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Fostemsavir (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 *Fostemsavir (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ART	antiretroviral therapy
CCR5	CC motif chemokine receptor 5
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
INI	integrase inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
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 fostemsavir. 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 26 March 2021.

Research question

The aim of the present report is the assessment of the added benefit of fostemsavir in combination with other antiretrovirals 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.

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

Table 2: Research question of the benefit assessment of fostemsavir

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 ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus 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. This concurs with the company's inclusion criteria.

Results

No relevant RCT on the direct comparison of fostemsavir against the ACT was identified from the check.

In its assessment, the company included the BRIGHTE study for the direct comparison of fostemsavir with the ACT, however. According to the information provided by the company in

Module 4 A, it conducted supplementary separate matching-adjusted indirect comparisons (MAICs) to support the results of the open-label phase of the BRIGHTE study.

Both the BRIGHTE study presented by the company and the MAIC analyses are not suitable for drawing conclusions on the added benefit of fostemsavir in comparison with the ACT specified by the G-BA. This is explained below.

Study pool of the company

Direct comparison

Study BRIGHTE

The BRIGHTE study is an ongoing, partially blinded, multicentre phase 3 study with 2 cohorts (one randomized cohort and one non-randomized cohort). The study included patients aged 18 years and older with multidrug resistant HIV-1 infection who had been pretreated with antiretroviral drugs. Multidrug resistant HIV-1 infection was defined as HIV-1 ribonucleic acid (RNA) viral load ≥ 400 copies/mL and a documented resistance, intolerability and/or contraindications to antiretrovirals in ≥ 3 drug classes.

Patients who had no fully active antiretroviral drugs that could be combined in a treatment regimen were assigned to the non-randomized cohort. These patients received open-label fostemsavir at a dose of 600 mg twice daily from day 1 in addition to optimized background treatment (OBT).

The randomized cohort included patients for whom 1 to 2 fully active antiretroviral drugs from ≤ 2 drug classes that can be combined in a treatment regimen are available. A total of 272 patients were randomly assigned to double-blind treatment with fostemsavir or placebo in a 3:1 ratio. From day 1 to day 8, patients received either fostemsavir 600 mg (intervention group: n = 203) or placebo (comparator group: n = 69) twice daily. In addition, the patients continued their currently failing antiretroviral therapy (ART). Starting on day 9, all 272 patients entered an unblinded treatment phase with fostemsavir (600 mg twice daily), during which they received concomitant OBT.

The dosage of fostemsavir used in the study is in compliance with the Summary of Product Characteristics (SPC). The OBT was composed according to the investigator's choice.

The treatment duration in the BRIGHTE study was 96 weeks. Treatment beyond 96 weeks was possible if there was still a clinical benefit for the patient.

The primary outcome of the study was the change in mean log10 HIV-1 RNA viral load from day 1 to day 8 in the randomized cohort.

No direct comparison against the appropriate comparator therapy

Overall, the first 8 days of treatment in the comparator arm in the randomized cohort of the BRIGHTE study was not in line with the ACT. For treatment-experienced adults with HIV-1

whose current ART is failing, there is a medically necessary indication for a treatment switch. Continuation of an inadequate therapy for another 8 days does not concur with the ACT. Regardless of this, the randomized comparison with a duration of only 8 days is too short to assess long-term effects of fostemsavir in comparison with the ACT on the chronic course of multidrug resistant HIV-1 infection.

Uncertainty in the BRIGHTE study regarding the patient population

The BRIGHTE study included patients with documented resistance, intolerability and/or contraindications to antiretrovirals in ≥ 3 drug classes. According to the study publication, no functional antiretroviral combination therapy was available to the patients because at least 4 of 6 antiretroviral drug classes (nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase inhibitors [INIs], protease inhibitors [PIs], CC motif chemokine receptor 5 [CCR5] antagonists, entry inhibitors) had been exhausted. However, partially active drugs were not taken into account when classifying whether an active drug class had been exhausted. The European Medicines Agency (EMA) also points out in the European Public Assessment Report (EPAR) that it was not specified, how many partially active drugs may have been available to the patients in the BRIGHTE study and could be used for the construction of the OBT. In summary, it is unclear whether all patients included in the BRIGHTE study represent the present therapeutic indication in that they had multidrug resistant HIV infection and in that no suppressive antiretroviral treatment regimen was available to them.

