weeks). After 48 weeks of treatment with the study medication, the patients and the investigator were unblinded. Patients from the placebo arm who had received placebo until the end of the double-blind period could switch to treatment with ibalizumab + OBT in the unblinded phase. Overall, all patients had the option to continue treatment with ibalizumab until week 216.

The primary outcome of study TNX-355.03 was the mean change in HIV-1 ribonucleic acid (RNA) concentration at week 24.

Data included by the company for the comparison presented

For the comparison of individual arms of different studies, the company added the study results from study TMB-301 and study TMB-311, cohorts 1 and 2, on the intervention side; from cohort 1, however, only data from patients who had been previously treated in study TMB-301 were taken into account. On the comparator side, the company included study results from the placebo arm of the RCT TNX-355.03.

In order to reflect the present therapeutic indication, the company selected a subpopulation with an overall susceptibility score of ≤ 2 from the individual arms of the studies TMB-301, TMB-311 and TNX-355.03. Thus, it included patients from the individual study arms who showed viral sensitivity to a maximum of 2 antiretroviral drugs (besides ibalizumab) of any drug class.

Assessment of the evidence presented by the company

ACT not implemented in the TNX-355.03 study

The ACT in the sense of an individual ART chosen from the approved drugs was not implemented in the comparator arm of the TNX-355.03 study. This is due to the fact that the TNX-355.03 study was conducted about 15 years ago, between 2004 and 2006, and that at the time of the study only a small proportion of the currently available antiretroviral drugs or drug classes were approved. Some of the treatment options that are relevant today in the therapeutic indication have only been approved after the study. For example, raltegravir, the first drug from the integrase inhibitor class, was approved in 2007. A large number of new drugs from already existing drug classes have also become available after 2006. In addition, various combination preparations have become available since 2011 to improve treatment adherence. This study is not suitable for showing the course of multidrug-resistant HIV infection under effective or partially effective individual ART that exhausts currently available treatment options.

Irrespective of this, the results of the studies presented are also not interpretable for other reasons. In the intervention studies TMB-301 and TMB-311, relevant proportions of patients received unapproved drugs as part of the OBT. On the side of the comparator therapy, a total of 70% of the patients from the subpopulation considered by the company switched their treatment from placebo + OBT to a treatment with ibalizumab + OBT that was not in compliance with the approval between weeks 16 and 48.

No suitable data were available for the assessment of ibalizumab for the treatment of adult patients with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen. This resulted in no hint of an added benefit of ibalizumab in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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].

Table 3: Ibalizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of ibalizumab in combination with other antiretroviral drugs in comparison with the ACT in adult patients with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of ibalizumab

Therapeutic indication	ACT[a]
Adults with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1	

The company followed the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 48 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 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 lists on ibalizumab (status: 1 July 2020)
- bibliographical literature search on ibalizumab (last search on 15 June 2020)
- search in trial registries/trial results databases for studies on ibalizumab (last search on 9 July 2020)
- search on the G-BA website for ibalizumab (last search on 9 July 2020)
- bibliographical literature search on the ACT (last search on 15 June 2020)
- search in trial registries/trial results databases for studies on the ACT (last search on 9 July 2020)
- search on the G-BA website for the ACT (last search on 9 July 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ibalizumab (last search on 4 September 2020)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of ibalizumab versus the ACT.

As there were no data on ibalizumab from comparative studies, the company searched for further investigations that would allow a comparison of individual arms of different studies. The company's search produced the non-comparative studies TMB-301 and TMB-311 for the intervention, and the RCT TNX-355.03 for the comparator therapy. The study pool of the company is shown in Table 5.

However, the search strategies used for the comparator therapy presented in Module 4 A are not suitable for ensuring the completeness of the study pool, as the choice of search terms severely limited the search in trial registries, for example. Thus, due to the limited search strategy, the TNX-355.03 study included by the company was not identified in the search for the comparator therapy in trial registries. As the comparison of individual arms from different studies conducted by the company on the basis of the identified studies is not suitable for the derivation of the added benefit of ibalizumab in comparison with the ACT, the completeness of the study pool for further investigations was not checked.

