

IQWiG Reports – Commission No. A17-13

Tenofovir alafenamide (chronic hepatitis B) –

Benefit assessment according to §35a Social Code Book V¹

Extract

¹ Translation of Sections 2.1 to 2.7 of the dossier assessment *Tenofovir alafenamid (chronische Hepatitis B) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2017). 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Tenofovir alafenamide (chronic hepatitis B) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

30 March 2017

Internal Commission No.:

A17-13

Address of publisher:

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Keywords: tenofovir alafenamide, hepatitis B, benefit assessment

Registry numbers: NCT01940341, NCT01940471

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Table of contents

	Page
List of tables	iv
List of abbreviations	v
2 Benefit assessment	1
2.1 Executive summary of the benefit assessment	1
2.2 Research questions	6
2.3 Research question 1: treatment-naive adults	8
2.3.1 Information retrieval and study pool (research question 1).....	8
2.3.2 Results on added benefit (research question 1)	13
2.3.3 Extent and probability of added benefit (research question 1).....	14
2.3.4 List of included studies (research question 1)	14
2.4 Research question 2: treatment-experienced adults	15
2.4.1 Information retrieval and study pool (research question 2).....	15
2.4.2 Results on added benefit (research question 2)	17
2.4.3 Extent and probability of added benefit (research question 2).....	17
2.4.4 List of included studies (research question 2)	17
2.5 Research question 3: treatment-naive adolescents	17
2.5.1 Information retrieval and study pool (research question 3).....	17
2.5.2 Results on added benefit (research question 3)	18
2.5.3 Extent and probability of added benefit (research question 3).....	18
2.5.4 List of included studies (research question 3)	18
2.6 Research question 4: treatment-experienced adolescents	18
2.6.1 Information retrieval and study pool (research question 4).....	18
2.6.2 Results on added benefit (research question 4)	18
2.6.3 Extent and probability of added benefit (research question 4).....	19
2.6.4 List of included studies (research question 4)	19
2.7 Probability and extent of added benefit – summary	19
References for English extract	21

List of tables³

	Page
Table 2: Research questions of the benefit assessment of TAF.....	1
Table 3: TAF – probability and extent of added benefit.....	6
Table 4: Research questions of the benefit assessment of TAF.....	6
Table 5: Data presented by the company claimed added benefit on the individual research questions.....	7
Table 6: Study pool – RCT, direct comparison: treatment-naive adults, TAF vs. TDF	8
Table 7: Overview of the patients erroneously allocated by the company to the subpopulations considered by the company – RCT, direct comparison: TAF vs. TDF	13
Table 8: TAF – probability and extent of added benefit	19

³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ALT	alanine aminotransferase
CHB	chronic hepatitis B
DNA	deoxyribonucleic acid
eGFR _{CG}	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
eGFR _{CKD-EPI Cr}	estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbeAG	hepatitis B e antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HLGT	High Level Group Term
HLT	High Level Term
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international unit
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil (fumarate)

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 tenofovir alafenamide (TAF). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as “the company”). The dossier was sent to IQWiG on 30 March 2017.

Research questions

The aim of the present report was to assess the added benefit of TAF in comparison with the appropriate comparator therapy (ACT) in adults and adolescents (12 years of age and older and with a body weight of at least 35 kg) for the treatment of chronic hepatitis B (CHB).

The G-BA’s specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 2.

Table 2: Research questions of the benefit assessment of TAF

Research question	Therapeutic indication	ACT ^b
1	Treatment-naïve adults	(PEG)interferon alfa-2a or tenofovir disoproxil (fumarate) or entecavir
2	Treatment-experienced adults	Individual antiretroviral therapy based on prior treatment(s) and under consideration of 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
3	Treatment-naïve adolescents ^a	Tenofovir disoproxil (fumarate) or entecavir
4	Treatment-experienced adolescents ^a	Tenofovir disoproxil (fumarate)

a: 12 years of age and older and with a body weight of at least 35 kg.
 b: Presentation of the respective ACT specified by the G-BA.
 ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide

The company principally followed the G-BA’s specification, but defined deviating therapeutic indications by differentiating between “oral antiviral treatment-naïve” and “oral antiviral treatment-experienced” patients instead of treatment-naïve and treatment-experienced patients. This would allocate patients with parenteral interferon pretreatment to a different research question than specified by the G-BA. This approach of the company was not followed and, correspondingly, the G-BA’s designations for the therapeutic indications are used in the present assessment. This deviation had no practical relevance for adolescent patients because only oral treatment options are available so that the therapeutic indications of G-BA and the company are congruent.