Indirect comparison

According to information provided by the company in Module 4 A it conducted separate MAIC analyses of the long-term results over 96 weeks to support the results of the open-label phase of the BRIGHTE study. On the intervention side, data from the BRIGHTE study (fostemsavir plus OBT) were included in the MAIC analyses. On the side of the comparator therapy, the company used the comparator arms of the studies BENCHMRK-1 and BENCHMRK-2 (pooled data on placebo plus OBT), and the single-arm study TMB-301 (ibalizumab plus OBT), as well as the single-arm study VIKING-3 (OBT including dolutegravir).

The MAIC analyses presented by the company without a common comparator are generally not an adequate option for confounder adjustment. Furthermore, the MAICs presented are also not suitable for deriving an added benefit of fostemsavir in comparison with the ACT, as the studies BENCHMRK-1, BENCHMRK-2, TMB-301 and VIKING-3 do not represent the ACT. Irrespective of this, the company did not provide an adequate presentation of the methods used for the MAIC analyses in Module 4 A.

Studies presented by the company for the appropriate comparator therapy

BENCHMRK-1 and BENCHMRK-2

The studies BENCHMRK-1 and BENCHMRK-2 are double-blind, 2-arm, placebo-controlled RCTs of raltegravir. The studies were conducted between 2006 and 2011. They included

INI-naive patients aged 16 years and older with an HIV-1 RNA viral load > 1000 copies/mL and resistance to at least 1 drug in each of the 3 drug classes (NRTI, NNRTI, PI).

TMB-301

The TMB-301 study is a single-arm study of ibalizumab, which was conducted between 2015 and 2016. It included adult patients with a viral load > 1000 copies/mL and resistance to at least 1 antiretroviral drug in each of the 3 drug classes (NRTI, NNRTI, PI).

VIKING-3

The VIKING-3 study is a single-arm study of dolutegravir, which was conducted from 2011 to 2015. It included INI-experienced adult patients with an HIV-1 RNA viral load ≥ 500 copies/mL and resistance to raltegravir and/or elvitegravir and ≥ 2 other drug classes.

Appropriate comparator therapy not implemented in the studies presented

The ACT in the sense of an individual ART chosen from the approved drugs was not implemented in the comparator arms of the studies BENCHMRK-1 and BENCHMRK-2, and in the single-arm VIKING-3 study. This is due to the fact that the studies were conducted about 6 to 15 years ago, between 2006 and 2015, and that only some of the currently available antiretroviral drugs or drug classes were approved at that time. Some of the treatment options that are relevant today in the therapeutic indication have only been approved after completion of the studies. It is also questionable whether the BRIGHTE study with the intervention fostemsavir, which started in 2015, reflects the current health care standard. For the VIKING-3 study and the TMB-301 study, it is also unclear whether dolutegravir (as part of the OBT) and ibalizumab (plus OBT) represent the patient-specific therapy in the sense of the ACT for all patients. Overall, the studies presented by the company are therefore not suitable for showing the course of multidrug resistant HIV infection under effective or partially effective individual antiretroviral therapy that exhausts currently available treatment options.

Further limitations of the studies TMB-301 and VIKING-3

The treatment used in the beginning of the studies TMB-301 and VIKING-3 does not correspond to the ACT and guideline recommendations. In addition, the TMB-301 study did not fulfil the minimum study duration of 48 weeks in the present therapeutic indication. Furthermore, 45% of patients in the TMB-301 study received fostemsavir as part of their OBT. For these patients, it is therefore unclear to what extent the study results can be attributed to the intervention with ibalizumab or to fostemsavir as part of the OBT.