In the following, the approach of the company is described and the lack of suitability of the presented comparison is justified.

Study pool of the company

The studies included by the company are listed in Table 5.

Table 5: Study pool of the company – RCT/non-RCT, further investigations: ibalizumab + OBT vs. placebo + OBT

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Studies with intervention						
TMB-301	Yes	Yes	No	No[c]	Yes [3,4]	Yes [5]
TMB-311	Yes	Yes	No	No[c]	Yes [6]	No
Studies with comparator therapy						
TNX-355.03	Yes	Yes	No	No[c]	Yes [7]	No

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; OBT: optimized background treatment; RCT: randomized controlled trial; vs.: versus

The characteristics of the studies included by the company and the interventions used in these studies are shown in Table 10 and Table 11 of the full dossier assessment.

Studies with the intervention

Study TMB-301

The TMB-301 study is a 25-week, single-arm study of ibalizumab in combination with individual OBT, which was conducted between 2015 and 2016.

This study included patients with multidrug-resistant HIV-1 infection who had received ART for at least 6 months and a stable active ART for at least 8 weeks before screening. Multidrug-resistant HIV-1 infection was defined as a viral load > 1000 copies/mL and documented resistance to at least one drug from each of 3 ART classes (3-class resistance). Module 4 A did not contain any information on which drug classes these were. In addition, there had to be full viral sensitivity to at least one antiretroviral drug other than ibalizumab at screening. A total of 40 patients were included in the study.

The TMB-301 study consisted of 3 periods: control period, monotherapy period and maintenance period. In the control period (days 0 to 6), patients on their current failing therapy were monitored or received no therapy if the failing therapy was discontinued within 8 weeks before screening. In the monotherapy period (days 7 to 13), patients continued their failing therapy, if any, and received one single loading dose of ibalizumab (2000 mg) on day 7. In the maintenance period (day 14 to week 25), the individual OBT was administered from day 14, and then the maintenance dose of ibalizumab (800 mg every 2 weeks) from day 21. Patients

who completed study TMB-301 could continue their treatment with ibalizumab + OBT in the extension study TMB-311 (cohort 1). A total of 31 patients completed the TMB-301 study, and 27 patients continued treatment with ibalizumab in the TMB-311 study.

The dosage of ibalizumab used in the study is in compliance with the SPC [8]. The OBT was a regimen selected by the investigator based on treatment history and the results of viral resistance testing. Overall, the treatment used in the TMB-301 study in the first 14 days does not meet the recommendations of the guidelines. Neither continuation of failing therapy [9] or treatment interruption in case of treatment failure [9,10] nor the combination of a failing therapy with an active drug (ibalizumab) [11,12] is adequate. Instead, such an approach carries the risk of further accumulation of resistance mutations [9]. Whether and how this approach affected the study results cannot be estimated. However, it is of no further consequence insofar as the comparison presented was not relevant for the assessment for other reasons (see below).

The primary outcome of the TMB-301 study was the ≥ 0.5 log10 reduction in viral load from day 7 to day 14.

Study TMB-311

The TMB-311 study is a 2-arm parallel-group study of ibalizumab + OBT, which was conducted between 2016 and 2018.

Both study cohorts included patients with multidrug-resistant HIV-1 infection who had been pretreated with antiretroviral drugs. The definition of multidrug-resistant disease was the same as in the TMB-301 study. Cohort 1 included a total of 41 patients who had already received ibalizumab, e.g. in other studies: 27 from the TMB-301 study, 12 from the TMB-202 study (phase 2b study with ibalizumab dosing that did not comply with the approval) and 2 patients with off-label pretreatment. In this cohort, treatment was continued with the pre-existing dosage of ibalizumab and individual OBT. Cohort 2 included 38 patients who had not been pretreated with ibalizumab. These patients received ibalizumab together with the individual OBT in compliance with the specifications of the SPC [8].

The TMB-311 study, which had been planned for 144 weeks, was discontinued after 110 weeks after ibalizumab had been approved by the Food and Drug Administration (FDA).