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

Research question 1: treatment-naive adults

Study pool and study characteristics

The company identified 2 RCTs for the assessment of the added benefit of TAF in treatment-naive adults with CHB: the studies GS-US-320-0108 (GS 108) and GS-US-320-0110 (GS 110). The presented data of the studies GS 108 and GS 110 were unsuitable to derive an added benefit of TAF in comparison with tenofovir disoproxil (fumarate) (TDF) because the data presented were incomplete with regard to content. Further limitations additionally restricted the interpretability of the data.

The studies GS 108 and GS 110 are multicentre, randomized, double-blind, active-controlled studies on the comparison of TAF with TDF. The studies included adult patients with hepatitis B e antigen (HBeAg)-negative (study GS 108) or HBeAg-positive (study GS 110) chronic hepatitis B virus (HBV) infection who were either treatment-naive or treatment-experienced regarding anti-HBV antiviral therapy. Randomization in both studies was stratified by oral antiviral treatment status (treatment-experienced versus treatment-naive), among other factors. If the duration of an oral antiviral pretreatment was shorter than 12 weeks, the patients were allocated to the stratum “oral antiviral treatment-naive”. Treatments were administered in accordance with the approval. Based on amendment 3 to the study protocols, both studies comprise a 144-week double-blind treatment phase and have not been completed. With the company’s dossier, data after 96 treatment weeks were available for study GS 108 and after 72 treatment weeks for study GS 110.

For the present research question, the company used a subpopulation of “oral antiviral treatment-naive” patients from both studies.

Data incomplete with regard to content

Selective reporting on specific adverse events in Module 4 A

The company described that it had considered those specific adverse events (AEs) that were “of particular interest” in relation to the intervention (TAF) or the ACT (TDF) for its analyses in the dossier and named “renal disorders” and “changes in bone density/fractures” as relevant outcomes. The company did not present analyses on other specific AEs, however. In addition, AE analyses on long-term late complications of CHB such as liver cirrhosis or hepatocellular carcinoma as well as on common serious adverse events (SAEs), severe AEs (grade 3 to 4) and discontinuation due to AEs were missing completely for the subpopulations for both studies (the company only reported the overall rates for the 3 latter outcomes).

Additional analyses of adverse events in Module 5 also incomplete, pages deleted to a large extent

The additional analyses presented by the company showed that analyses on specific AEs for the subpopulation were conducted, but only selectively made available by the company in Module 5. For example, the company only presented an extract of 3 pages from a table of 38 pages for the analysis of specific AEs on the GS 108 study. This extract only contains data tables on those specific AEs that the company considered to be relevant. The pages on other System Organ Classes (SOCs) and Preferred Terms (PTs), however, were apparently subsequently removed from the document by the company. This also concerned the analyses on AEs from the GS 110 study, which were shortened by the company following an identical pattern.

Company's postulate on added benefit based on "improved tolerability profile" not tenable

The company derived an added benefit of TAF versus the ACT TDF for the subpopulation of "oral antiviral treatment-naïve" patients particularly based on an "improved tolerability profile", referring to significant advantages of TAF regarding renal disorders and changes in bone density/fractures. The company considered renal disorders and changes in bone density/fractures in different operationalizations, which showed statistically significant results only in surrogate outcomes of the estimated glomerular filtration rate calculated using the Cockcroft-Gault equation (eGFR_{CG}) and changes in bone density. The company also presented no adequate evidence to prove the validity of these surrogate outcomes. Patient-relevant operationalizations (such as bone fractures, for example), in contrast, showed no statistically significant result.

Results on the total population of the studies GS 108 and GS 110 additionally showed differences to the disadvantage of TAF in the SOC "nervous system disorders". Results from the early benefit assessment of a TAF-containing drug combination on the treatment of patients with human immunodeficiency virus (HIV) also showed a statistically significant difference to the disadvantage of the TAF-containing drug combination in comparison with a TDF-containing drug combination for this outcome. Hence the hypothesis can be proposed that such a disadvantage of TAF also exists in the present therapeutic indication. In its dossier, the company did not present the corresponding analyses for the subpopulation to be assessed, however.

Overall, the company's own dossier did not support the company's postulate of "better tolerability" of TAF. Lesser benefit of TAF cannot be excluded due to missing reporting on numerous AEs and their different operationalizations, however.

Creation of subpopulation not adequate, erroneous allocation of patients with opposing pretreatment status to the subpopulation

In addition, the company's approach in the creation of the subpopulations was inadequate. This concerned the inadequate allocation of 61 patients pretreated with interferon (approximately 5% of the study participants) to the subpopulation of "oral antiviral treatment-naive" patients. Instead, creation of a subpopulation with completely treatment-naive patients would have been required. In addition, there were further erroneous allocations to the subpopulations of 69 patients in total (also approximately 5% of the study participants), without explanations by the company.

