IQWiG Reports – Commission No. A19-55

Dolutegravir/lamivudine (HIV infection) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dolutegravir/Lamivudin (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 October 2019). 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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Table of contents

Page

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
3TC	lamivudine
ACT	appropriate comparator therapy
AE	adverse event
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CDC	Centers for Disease Control and Prevention
$CD4^+$	Cluster-of-Differentiation-4-positive
DAIDS	Division of AIDS
DTG	dolutegravir
EQ-5D	European Quality of Life Questionnaire 5 Dimensions
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
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)
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/ nucleotide reverse transcriptase inhibitor
PI	Protease inhibitor
RCT	randomized controlled trial
RNA	Ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TDF	Tenofovir disoproxil
VAS	visual analogue scale

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 dolutegravir/lamivudine (DTG/3TC). 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 4 July 2019.

Research question

The aim of this report was to assess the added benefit of DTG/3TC 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 40 kg) infected with human immunodeficiency virus type 1 (HIV-1). The HI virus was not to have any known or suspected resistances to the class of integrase inhibitors (INI) or 3TC.

Four research questions resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of DTG/3TC

Research question	Subindication	ACT[a]
1	Treatment-naive adults infected with HIV-1[b]	Rilpivirine in combination with TDF/tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or **DTG in combination with TDF**/tenofovir alafenamide **plus FTC** or in combination with abacavir plus 3TC
2	Pretreated adults infected with HIV-1[b]	ART depending 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-naive adolescents[c] infected with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or DTG in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus lamivudine
4	Pretreated adolescents[c] infected with HIV-1[b]	Individual ART depending 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

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI virus was not to have any known or suspected resistances to the INI class or 3TC.
c: Twelve years of age and older and with a body weight of at least 40 kg.
3TC: lamivudine; ACT: appropriate comparator therapy; ART: antiretroviral therapy; DTG: dolutegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; TDF: tenofovir disoproxil

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 for research question 1 (treatment-naive adults)

Study pool and study characteristics

The study pool for the benefit assessment of DTG/3TC in treatment-naive HIV-1 infected adults consisted of the studies 204861 and 205543 (hereinafter referred to as GEMINI-1 or GEMINI-2).

The studies GEMINI-1 and GEMINI-2 were double-blind, randomized parallel-group studies on treatment-naive HIV-1 infected adults with identical design. Both studies compare treatment with the free combination of DTG and 3TC (DTG + 3TC) with treatment with the free combination of DTG and the fixed combination of tenofovir disoproxil (TDF) and FTC (DTG + TDF/FTC). In GEMINI-1, a total of 719 patients were randomly allocated to treatment with

DTG + 3TC (N = 359) or DTG + TDF/FTC (N = 360). In GEMINI-2, a total of 722 patients were randomly allocated to treatment with DTG + 3TC (N = 360) or DTG + TDF/FTC (N = 362).

Both studies are ongoing. Randomized treatment duration of each study is 148 weeks. Assessment was based on the data available at the date of analysis "48 weeks". If possible, the results of both studies are summarized in a meta-analysis.

Risk of bias

Both the risk of bias across outcomes and the risk of bias of the results of the considered outcomes are rated as low for both studies.

Mortality

All-cause mortality

Up to week 48, no deaths occurred in the GEMINI-1 study. Two patients died in the intervention arm of GEMINI-2. There was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for the outcome "all-cause mortality"; an added benefit is therefore not proven.

Morbidity

Acquired immunodeficiency syndrome (AIDS)-defining events (Centers for Disease Control and Prevention [CDC] class C); supplementary consideration of the surrogate outcomes "virologic response", "virologic failure" and "Cluster-of-Differentiation-4-positive" ($CD4^+$) cell count"

The meta-analysis shows no statistically significant difference between the treatment groups, neither for the outcome "CDC class C AIDS-defining events" nor for the outcomes "virologic response", "virologic failure" and "$CD4^+$ cell count" presented as supplementary information. This resulted in no hint of an added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for the outcome "AIDS-defining events (CDC class C)"; an added benefit is therefore not proven.

Health status (visual analogue scale [VAS] of the European Quality of Life Questionnaire 5 Dimensions [EQ-5D])

For the outcome "health status" recorded using the EQ-5D VAS, there was heterogeneity between GEMINI-1 and GEMINI-2 ($p < 0.05$) without effects in the same direction. Due to the heterogeneous study situation, no pooled presentation of the results is provided. GEMINI-1 shows a statistically significant difference in favour of DTG/3TC versus DTG + TDF/FTC. In the GEMINI-2 study, there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for this outcome; an added benefit is therefore not proven.