The primary outcomes of the TMB-311 study were the ≥ 0.5 log10 reduction in viral load on day 7 (only cohort 2) and adverse events.

Study with the comparator therapy

Study TNX-355.03

The TNX-355.03 study is a double-blind, 3-arm RCT comparing 2 dosages of ibalizumab + OBT with placebo + OBT, which was conducted between 2004 and 2006. It included patients who had been treated with highly active ART for at least 6 months cumulatively. Antiretroviral pretreatment had to include drugs from the classes of the nucleoside/nucleotide reverse

transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Antiretroviral pretreatment with fusion/entry inhibitors was not allowed prior to study inclusion. Furthermore, patients had to have a stable HIV-1 RNA concentration ≥ 10 000 copies/mL under stable, highly active ART (at least 4 weeks before screening) 8 weeks before randomization. Documented resistance to certain antiretroviral drug classes was not necessary for inclusion in the TNX-355.03 study.

The OBT was a regimen selected by the investigator based on treatment history and the results of viral resistance testing. For study inclusion, patients had to show full viral sensitivity to at least one antiretroviral drug other than ibalizumab at screening.

A total of 82 patients were included and randomly allocated in a 1:1:1 ratio to the following study arms after selection of the individual OBTs:

- arm A: alternating ibalizumab 15 mg/kg and placebo weekly for the first 9 doses; then ibalizumab 15 mg/kg every 2 weeks + OBT (N = 28)
- arm B: ibalizumab 10 mg/kg weekly for the first 9 doses; then ibalizumab 10 mg/kg every 2 weeks + OBT (N = 27)
- placebo arm: placebo weekly for the first 9 doses; then placebo every 2 weeks + OBT (N = 27)

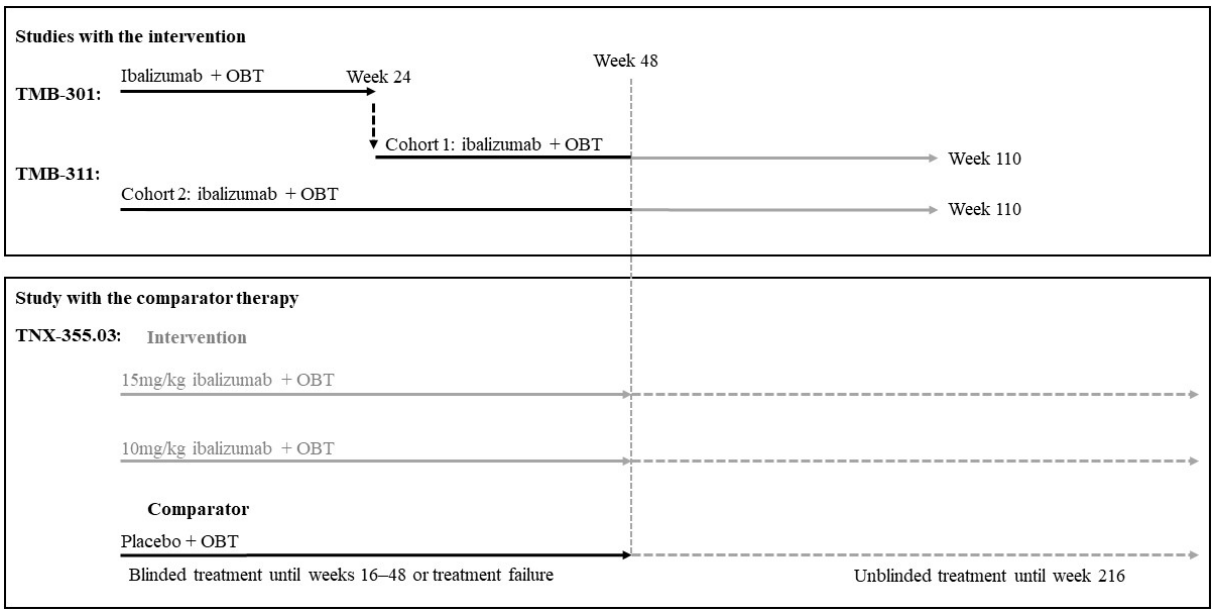
The therapy regimens used in the ibalizumab arms (arms A and B) do not comply with the specifications in the SPC [8]. Therefore, the company only used the placebo arm on the side of the comparator therapy for the comparison of individual arms.