Research question 2: treatment-experienced adults

For the present research question, the company also used subpopulations from the studies GS 108 and GS 110. The data presented by the company on the subpopulations of "oral antiviral treatment-experienced" patients were irrelevant for the present benefit assessment for the following reasons:

- Analogous to research question 1, the company reported the results only selectively. The data presented were therefore incomplete with regard to content.
- Likewise, the subpopulation cut-off to delineate treatment-experienced patients was inadequate and contradictory.
- However, the studies could not be used for research question 2 also if the data had been submitted completely because the ACT was not implemented:
 - In the comparator arm of both studies, all "oral antiviral treatment-experienced" patients considered by the company received a uniform treatment regimen in form of a daily dose of 300 mg TDF. Hence the ACT of individually optimized antiviral treatment based on prior treatment(s) and under consideration of the reason for the switch of treatment was not implemented. The company provided no adequate justification for TDF being the individually optimized treatment for the patients included in the studies GS 108 and GS 110.
 - According to guidelines, TDF was 1 of several treatment options for patients who had not been pretreated with TDF until study inclusion. If multiple resistances to different nucleoside/nucleotide analogues developed during pretreatment, guidelines recommend switching to combination therapy with TDF and entecavir. The study documents on GS 108 and GS 110 did not show that the "oral antiviral treatment-experienced" patients included were examined at all for resistances to nucleoside/nucleotide analogues. It therefore remains unclear whether TDF monotherapy was the individually optimized antiviral therapy for all "oral antiviral treatment-experienced" patients who had not been pretreated with TDF until their inclusion in the studies GS 108 and GS 110.

- For patients who had already received TDF pretreatment before study inclusion, guidelines recommend switching to entecavir or adding lamivudine, telbivudine or entecavir to the ongoing TDF treatment in case of inadequate virologic response or development of resistance. Unchanged continuation of TDF treatment was therefore inadequate. In contrast to the company's presentation, the proportion of these patients is not negligible, but was over 20% in the subpopulation of "oral antiviral treatment-experienced" patients in each of both arms of both studies.

Summary

No relevant data were available for the assessment of the added benefit of TAF in treatment-experienced adults. Hence there was no hint of an added benefit of TAF in comparison with the ACT. An added benefit is therefore not proven.

Research question 3: treatment-naïve adolescents

The company presented no data for research question 3. Hence the added benefit of TAF for treatment-naïve adolescents 12 years of age and older and with a body weight of at least 35 kg is not proven.

Research question 4: treatment-experienced adolescents

The company presented no data for research question 4. Hence the added benefit of TAF for treatment-experienced adolescents 12 years of age and older and with a body weight of at least 35 kg is not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the probability and extent of the added benefit of the drug TAF compared with the ACT is assessed as shown in Table 3.

⁴ 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, no added benefit, or less benefit). For further details see [1,2].

Table 3: TAF – probability and extent of added benefit

Research question	Therapeutic indication	ACT ^b	Probability and extent of added benefit
1	Treatment-naïve adults	(PEG)interferon alfa-2a or tenofovir disoproxil (fumarate) or entecavir	Added benefit not proven
2	Treatment-experienced adults	Individual antiretroviral therapy based on prior treatment(s) and under consideration of 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
3	Treatment-naïve adolescents ^a	Tenofovir disoproxil (fumarate) or entecavir	Added benefit not proven
4	Treatment-experienced adolescents ^a	Tenofovir disoproxil (fumarate)	Added benefit not proven
a: 12 years of age and older and with a body weight of at least 35 kg. b: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide			

The G-BA decides on the added benefit.

2.2 Research questions

The aim of the present report was to assess the added benefit of TAF in comparison with the ACT in adults and adolescents (12 years of age and older and with a body weight of at least 35 kg) for the treatment of CHB.

The G-BA's specification of the ACT for different patient groups resulted in 4 research questions, which are presented in the following Table 4.

Table 4: Research questions of the benefit assessment of TAF

Research question	Therapeutic indication	ACT ^b
1	Treatment-naïve adults	(PEG)interferon alfa-2a or tenofovir disoproxil (fumarate) or entecavir
2	Treatment-experienced adults	Individual antiretroviral therapy based on prior treatment(s) and under consideration of 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
3	Treatment-naïve adolescents ^a	Tenofovir disoproxil (fumarate) or entecavir
4	Treatment-experienced adolescents ^a	Tenofovir disoproxil (fumarate)
a: 12 years of age and older and with a body weight of at least 35 kg. b: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide		

The company principally followed the G-BA’s specification, but defined deviating therapeutic indications by differentiating between “oral antiviral treatment-naive” and “oral antiviral treatment-experienced” patients instead of treatment-naive and treatment-experienced patients. This would allocate patients with parenteral interferon pretreatment to a different research question than specified by the G-BA. This approach of the company was not followed (see Section 2.8.1 of the full dossier assessment) and, correspondingly, the G-BA’s designations for the therapeutic indications are used in the present assessment. This deviation had no practical relevance for adolescent patients because only oral treatment options are available so that the therapeutic indications of G-BA and the company are congruent.