Health-related quality of life

The outcome "health-related quality of life" was not investigated in the studies GEMINI-1 and GEMINI-2. This resulted in no hint of an added benefit of DTG + 3TC in comparison with DTG + TDF/FTC; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), severe adverse events (severe AEs) (DAIDS grade 3–4) and discontinuation due to adverse events

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "SAEs", "severe AEs" (Division of AIDS (DAIDS grade 3–4) and "discontinuation due to AEs". Hence, for these outcomes, there was no hint of greater or lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC; greater or lesser harm is therefore not proven for these outcomes.

Specific AEs

Gastrointestinal disorders, including: nausea

The meta-analysis showed a statistically significant difference in favour of DTG + 3TC versus DTG + TDF/FTC for the outcome "gastrointestinal disorders". However, the effect is no more than marginal. This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for the said outcome. Greater or lesser harm is therefore not proven.

For the outcome "nausea", the meta-analysis showed a statistically significant difference in favour of DTG + 3TC versus DTG + TDF/FTC. This resulted in a proof of lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for the outcome "nausea".

Skin and subcutaneous tissue disorders, nervous system disorders

The meta-analysis showed no statistically significant difference between the treatment groups for each of the outcomes "skin and subcutaneous tissue disorders" and "nervous system disorders". Hence, there was no hint of greater or lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC; greater or lesser harm is therefore not proven for these outcomes.

Psychiatric disorders, including: insomnia

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "psychiatric disorders". For the outcome "insomnia", the meta-analysis showed a statistically significant difference in favour of DTG + 3TC versus DTG + TDF/FTC. However, the effect is no more than marginal. Overall, there was no hint of greater or lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for the two outcomes "psychiatric disorders" and "insomnia"; greater or lesser harm is therefore not proven for these outcomes.

Results for research question 2 (pretreated adults)

Study pool and study characteristics

The study pool for the benefit assessment of DTG/3TC in pretreated HIV-1 infected adults consisted of the ASPIRE study.

The ASPIRE study was a 48-week open-label, randomized parallel group study on pretreated and virologically suppressed HIV-1 infected adults (HIV-1 ribonucleic acid (RNA) viral load < 50 copies/mL ≥ 48 weeks before start of the study and < 20 copies/mL at screening). The study compared DTG + 3TC with a continuation of the ongoing treatment.

A total of 90 patients were randomly allocated to treatment with DTG + 3TC (N = 45) or continuation of their ongoing antiretroviral therapy (ART) (N = 45) in a 1:1 ratio.

Patients of the ASPIRE study were attributed to the subpopulation of pretreated adults without indication for a treatment switch. There are no indications implying that treatment switch was indicated, for instance, due to side effects. Continuation of the ongoing individual treatment in the comparator arm of the ASPIRE study was thus considered to be an adequate implementation of the ACT specified by the G-BA. Relevant studies for patients with an indication for treatment switch were not available.

Risk of bias

The risk of bias across outcomes and the outcome-specific risk of bias were rated as high.

Mortality

All-cause mortality

Until week 48, no deaths occurred in the ASPIRE study. This resulted in no hint of an added benefit of DTG + 3TC in comparison with continuation of ongoing treatment for the outcome "overall survival". An added benefit is therefore not proven.

Morbidity

AIDS-defining events (CDC class C), supplementary consideration of the surrogate outcomes "virologic response", "virologic failure" and "$CD4^+$ cell count"

There are no results for the outcome "AIDS-defining events (CDC class C)". No statistically significant difference between the treatment groups was shown for the outcomes "virologic response" and "$CD4^+$ cell count" presented as supplementary information. At week 48, there were no results for the outcome "virologic failure" presented as supplementary information. This resulted in no hint of an added benefit of DTG + 3TC in comparison with continuation of the ongoing treatment for the outcome "AIDS-defining events (CDC class C)". An added benefit is therefore not proven.

Health-related quality of life

The outcome "health-related quality of life" was not investigated in the ASPIRE study. This resulted in no hint of an added benefit of DTG + 3TC in comparison with "continuation of ongoing treatment". An added benefit is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with continuation of ongoing treatment for these outcomes. Hence, greater or lesser harm is not proven for these outcomes.

Severe AEs (DAIDS grade 3–4)

There are no usable data for the outcome "severe AEs (DAIDS grade 3−4)" due to possible multiple answers per patient. This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with continuation of ongoing treatment for this outcome. Hence, greater or lesser harm is not proven for this outcome.

Specific AEs

The ASPIRE study yielded no results on the specific AEs "gastrointestinal disorders", "skin and subcutaneous tissue disorders", "nervous system disorders" and "psychiatric disorders". This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with continuation of ongoing treatment for these outcomes. Hence, greater or lesser harm is not proven for these outcomes.