Inadequate presentation of the MAIC

Irrespective of the lack of implementation of the ACT in the studies included by the company in the MAIC analyses and the further limitations mentioned, the company provided no adequate presentation the MAICs in Module 4 A of the dossier. On the one hand, the dossier contained no information retrieval for the ACT for the MAIC analyses. It is therefore unclear to what extent the data used in the MAIC analyses are complete. On the other hand, Module 4 A of the

dossier provided no adequate presentation of the methods of the studies used by the company on the side of the comparator therapy and of the patient characteristics. Thus, it is not possible to assess whether the BRIGHTE study and the studies BENCHMRK-1, BENCHMRK-2, TMB-301 and VIKING-3 are sufficiently comparable with regard to prognostic and predictive factors.

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 fostemsavir.

Table 3: Fostemsavir – 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 ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus 1		

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].

2.2 Research question

The aim of the present report is the assessment of the added benefit of fostemsavir in combination with other antiretrovirals 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.

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

Table 4: Research question of the benefit assessment of fostemsavir

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 ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus 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 list on fostemsavir (status: 29 January 2021)
- bibliographical literature search on fostemsavir (last search on 29 January 2021)
- search in trial registries/trial results databases for studies on fostemsavir (last search on 29 January 2021)
- search on the G-BA website for fostemsavir (last search on 29 January 2021)

To check the completeness of the study pool:

- search in trial registries for studies on fostemsavir (last search on 12 April 2021); for search strategies, see Appendix A of the full dossier assessment

No relevant RCT on the direct comparison of fostemsavir against the ACT was identified from the check.

In its assessment, the company included the BRIGHTE study for the direct comparison of fostemsavir with the ACT, however. According to its information provided in Module 4 A, it conducted supplementary separate MAICs to support the results of the open-label phase of the BRIGHTE study.

Both the BRIGHTE study presented by the company and the MAIC analyses are not suitable for drawing conclusions on the added benefit of fostemsavir in comparison with the ACT specified by the G-BA. This is explained below.

2.3.1 Direct comparison

The company included the BRIGHTE study for the direct comparison of fostemsavir with the ACT. It used both the results of the randomized controlled study phase and the results of the single-arm study phase for the derivation of an added benefit in Module 4 A. However, the study is not suitable for a direct comparison of fostemsavir with the ACT and is not used for the benefit assessment. The study is described below and the exclusion of the study is explained. Further information on the study and intervention characteristics of the BRIGHTE study can be found in Table 9 and Table 10 in Appendix B of the full dossier assessment.

Study BRIGHTE

The BRIGHTE study [3-9] is an ongoing, partially blinded, multicentre phase 3 study with 2 cohorts (one randomized cohort and one non-randomized cohort). The study included patients aged 18 years and older with multidrug resistant HIV-1 infection who had been pretreated with antiretroviral drugs. Multidrug resistant HIV-1 infection was defined as HIV-1 RNA viral load ≥ 400 copies/mL and a documented resistance, intolerability and/or contraindications to antiretrovirals in ≥ 3 drug classes.

Depending on how many fully active antiretroviral drugs remained available for treatment, the patient was included in either the randomized or the non-randomized cohort. An antiretroviral drug class was considered available if at least one drug in that class was fully active and a viable treatment option for the patient, based on current and/or documented historical resistance testing, under consideration of tolerability and other safety concerns. Fully active drugs were those to which the virus was classified as sensitive, or for which an activity of the CCR5 was anticipated according to the tropism assay (tests used: Phenosense GT Plus Integrase Assay, Trofile Co-Receptor Tropism Assay, Phenosense Entry Assay). Partially active drugs and drugs that the patient was unwilling to take (e.g. drug to be injected) were not considered (fully) active remaining drugs.