An overview of the data presented by the company and of the added benefit claimed in each case is shown in Table 5.

Table 5: Data presented by the company claimed added benefit on the individual research questions

Research question	Therapeutic indication	Comparator therapy of the company	Data presented by the company	Added benefit claimed by the company
CHB in adults				
1	Treatment-naive	TDF ^a	2 RCTs (GS 108 and GS 110) ^b	Proof of considerable added benefit of TAF
2	Treatment-experienced	TDF ^a	2 RCTs (GS 108 and GS 110) ^b	Indication of minor added benefit of TAF
CHB in adolescents^c				
3	Treatment-naive	ETV or TDF	No data	No added benefit claimed for TAF
4	Treatment-experienced	TDF	No data	No added benefit claimed for TAF
a: Comparator of the studies included by the company. b: Instead of treatment-naive and treatment-experienced patients, the company differentiates between “oral antiviral treatment-naive” and “oral antiviral treatment-experienced” patients. c: 12 years of age and older and with a body weight of at least 35 kg. CHB: chronic hepatitis B; ETV: entecavir; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil (fumarate)				

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 Research question 1: treatment-naive adults

2.3.1 Information retrieval and study pool (research question 1)

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 TAF (status: 18 January 2017)
- bibliographical literature search on TAF (status: 18 January 2017)
- search in trial registries for studies on TAF (status: 18 January 2017)

To check the completeness of the study pool:

- search in trial registries for studies on TAF (last search on 12 April 2017)

No additional relevant study was identified from the check.

The company identified 2 RCTs for the assessment of the added benefit of TAF in treatment-naive adults: the studies GS 108 and GS 110. Table 6 shows an overview of the study pool.

Table 6: Study pool – RCT, direct comparison: treatment-naive adults, TAF vs. TDF

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)
GS-US-320-0108 (GS 108 ^b)	Yes	Yes	No
GS-US-320-0110 (GS 110 ^b)	Yes	Yes	No

a: Study for which the company was sponsor.
 b: In the following tables, the study is referred to with this abbreviated form.
 RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil (fumarate);
 vs.: versus

The presented data of the studies GS 108 and GS 110 were unsuitable to derive an added benefit of TAF in comparison with TDF because the data presented were incomplete with regard to content. Further limitations additionally restricted the interpretability of the data.

The studies are described below and the incompleteness of the data and the further limitations are described in detail.

Section 2.3.4 contains a reference list for the studies GS 108 and GS 110.

Description of the studies GS 108 and GS 110

Study design

Both studies were conducted following a comparable protocol and are described together below.

The studies GS 108 and GS 110 are multicentre, randomized, double-blind, active-controlled studies on the comparison of TAF with TDF. The studies included adult patients with HBeAg-negative (study GS 108) or HBeAg-positive (study GS 110) chronic HBV infection who were either treatment-naïve or treatment-experienced regarding anti-HBV antiviral therapy. Further inclusion criteria included a viral load of at least 2×10^4 international units (IU)/mL HBV deoxyribonucleic acid (DNA) as well as an increased alanine aminotransferase (ALT) plasma level, operationalized as over 60 units (U)/L in male patients, and as over 38 U/L in female patients.

In both studies, patients were randomized in a 2:1 ratio. Randomization was stratified by plasma HBV DNA level ($< 10^7$ IU/mL versus $\geq 10^7$ to $< 10^8$ IU/mL versus $\geq 10^8$ IU/mL in study GS 108, and $< 10^8$ IU/mL versus $\geq 10^8$ IU/mL in study GS 110) and oral antiviral treatment status (treatment-experienced versus treatment-naïve). If the duration of the oral antiviral pretreatment was shorter than 12 weeks, the patients were allocated to the stratum “oral antiviral treatment-naïve”.

Patients in the TAF arm of both studies received a daily dose of 25 mg TAF orally, patients in the TDF arm a daily dose of 300 mg TDF (equivalent to 245 mg tenofovir disoproxil [fumarate]) orally. Treatments were administered in accordance with the approval [3,4].

Each of both studies comprised a double-blind treatment phase, followed by an open-label extension phase, in which all participants received TAF. For both studies, the duration of the study phases was adjusted with protocol amendments. The originally planned duration of the double-blind treatment phase was 48 weeks (GS 108) and 96 weeks (GS 110). With protocol amendment 1 and 2, the treatment phase was extended to 96 weeks for study GS 108 and, with amendment 3, to 144 weeks for both studies. The additional extension phase was 240 weeks. Both studies have not yet been completed. Further information on the studies GS 108 and GS 110 can be found in Table 13, Table 14 and Table 15 in Appendix A of the full dossier assessment.