The blinded treatment duration was a minimum of 16 to a maximum of 48 weeks or until treatment failure. Treatment failure was defined as a lack of viral load reduction of at least 0.5 log10 from baseline at 2 consecutive protocol-defined measurements starting at week 12. In case of documented treatment failure, patients from all study arms could switch to unblinded treatment with a new OBT and ibalizumab (15 mg/kg; every 2 weeks). After a documented second treatment failure, treatment in the TNX-355.03 study was discontinued. After 48 weeks of treatment with the study medication, the patients and the investigator were unblinded. Patients from the intervention arms (arms A and B) who achieved a clinical benefit from ibalizumab at week 48 (defined as achieving or maintaining a ≥ 0.5 log10 reduction in HIV-1 RNA viral load from baseline) were given the option to continue treatment with ibalizumab + OBT. Patients from the placebo arm who had received placebo until completion of the double-blind period could also switch to treatment with ibalizumab + OBT in the unblinded phase. Overall, all patients had the option to continue treatment with ibalizumab until week 216.

The primary outcome of study TNX-355.03 was the mean change in HIV-1 RNA concentration at week 24.

Data included by the company for the comparison presented

For the comparison of individual arms of different studies, the company added the study results from study TMB-301 and study TMB-311, cohorts 1 and 2, on the intervention side; from cohort 1, however, only data from patients who had been previously treated in study TMB-301 were taken into account. On the comparator side, the company included study results from the placebo arm of the RCT TNX-355.03 (included study arms are shown in black in Figure 1).



OBT: optimized background treatment

Figure 1: Data included by the company for the comparison of individual arms from different studies

In order to reflect the present therapeutic indication, the company selected a subpopulation with an overall susceptibility score of ≤ 2 from the individual arms of the studies TMB-301, TMB-311 and TNX-355.03. Thus, it included patients from the individual study arms who showed viral sensitivity to a maximum of 2 antiretroviral drugs (besides ibalizumab) of any drug class.

On the intervention side, this subpopulation included a total of 67 patients, which were composed as follows:

- 35 patients from the TMB-301 study, of which
  - 25 patients were observed for 24 weeks in study TMB-301 and continued to be observed in study TMB-311 (cohort 1) until the end of study or study discontinuation
  - 10 patients were observed for a maximum of 24 weeks in study TMB-301
- 32 patients from the TMB-311 study, cohort 2

On the side of the comparator therapy, this subpopulation included a total of 20 patients.

In the comparison presented, the company provided analyses at week 48 for the efficacy outcome "virologic response". For patients who were observed for a maximum of 24 weeks in the TMB-301 study or for whom no values until week 48 were available for other reasons, the company imputed missing values in the analysis, rating these patients as non-responders. In the analysis on side effect outcomes, the company included individual patient data at the longest available points in time.

Assessment of the subpopulation selected by the company

The intervention studies TMB-301 and TMB-311 included patients with documented resistance to at least one drug from each of 3 ART classes. Module 4 A did not contain any information on which drug classes these were. However, guidelines define multidrug-resistant HIV infection as the presence of resistance to at least one drug from the following drug classes: NRTI, NNRTI and PI [12,13]. Documented resistance to certain antiretroviral drug classes was not necessary for inclusion in the comparator study TNX-355.03. It cannot be verified on the basis of the available data how many patients included in the studies TMB-301, TMB-311 and TNX-355.03 did not have multidrug-resistant HIV-1 infection according to the definition of the guidelines.

Furthermore, the company selected patients with an overall susceptibility score ≤ 2 on both sides of the comparison, also without restriction to certain drug classes. It justified the choice of its selection criterion with national and international guidelines that recommend the combination of at least 2, preferably 3 active antiretroviral drugs for ART. The company concluded from this that the construction of an active ART without ibalizumab was not possible for the selected patients who showed viral susceptibility to a maximum of 2 antiretroviral drugs. There is no information on whether a combination of 2 antiretroviral drugs with the goal of complete viral suppression would have been possible for the included patients. It is therefore not possible to assess whether it was actually not possible to construct an active antiviral regimen without ibalizumab for these patients. In addition, guidelines generally recommend optimizing therapy and treatment with ART for patients for whom no fully suppressive antiretroviral regimen can be constructed [9]. This should be continued even in case of incomplete viral suppression to slow disease progression [12]. This approach corresponds to the ACT.