Patients who had no fully active antiretroviral drugs that could be combined in a treatment regimen were assigned to the non-randomized cohort. These patients received open-label fostemsavir at a dose of 600 mg twice daily from day 1 in addition to OBT.

The randomized cohort included patients for whom 1 to 2 fully active antiretroviral drugs from ≤ 2 drug classes that can be combined in a treatment regimen are available. Randomization of patients in the randomized cohort was stratified by HIV-1 RNA viral load at screening (≤ 1000 copies/mL versus > 1000 copies/mL). A total of 272 patients were randomly assigned to double-blind treatment with fostemsavir or placebo in a 3:1 ratio. From day 1 to day 8, patients received either fostemsavir 600 mg (intervention group: n = 203) or placebo (comparator group: n = 69) twice daily. In addition, the patients continued their currently failing ART. Starting on day 9, all 272 patients entered an unblinded treatment phase with fostemsavir (600 mg twice daily), during which they received concomitant OBT.

The dosage of fostemsavir used in the study is in compliance with the SPC [10]. The OBT was composed according to the investigator's choice.

The treatment duration in the BRIGHTE study was 96 weeks. Treatment beyond 96 weeks was possible if there was still a clinical benefit for the patient.

The primary outcome of the study was the change in mean log10 HIV-1 RNA viral load from day 1 to day 8 in the randomized cohort. Secondary outcomes included outcomes on morbidity, health-related quality of life and side effects (including deaths).

The company used the interim analysis at the third data cut-off (14 August 2018) of the BRIGHTE study, after the last patient had completed the visit at week 96.

No direct comparison against the appropriate comparator therapy

Overall, the first 8 days of treatment in the comparator arm in the randomized cohort of the BRIGHTE study was not in line with the ACT. For treatment-experienced adults with HIV-1 whose current ART is failing, there is a medically necessary indication for a treatment switch. Continuation of an inadequate therapy for another 8 days does not concur with the ACT. Such an approach is also not in compliance with the recommendations of the guidelines. Neither continuation of failing therapy [11] or treatment interruption in case of treatment failure [11,12], nor the combination of a failing therapy with an active drug (fostemsavir) [13,14] is adequate. Instead, such an approach carries the risk of further accumulation of resistance mutations [11]. Regardless of this, the randomized comparison with a duration of only 8 days is too short to assess long-term effects of fostemsavir in comparison with the ACT on the chronic course of multidrug resistant HIV-1 infection.

Uncertainty in the BRIGHTE study regarding the patient population

The BRIGHTE study included patients with documented resistance, intolerability and/or contraindications to antiretrovirals in ≥ 3 drug classes. Information is available on how many antiretroviral drug classes had already been exhausted and how many drugs were still available to the patient. According to the study publication [6], no functional antiretroviral combination therapy was available to the patients because at least 4 of 6 antiretroviral drug classes (NRTIs, NNRTIs], INIs, PIs, CCR5 antagonists, entry inhibitors) had been exhausted. However,

partially active drugs were not taken into account when classifying whether an active drug class had been exhausted. The EMA also points out in the EPAR that it was not specified, how many partially active drugs may have been available to the patients in the BRIGHTE study and could be used for the construction of the OBT [8]. In summary, it is unclear whether all patients included in the BRIGHTE study represent the present therapeutic indication in that they had multidrug resistant HIV infection and in that no suppressive antiretroviral treatment regimen was available to them.

2.3.2 Indirect comparison

According to information provided by the company in Module 4 A it conducted separate MAIC analyses of the long-term results over 96 weeks to support the results of the open-label phase of the BRIGHTE study. Information on the methods and results of the MAIC analyses is provided in Module 4 A exclusively in Section 4.1 (summary of the contents of Module 4). On the intervention side, data from the BRIGHTE study (fostemsavir plus OBT) were included in the MAIC analyses. On the side of the comparator therapy, the company used the comparator arms of the studies BENCHMRK-1 and BENCHMRK-2 (pooled data on placebo plus OBT), and the single-arm study TMB-301 (ibalizumab plus OBT), as well as the single-arm study VIKING-3 (OBT including dolutegravir).