Data cut-offs

The data cut-off for the analysis of the primary outcome was conducted on 1 October 2015 in study GS 108 and on 16 November 2015 in study GS 110. Further data cut-offs on outcomes such as mortality, morbidity and AEs were planned a priori in both studies after 96 and 144 treatment weeks. At the instigation of the European Medicines Agency, a further data cut-off after 72 treatment weeks was conducted for both studies [5].

For the current dossier, the company presented data after 96 treatment weeks for the GS 108 study; the data cut-off for this analysis was conducted on 17 October 2016. For the GS 110 study, the company presented data after 72 treatment weeks; the data cut-off for this analysis was conducted on 3 June 2016. Hence the data cut-off after 96 weeks for the GS 110 study could have been conducted in November 2016 (shortly after the one for the GS 108 study). The company did not address the issue why the dossier did not contain analyses after 96 treatment weeks for the GS 110 study.

Data for Chinese patients

In addition, a country-specific protocol amendment for China mandated additional inclusion of 150 Chinese participants into each of the studies GS 108 and GS 110. The study documents showed that the Chinese patients were to receive treatment over a period of 48 weeks and be analysed separately from the other study participants. These were not part of the clinical study reports submitted by the company. It remains unclear whether these results could have been available or when results for the Chinese subpopulation can be expected.

Data incomplete with regard to content

For the present research question, the company used a subpopulation of “oral antiviral treatment-naïve” patients from each of both studies. This subpopulation consisted of 335 patients from the GS 108 study and of 667 patients from the GS 110 study. The data presented by the company on the subpopulations were incomplete with regard to content, however, because it reported the results only selectively. This is described in detail below.

Selective reporting on specific adverse events in Module 4 A

The company described that it had considered those specific AEs that were “of particular interest” in relation to the intervention (TAF) or the ACT (TDF) for its analyses in the dossier. In this context, it named “renal disorders” and “changes in bone density/fractures” as relevant outcomes. For the subpopulation of “oral antiviral treatment-naïve” patients, the company therefore only presented analyses for the following outcomes in Module 4A:

- renal and urinary disorders (Medical Dictionary for Regulatory Activities [MedDRA] SOC)
- renal failure and renal function disorders (MedDRA High Level Term [HLT])
- renal function disorders (mean change from baseline of the eGFR_{CG} [mL/min] and of the estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [eGFR_{CKD-EPI Cr}] [mL/min/1.73 m²])
- bone fractures (High Level Group Term [HLGT] and Standardized MedDRA Query [SMQ])
- osteoporosis and osteopenia (MedDRA PT)
- percentage change in bone density in hip and spine

The company did not present analyses on other specific AEs. In addition, AE analyses on long-term late complications of CHB such as liver cirrhosis or hepatocellular carcinoma as well as on common SAEs, severe AEs (grade 3 to 4) and discontinuation due to AEs were missing completely for the subpopulations for both studies (the company only reported the overall rates for the 3 latter outcomes).

Additional analyses of adverse events in Module 5 also incomplete, pages deleted to a large extent

The additional analyses presented by the company showed that analyses on specific AEs for the subpopulation were conducted, but only selectively made available by the company in Module 5. A table from the additional analyses presented by the company shown in Appendix B of the full dossier assessment serves as an example [6]. Appendix B shows a complete presentation of Table 95 of the additional analyses on the GS 108 study provided in Module 5. The description of the table shows that this table on AEs (SOCs and PTs) has a total of 38 pages. The company only provided a small part of this table, i.e. 3 of the 38 pages, in Module 5. These were the pages 24, 31 and 32. This extract only contains data tables on those specific AEs that the company considered to be relevant. The pages on other SOC and PTs, however, were apparently subsequently removed from the document by the company. This also concerned the analyses on AEs from the GS 110 study, which were shortened by the company following an identical pattern.

Company's postulate on added benefit based on "improved tolerability profile" not tenable

For the subpopulation of "oral antiviral treatment-naïve" patients, the company derived an added benefit of TAF in comparison with the ACT TDF particularly based on an "improved tolerability profile". According to the company, this was mainly due to significant advantages of TAF regarding renal disorders and changes in bone density/fractures. For the outcomes "SAEs", "severe AEs" (grade 3 to 4) and "discontinuation due to AEs" in contrast, the company derived no advantages of TAF because, according to the company, no differences between the treatment groups were shown. There were also no statistically significant differences between the treatment groups for the outcomes "all-cause mortality", "virologic response" and "serological response" (see Table 24 in Appendix D of the full dossier assessment).

The company considered renal disorders and changes in bone density/fractures in different operationalizations. Statistically significant results were shown only in the surrogate outcomes "change in eGFR_{CG}" and "change in bone density", whereas patient-relevant operationalizations (e.g. bone fractures) showed no statistically significant result. The evidence provided by the company was unsuitable to prove the validity of these surrogate outcomes (see Section 2.8.2.9.4 of the full dossier assessment).