Results for research question 3 (treatment-naive adolescents)

For the derivation of an added benefit, the company transferred the results of GEMINI-1 and GEMINI-2 in treatment-naive HIV-1 infected adults to the target population of treatment-naive HIV-1 infected adolescents. The company's approach to transfer study results for adults to adolescents is comprehensible as there are no comparative data for adolescents; however, the concrete implementation was inadequate:

- The company presented no data for treatment-naive adolescents.
- With the GEMINI-1 and GEMINI-2 studies, the company additionally used RCTs in which patients in the comparator arm were treated with the ACT "DTG + TDF/FTC" specified for treatment-naive adults. However, this does not correspond to the ACT for treatment-naive HIV-1-infected adolescents. TDF is thus explicitly not part of the ACT for treatment-naive HIV-1-infected adolescents.

In summary, this resulted in no hint of an added benefit of DTG/3TC in comparison with the ACT for treatment-naive HIV-1 infected adolescents. An added benefit of DTG/3TC in comparison with the ACT is therefore not proven for these patients.

Results for research question 4 (pretreated adolescents)

The company presented no data for the assessment of the added benefit of DTG/3TC in comparison with the ACT in pretreated HIV-1 infected adolescents. This resulted in no hint of an added benefit of DTG/3TC in comparison with the ACT. An added benefit of DTG/3TC in comparison with the ACT is therefore not proven for these patients.

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

Based on the results presented, probability and extent of the added benefit of the drug DTG/3TC in comparison with the ACT are assessed as follows:

Research question 1 (treatment-naive adults)

On the side of the positive effects, the overall consideration of the results shows proof of lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for treatment-naive HIV-1 infected[4] adults. This positive effect with the extent "minor" was shown for the non-serious/non-severe side effects of the outcome "nausea".

In summary, this resulted in a proof of minor added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for treatment-naive HIV-1 infected[4] adults.

Research question 2 (pretreated adults)

The overall consideration of the results revealed neither positive nor negative effects of DTG + 3TC in comparison with continuation of ongoing treatment.

In summary, there was no hint of an added benefit of DTG + 3TC in comparison with continuation of ongoing treatment for pretreated HIV-1 infected[5] adults without an indication for treatment switch.

No data for the assessment of the added benefit were available for pretreated HIV-1 infected[5] adults with indication for a treatment switch. This resulted in no hint of an added benefit for this population; an added benefit is therefore not proven.

[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].

[4] The HI virus was not to have any known or suspected resistances to the INI class or 3TC.

[5] Adolescents aged 12 years and older with a body weight of at least 40 kg. The HI virus must not show any known or suspected resistance to the class of INIs or 3TC. The HI virus was not to have any known or suspected resistances to the INI class or 3TC.

Research question 3 (treatment-naive adolescents)

The company presented no suitable data for the assessment of the added benefit of DTG/3TC in comparison with the ACT in treatment-naive HIV-1 infected adolescents[5]. This resulted in no hint of an added benefit of DTG/3TC in comparison with the ACT for this research question; an added benefit is therefore not proven.

Research question 4 (pretreated adolescents)

The company presented no data for the assessment of the added benefit of DTG/3TC in comparison with the ACT in pretreated HIV-1 infected adolescents[5]. This resulted in no hint of an added benefit of DTG/3TC in comparison with the ACT for this research question; an added benefit is therefore not proven.

Summary

Table 3 presents a summary of probability and extent of the added benefit of DTG/3TC.

Table 3: DTG/3TC – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adults infected with HIV-1[b]	Rilpivirine in combination with TDF/tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or **DTG in combination with TDF**/tenofovir alafenamide **plus FTC** or in combination with abacavir plus lamivudine	Proof of minor added benefit
2	Pretreated adults infected with HIV-1[b]	Individual ART depending 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	
	With indication for a treatment switch		Added benefit not proven
	Without indication for a treatment switch		Added benefit not proven
3	Treatment-naive adolescents[c] infected with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or DTG in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus lamivudine	Added benefit not proven
4	Pretreated adolescents[c] infected with HIV-1[b]	Individual ART depending 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

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI virus must not have any known or suspected resistances to the INI class or 3TC.
c: Twelve years of age and older and with a body weight of at least 40 kg.
3TC: lamivudine; ACT: appropriate comparator therapy; ART: antiretroviral therapy; DTG: dolutegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; TDF: tenofovir disoproxil

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of DTG/3TC in comparison with the ACT in adults and adolescents (12 years of age and older and with a body weight of at least 40 kg) infected with HIV-1. The HI virus was not to have any known or suspected resistances to the class of INI or 3TC.

Four research questions resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of DTG/3TC

Research question	Subindication	ACT[a]
1	Treatment-naive adults infected with HIV-1[b]	Rilpivirine in combination with TDF/tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or **DTG in combination with TDF**/tenofovir alafenamide **plus FTC** or in combination with abacavir plus lamivudine
2	Pretreated adults infected with HIV-1[b]	Individual ART depending 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-naive adolescents[c] infected with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or DTG in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus lamivudine
4	Pretreated adolescents[c] infected with HIV-1[b]	Individual ART depending 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

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI virus was not to have any known or suspected resistances to the INI class or 3TC.
c: Twelve years of age and older and with a body weight of at least 40 kg.
3TC: lamivudine; ACT: appropriate comparator therapy; ART: antiretroviral therapy; DTG: dolutegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; TDF: tenofovir disoproxil

The company followed the G-BA's specification of the ACT for all research questions.