The MAIC analyses presented by the company without a common comparator are generally not an adequate option for confounder adjustment [1]. Furthermore, the MAICs presented are also not suitable for deriving an added benefit of fostemsavir in comparison with the ACT, as the studies BENCHMRK-1, BENCHMRK-2, TMB-301 and VIKING-3 do not represent the ACT. Irrespective of this, the company did not provide an adequate presentation of the methods used for the MAIC analyses in Module 4 A.

Studies presented by the company for the appropriate comparator therapy

BENCHMRK-1 and BENCHMRK-2

The studies BENCHMRK-1 and BENCHMRK-2 [15-18] are double-blind, 2-arm, placebo-controlled RCTs of raltegravir. The studies were conducted between 2006 and 2011. They included INI-naive patients aged 16 years and older with an HIV-1 RNA viral load > 1000 copies/mL and resistance to at least 1 drug in each of the 3 drug classes (NRTI, NNRTI, PI). The company included the results after 96 weeks in the MAIC analyses.

TMB-301

The TMB-301 study [19,20] is a single-arm study of ibalizumab, which was conducted between 2015 and 2016. It included adult patients with a viral load > 1000 copies/mL and resistance to at least 1 antiretroviral drug in each of the 3 drug classes (NRTI, NNRTI, PI). In addition, all patients had to have full viral sensitivity/susceptibility to at least one antiretroviral drug other than ibalizumab. The TBM-301 study was already assessed in the benefit assessment of ibalizumab [21]. The company included the results after 24 weeks in the MAIC analyses.

VIKING-3

The VIKING-3 study [22,23] is a single-arm study of dolutegravir, which was conducted from 2011 to 2015. It included INI-experienced adult patients with an HIV-1 RNA viral load ≥ 500 copies/mL and resistance to raltegravir and/or elvitegravir and ≥ 2 other drug classes. At least one fully active drug had to remain available to the patients. The company had already presented the VIKING-3 study for the benefit assessment of dolutegravir (A14-08) [24]. The company included the results after 24 and 48 weeks in the MAIC analyses.

Appropriate comparator therapy not implemented in the studies presented

Overall, the studies presented by the company are not suitable for drawing conclusions on the added benefit of fostemsavir in comparison with the ACT. This is explained below.

The ACT in the sense of an individual ART chosen from the approved drugs was not implemented in the comparator arms of the studies BENCHMRK-1 and BENCHMRK-2, and in the single-arm VIKING-3 study. This is due to the fact that the studies were conducted about 6 to 15 years ago, between 2006 and 2015, and that only some of the currently available antiretroviral drugs or drug classes were approved at that time. Some of the treatment options that are relevant today in the therapeutic indication [11,12,14] have only been approved after completion of the studies. For example, the first post-attachment inhibitor, ibalizumab, was approved in 2019. Additional new drugs from already existing drug classes have also become available after 2015. For example, bictegravir, another INI (in combination), and doravirine, another NNRTI, have been approved for the treatment of HIV infection. In addition, various combination preparations have become available since 2011 to improve treatment adherence [25-27]. Numerous such combination preparations have been approved for the treatment of HIV infection in subsequent years, particularly in 2018 [25-27]. It is also questionable whether the BRIGHTE study with the intervention fostemsavir, which started in 2015, reflects the current health care standard. For the VIKING-3 study and the TMB-301 study, it is also unclear whether dolutegravir (as part of the OBT) and ibalizumab (plus OBT) represent the patient-specific therapy in the sense of the ACT for all patients. Overall, the studies presented by the company are therefore not suitable for showing the course of multidrug resistant HIV infection under effective or partially effective individual antiretroviral therapy that exhausts currently available treatment options.