In contrast, the tables on common AEs, SAEs, severe AEs (grade 3 to 4) and discontinuations due to AEs presented in Appendix C of the full dossier assessment on the total population of the studies GS 108 and GS 110 showed differences to the disadvantage of TAF for the SOC

“nervous system disorders”. Results from the early benefit assessment of a TAF-containing drug combination on the treatment of patients with HIV showed a statistically significant difference to the disadvantage of the TAF-containing drug combination in comparison with a TDF-containing drug combination for this outcome “nervous system disorders” (SOC) [7]. Hence the hypothesis can be proposed that such a disadvantage of TAF also exists in the present therapeutic indication. As described above, in its dossier, the company did not present the corresponding analyses for the subpopulation to be assessed.

Overall, the company’s own dossier did not support the company’s postulate of “better tolerability” of TAF. Lesser benefit of TAF cannot be excluded due to missing reporting on numerous AEs and their different operationalizations, however.

Creation of subpopulation not adequate, erroneous allocation of patients with opposing pretreatment status to the subpopulation

As described above, the company used a subpopulation from each of both studies for the present research question. This subpopulation consisted of 335 patients from the GS 108 study and of 667 patients from the GS 110 study. The company described in Module 4 A of its dossier that the subpopulation of “oral antiviral treatment-naive” patients considered by the company corresponded to the stratum of “oral antiviral treatment-naive” patients from the studies GS 108 and GS 110. The company’s approach was inadequate for the following reasons:

- The patients in the studies GS 108 and GS 110 were stratified according to their oral antiviral treatment status at the start of the study. Patients who had only received interferon in their pretreatment were therefore also allocated to the stratum of “oral antiviral treatment-naive” patients. This concerned 61 patients in both studies (approximately 5% of the study participants). This allocation deviates from the specification of the G-BA, which did not differentiate between oral or parenteral pretreatment (see Section 2.8.1 of the full dossier assessment). In addition, the proportion of patients pretreated with interferon in the studies was notably above the information provided by the company, which gave a number of 0.2% for their proportion in Germany, rating it as negligible.
- Irrespective of this, the cut-off criterion used by the company for the categorization of the study population according to the stratification characteristic “oral antiviral treatment status” allowed no exact delineation of “oral antiviral treatment-naive” patients. In the studies GS 108 and GS 110, patients were also allocated to the stratum “oral antiviral treatment-naive” if they had received oral antiviral pretreatment for less than 12 weeks. Patients with primary treatment failure due to inadequate response to their pretreatment within the first 3 months of treatment [8] were therefore erroneously allocated to the stratum “oral antiviral treatment-naive”. The number of patients affected is unclear because the company did not address this issue.

- Finally, it can be inferred from information provided in Module 4 A on the oral antiviral treatment status that the company allocated patients with opposing pretreatment status to the subpopulations considered by the company (“oral antiviral treatment-naive” versus “oral antiviral treatment-experienced”) (see also Table 7). However, the company did not provide any justifications for these erroneous allocations. The company’s principle criteria for allocating the patients to the subpopulations considered by the company therefore remain unclear.

Table 7: Overview of the patients erroneously allocated by the company to the subpopulations considered by the company – RCT, direct comparison: TAF vs. TDF

Study	TAF	TDF
Information on the pretreatment status with nucleoside/nucleotide analogues	n (%)	n (%)
Subpopulation from Module 4 A ^a		
Group within the subpopulation from Module 4 A ^b		
GS 108	N = 285	N = 140
Stratum “oral antiviral treatment-naive” (according to Module 4 A)	225 (78.9) ^c	110 (78.6) ^c
Patients thereof who actually were oral antiviral treatment-experienced	8 (3.6)	3 (2.7)
Stratum “oral antiviral treatment-experienced” (according to Module 4 A)	60 (21.1) ^c	30 (21.4) ^c
Patients thereof who actually were oral antiviral treatment-naive	8 (13.3)	2 (6.7)
GS 110	N = 581	N = 292
Stratum “oral antiviral treatment-naive” (according to Module 4 A)	444 (76.4)	223 (76.4)
Patients thereof who actually were oral antiviral treatment-experienced	25 (5.6)	10 (4.5)
Stratum “oral antiviral treatment-experienced” (according to Module 4 A)	137 (23.6)	69 (23.6)
Patients thereof who actually were oral antiviral treatment-naive	11 (8.0)	2 (2.9)
<i>Information presented in italics indicates that the percentages refer to the “stratum”.</i>		
a: If the duration of the pretreatment was shorter than 12 weeks, the patients were allocated to the stratum “oral antiviral treatment-naive”.		
b: A patient was categorized as “oral antiviral treatment-experienced” irrespective of the duration of the pretreatment.		
c: Institute’s calculation.		
n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil (fumarate)		

Even though the points of criticism described only concern comparatively small numbers of patients, their overall effects on the results remain unclear. Potential bias can therefore not be excluded.