In summary, it cannot be assessed on the basis of the available data whether all patients included by the company represent the present therapeutic indication in that they have a multidrug-resistant HIV infection and that it is not possible to construct a fully suppressive antiretroviral regimen for these patients.

Assessment of the evidence presented by the company

ACT not implemented in the TNX-355.03 study

The ACT in the sense of an individual ART chosen from the approved drugs was not implemented in the comparator arm of the TNX-355.03 study. This is due to the fact that the

TNX-355.03 study was conducted about 15 years ago, between 2004 and 2006, and that at the time of the study only a small proportion of the currently available antiretroviral drugs or drug classes were approved. Some of the treatment options that are relevant today in the therapeutic indication [9,10,12] have only been approved after the study. For example, raltegravir, the first drug from the integrase inhibitor class, was approved in 2007. A large number of new drugs from already existing drug classes have also become available after 2006. In addition, various combination preparations have become available since 2011 to improve treatment adherence [14,15]. This study is not suitable for showing the course of multidrug-resistant HIV infection under effective or partially effective individual ART that exhausts currently available treatment options.

Treatment switch from placebo to an ibalizumab dosage that is not in compliance with the approval on the side of the comparator therapy

In the TNX-355.03 study, a treatment switch from the placebo + OBT arm to the ibalizumab + OBT arm (arm A), in which an ibalizumab dosage that was not in compliance with the approval was used, was permitted in the event of documented virologic failure. Overall, 70% of the patients in the subpopulation considered by the company switched their study treatment between weeks 16 and 48. Information on the exact time of the treatment switch is not available. Due to the high proportion of patients with treatment switching and the probably early time of the switch, the results for the comparator therapy used in the TNX-355.03 study cannot be interpreted meaningfully for this reason either.

Unapproved drugs as part of the optimized background treatment on the intervention side

In the TMB-301 intervention study, the unapproved drug fostemsavir was allowed as a component of the individual OBT. In the TMB-311 study, patients were also allowed to receive unapproved drugs such as fostemsavir, cabotegravir and PRO140 as part of the OBT. Based on the information provided in Module 4 A, it is assumed that a relevant proportion of patients in the subpopulation received an unapproved drug as part of their OBT. The company stated in Module 4 A that 51.4% of the patients in the TMB-301 study, as well as 56% of the patients in cohort 1 and 25% in cohort 2 of the TMB-311 study had required an unspecified investigational preparation as part of their OBT. Precise information on the composition of the respective OBT in the studies is not available. Overall, it is unclear to what extent the present study results can be attributed to the intervention or to the administration of other unapproved drugs.

Results on virologic response in the comparison of individual arms from different studies

Conclusions on the added benefit based on a comparison of individual arms from different studies are only possible in the presence of very large effects [1]. The company considered this to be fulfilled for the outcome “virologic response”. However, since the comparator therapy used by the company does not correspond to the ACT, the size of the effects observed in the study cannot be interpreted. Regardless of this, virologic response is not a directly patient-relevant outcome, but a surrogate outcome for the patient-relevant outcome “AIDS-defining events”. This outcome was directly recorded in the included studies.

Summary

In summary, the comparison of individual arms from different studies presented by the company is unsuitable for the assessment of the added benefit of ibalizumab in comparison with the ACT. Overall, no suitable data are therefore available for the present assessment.

2.4 Results on added benefit

No suitable data were available for the assessment of ibalizumab for the treatment of adult patients with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen. This resulted in no hint of an added benefit of ibalizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of ibalizumab in comparison with the ACT is summarized in Table 6.

Table 6: Ibalizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive antiviral regimen	Individual antiretroviral therapy chosen from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1		

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

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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