Further limitations of the studies TMB-301 and VIKING-3

Treatment at the start of the study was not in compliance with guidelines and did not concur with the ACT

The treatment used in the beginning of the studies TMB-301 and VIKING-3 does not correspond to the ACT and guideline recommendations (see corresponding explanations regarding the BRIGHTE study). Instead, the patients in the TMB-301 study were monitored until day 6 (control period) on their current failing therapy or received no therapy if the failing therapy was discontinued within 8 weeks before screening. In the subsequent 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. Only in the maintenance period (day 14 to week 25), the patients received individual OBT from day 14, and the subsequent maintenance dose of ibalizumab (800 mg every 2 weeks) from day 21. In the VIKING-3 study, patients initially received their previously failing ART until day 7, in which dolutegravir replaced raltegravir or elvitegravir (functional monotherapy period). Only from day 8 was OBT initiated in addition to dolutegravir.

Duration of study TMB-301 too short to assess long-term effects on chronic course of HIV infection

The treatment duration of the TMB-301 study was 25 weeks. Thus, the study did not fulfil the minimum study duration of 48 weeks in the present therapeutic indication. Due to the chronic course of the disease and the required long-term treatment of patients with HIV-1, a minimum study duration of 48 weeks is required for the early benefit assessment.

Fostemsavir as part of the optimized background treatment in the TMB-301 study

In the TMB-301 study, the drug fostemsavir, which was not approved at the time the study was conducted and is to be assessed in the present benefit assessment, was permitted as part of the patient-specific OBT. According to the medical review of the Food and Drug Administration (FDA), 45% of the patients in the TMB-301 study received fostemsavir as part of their OBT [28]. For these patients, it is therefore unclear to what extent the study results can be attributed to the intervention with ibalizumab or to fostemsavir as part of the OBT.

Inadequate presentation of the MAIC

Irrespective of the lack of implementation of the ACT in the studies included by the company in the MAIC analyses and the further limitations mentioned, the company provided no adequate presentation the MAICs in Module 4 A of the dossier.

On the one hand, the dossier contained no information retrieval for the ACT for the MAIC analyses. It is therefore unclear to what extent the data used in the MAIC analyses are complete. In Module 4 A, the company only stated that it had conducted a systematic literature search, which included a heavily pretreated patient population, closely following the inclusion criteria of the BRIGHTE study. According to the company, the studies had been filtered for their eligibility for inclusion in the MAIC analysis, taking into account inclusion/exclusion criteria, the question whether key outcomes had been reported, and expert clinical judgement.

On the other hand, Module 4 A of the dossier provided no adequate presentation of the methods of the studies used by the company on the side of the comparator therapy and of the patient characteristics. Thus, it is not possible to assess whether the BRIGHTE study and the studies BENCHMRK-1, BENCHMRK-2, TMB-301 and VIKING-3 are sufficiently comparable with regard to prognostic and predictive factors. Irrespective of this, this was a comparison of individual arms from different studies. Although an adjustment was made in the analysis with regard to potentially relevant effect modifiers or prognostic factors, the results are subject to inherent uncertainty due to the lack of randomization, so an added benefit can only be derived

if the effects are sufficiently large. As the studies used by the company on the side of the comparator therapy do not represent the ACT, the size of the observed effects cannot be interpreted, however.

2.4 Results on added benefit

No suitable data are available for the assessment of fostemsavir 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 results in no hint of an added benefit of fostemsavir 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 fostemsavir in comparison with the ACT is summarized in Table 5.

Table 5: Fostemsavir – 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 ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus 1		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit in Module 4 A on the basis of the results of the BRIGHTE study. According to the information provided by the company in Module 4 A, Section 4.4.2, the high efficacy of fostemsavir is supported by the results of the conducted MAICs.

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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