2.3.2 Results on added benefit (research question 1)

The data presented by the company for the assessment of the added benefit of TAF in treatment-naive adults were incomplete with regard to content. Based on these data, there was

therefore no hint of an added benefit of TAF in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit (research question 1)

Since the company presented no suitable data for treatment-naive adults, an added benefit of TAF for these patients is not proven.

2.3.4 List of included studies (research question 1)

GS 108

Buti M, Gane E, Seto WK, Chan HLY, Chuang WL, Stepanova T et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; 1(3): 196-206.

Gilead Sciences. Tenofovir alafenamide versus tenofovir disoproxil fumarate for treatment of hepatitis B e antigen-negative hepatitis B: full text view [online]. In: *ClinicalTrials.gov*. 10.02.2017 [Accessed: 26.04.2017]. URL: <https://ClinicalTrials.gov/show/NCT01940341>.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B [online]. In: *EU Clinical Trials Register*. [Accessed: 26.04.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000626-63.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B [online]. In: *Clinical Trials Registry India*. 27.09.2016 [Accessed: 26.04.2017]. URL: <http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=8288>.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B: study GS-US-320-0108; interim week 96 clinical study report [unpublished]. 2017.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-negative, chronic hepatitis B: study GS-US-320-0108; Zusatzanalysen [unpublished]. 2017.

GS 110

Chan HL, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; 1(3): 185-195.

Gilead Sciences. Tenofovir alafenamide versus tenofovir disoproxil fumarate for treatment of hepatitis B e antigen-positive hepatitis B: full text view [online]. In: *ClinicalTrials.gov*. 10.02.2017 [Accessed: 26.04.2017]. URL: <https://ClinicalTrials.gov/show/NCT01940471>.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg positive, chronic hepatitis B [online]. In: *EU Clinical Trials Register*. [Accessed: 26.04.2017].

URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000636-10.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-positive, chronic hepatitis B [online]. In: *Clinical Trials Registry India*. 27.09.2016 [Accessed: 26.04.2017].

URL: <http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=8295>.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg positive, chronic hepatitis B: study GS-US-320-0110; interim week 48 clinical study report [unpublished]. 2015.

Gilead Sciences. A phase 3, randomized, double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg positive, chronic hepatitis B: study GS-US-320-0110; Zusatzanalysen [unpublished]. 2017.

2.4 Research question 2: treatment-experienced adults

2.4.1 Information retrieval and study pool (research question 2)

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 TAF (status: 18 January 2017)
- bibliographical literature search on TAF (status: 18 January 2017)
- search in trial registries for studies on TAF (status: 18 January 2017)

To check the completeness of the study pool:

- search in trial registries for studies on TAF (last search on 12 April 2017)

No additional relevant study was identified from the check.

Study pool of the company for the direct comparison

From the steps of information retrieval mentioned, the company identified a total of 2 randomized, active-controlled studies (GS 108 and GS 110) for research question 2. The company also used both studies (in each case a different subpopulation) for research question 1. The respective information on study design, treatment regimen and study population can therefore be found in Section 2.3.1 and in Table 13 and Table 14 in Appendix A of the full dossier assessment.

The data presented by the company on the subpopulations of “oral antiviral treatment-experienced” patients were irrelevant for the present benefit assessment for the following reasons:

- Analogous to research question 1, the company reported the results only selectively (see Section 2.3.1). The data presented were therefore incomplete with regard to content.
- Likewise, the subpopulation cut-off to delineate treatment-experienced patients was inadequate and contradictory (see Table 7 in Section 2.3.1).
- However, the studies could not be used for research question 2 also if the data had been submitted completely because the ACT was not implemented. This is explained below.

Appropriate comparator therapy not implemented in the studies presented

The studies GS 108 and GS 110 are unsuitable for the assessment of the added benefit of TAF in treatment-experienced adults in comparison with the ACT specified by the G-BA because in both studies the ACT was not implemented:

- In the comparator arm of both studies, all “oral antiviral treatment-experienced” patients considered by the company received a uniform treatment regimen in form of a daily dose of 300 mg TDF. Hence the ACT of individually optimized antiviral treatment based on prior treatment(s) and under consideration of the reason for the switch of treatment was not implemented. The company provided no adequate justification for TDF being the individually optimized treatment for the patients included in the studies GS 108 and GS 110.
- According to guidelines, TDF was 1 of several treatment options for patients who had not been pretreated with TDF until study inclusion [8-10]. If multiple resistances to different nucleoside/nucleotide analogues developed during pretreatment, guidelines recommend switching to combination therapy with TDF and entecavir. The study documents on GS 108 and GS 110 did not show that the “oral antiviral treatment-experienced” patients

included were examined at all for resistances to nucleoside/nucleotide analogues. It therefore remains unclear whether TDF monotherapy was the individually optimized antiviral therapy for all “oral antiviral treatment-experienced” patients who had not been pretreated with TDF until their inclusion in the studies GS 108 and GS 110 (see Section 2.8.1 of the full dossier assessment).

- For patients who had already received TDF pretreatment before study inclusion, guidelines recommend switching to entecavir or adding lamivudine, telbivudine or entecavir to the ongoing TDF treatment in case of inadequate virologic response or development of resistance [8-10]. Unchanged continuation of TDF treatment was therefore inadequate. In contrast to the company’s presentation, the proportion of these patients is not negligible, but was over 20% in the subpopulation of “oral antiviral treatment-experienced” patients in each of both arms of both studies (see Section 2.8.2.3.2 of the full dossier assessment).

2.4.2 Results on added benefit (research question 2)

No relevant data were available for the assessment of the added benefit of TAF in treatment-experienced adults. Hence there was no hint of an added benefit of TAF in comparison with the ACT. An added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit (research question 2)

Since the company presented no relevant data for treatment-experienced adults, an added benefit of TAF for these patients is not proven.

2.4.4 List of included studies (research question 2)

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Research question 3: treatment-naive adolescents

2.5.1 Information retrieval and study pool (research question 3)

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 TAF (status: 18 January 2017)
- bibliographical literature search on TAF (status: 18 January 2017)
- search in trial registries for studies on TAF (status: 18 January 2017)

To check the completeness of the study pool:

- search in trial registries for studies on TAF (last search on 12 April 2017)

The company identified no relevant study. No relevant study was identified from the check either.

2.5.2 Results on added benefit (research question 3)

The company presented no data for the assessment of the added benefit of TAF in treatment-naive adolescents 12 years of age and older and with a body weight of at least 35 kg. As a result, there was no hint of an added benefit of TAF in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Extent and probability of added benefit (research question 3)

Since the company presented no data for treatment-naive adolescents 12 years of age and older and with a body weight of at least 35 kg, an added benefit of TAF for these patients is not proven.

This concurs with the assessment of the company, which also claimed no added benefit for these patients.

2.5.4 List of included studies (research question 3)

Not applicable as the company presented no relevant data for the benefit assessment.

2.6 Research question 4: treatment-experienced adolescents

2.6.1 Information retrieval and study pool (research question 4)

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 TAF (status: 18 January 2017)
- bibliographical literature search on TAF (status: 18 January 2017)
- search in trial registries for studies on TAF (status: 18 January 2017)

To check the completeness of the study pool:

- search in trial registries for studies on TAF (last search on 12 April 2017)

The company identified no relevant study. No relevant study was identified from the check either.

2.6.2 Results on added benefit (research question 4)

The company presented no data for the assessment of the added benefit of TAF in treatment-experienced adolescents 12 years of age and older and with a body weight of at least 35 kg. As a result, there was no hint of an added benefit of TAF in comparison with the ACT. An added benefit is therefore not proven.

2.6.3 Extent and probability of added benefit (research question 4)

Since the company presented no data for treatment-experienced adolescents 12 years of age and older and with a body weight of at least 35 kg, an added benefit of TAF for these patients is not proven.

This concurs with the assessment of the company, which also claimed no added benefit for these patients.

2.6.4 List of included studies (research question 4)

Not applicable as the company presented no relevant data for the benefit assessment.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of TAF in comparison with the ACT is summarized in Table 8.

Table 8: TAF – probability and extent of added benefit

Research question	Therapeutic indication	ACT ^b	Probability and extent of added benefit
1	Treatment-naive adults	(PEG)interferon alfa-2a or tenofovir disoproxil (fumarate) or entecavir	Added benefit not proven
2	Treatment-experienced adults	Individual antiretroviral therapy based on prior treatment(s) and under consideration of 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
3	Treatment-naive adolescents ^a	Tenofovir disoproxil (fumarate) or entecavir	Added benefit not proven
4	Treatment-experienced adolescents ^a	Tenofovir disoproxil (fumarate)	Added benefit not proven

a: 12 years of age and older and with a body weight of at least 35 kg.

b: Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide

In summary, an added benefit of TAF in comparison with the ACT for the treatment of chronic hepatitis B is not proven for treatment-naive adults (research question 1) or for treatment-experienced adults (research question 2). This deviates from the assessment of the company, which derived proof of considerable added benefit for “oral antiviral treatment-naive” adults and an indication of a minor added benefit for “oral antiviral treatment-experienced” adults.

Concurring with the results of the benefit assessment, the company derived no added benefit for treatment-naïve and pretreated adolescents (12 years of age and older and with a body weight of at least 35 kg).

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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