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

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 DTG/3TC (status: 2 May 2019)
- bibliographical literature search on DTG/3TC (last search on 2 May 2019)

- search in trial registries for studies on DTG/3TC (last search on 2 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/3TC (last search on 15 July 2019)

The check identified no additional relevant study.

2.3.1.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
204861 (GEMINI-1[b])	Yes	Yes	No
205543 (GEMINI-2[b])	Yes	Yes	No

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this abbreviated form.
3TC: lamivudine; DTG: dolutegravir; FTC: emtricitabine; RCT: randomized controlled trial; TDF: tenofovir disoproxil; vs.: versus

The study pool for the benefit assessment of DTG/3TC in treatment-naive HIV-1 infected adults consisted of the studies 204861 and 205543 (hereinafter referred to as GEMINI-1 or GEMINI-2). In the studies, DTG and 3TC were administered as free combination (DTG +3TC). This concurs with the company's study pool.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
GEMINI-1	RCT, double-blind[b], parallel	HIV-1 infected adults not pretreated with an antiretroviral drug[c] (≥ 18 years) with an HIV-1 RNA viral load of 1000 to 500 000[c] copies/mL at screening	▪ DTG + 3TC (N = 359)[e] ▪ DTG + TDF/FTC (N = 360)[e]	▪ Screening: 28–35 days before start of the study ▪ treatment: 148 weeks[b] ▪ observation: 4 weeks after last dose	87 centres in: Argentina, Australia, Belgium, Canada, France, Germany, Italy, Mexico, The Netherlands, Portugal, Romania, Russia, South Africa, South Korea, Spain, Taiwan, United Kingdom, USA 07/2016–ongoing (data cut-off at week 48: 22 May 2018)	primary: proportion of patients with viral load < 50 RNA copies/mL at week 48 secondary: mortality, morbidity, AEs
GEMINI-2	RCT, double-blind[b], parallel	HIV-1 infected adults not pretreated with an antiretroviral drug[c] (≥ 18 years) with an HIV-1 RNA viral load of 1000 to 500 000[c] copies/mL at screening	▪ DTG + 3TC (N = 360) ▪ DTG + TDF/FTC (N = 362)[f]	▪ Screening: 28–35 days before start of the study ▪ treatment: 148 weeks[b] ▪ observation: 4 weeks after last dose	104 centres in: Argentina, Australia, Belgium, Canada, France, Germany, Italy, Mexico, Peru, Poland, Portugal, Romania, Russia, Spain, Switzerland, Taiwan, United Kingdom, USA 07/2016–ongoing (data cut-off at week 48: 22 May 2018)	primary: proportion of patients with viral load < 50 RNA copies/mL at week 48 secondary: mortality, morbidity, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults) (continued)

a: Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
b: Double-blind treatment until week 96, followed by unblinding and further treatment with the randomized study medication until week 148. After week 148, patients in the intervention arm were allowed to continue treatment with DTG + 3TC.
c: Pretreatment with ART ≤ 10 days (prophylactic treatment before/after exposure was allowed if the last dose had been administered ≥ 1 year before HIV diagnosis or in case of documented seronegativity between dosage and HIV diagnosis).
d: When the study started, only patients with a maximum HIV viral load of 100 000 copies/mL were included; in November 2016, the upper limit was raised to 500 000 copies/mL.
e: 3 of the 359 randomized patients in the DTG + 3TC arm or 2 of the 360 randomized patients in the comparator arm received no study medication and were excluded from the analyses.
f: 3 of the 362 randomized patients received no study mediation and were excluded from the analyses.

3TC: lamivudine; AE: adverse event; ART: antiretroviral therapy; DTG: dolutegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; N: number of randomized patients; RCT: randomized controlled trial; RNA: ribonucleic acid; TDF: tenofovir disoproxil; vs.: versus

Table 7: Characteristics of the intervention – DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Study	Intervention	Comparison
GEMINI-1	DTG 50 mg + 3TC 300 mg once daily, orally	DTG 50 mg + TDF 300 mg/FTC 200 mg once daily, orally
	prohibited prior/concomitant treatment ▪ further HIV-1 therapies[a] ▪ HIV vaccines ≤ 90 days before screening and during the study ▪ radiotherapy, cytotoxic chemotherapy and any systemic immunosuppressants[b] ≤ 28 days before screening and during the study ▪ expectable start of any hepatitis C treatment until week 48 as well as hepatitis C therapies based on interferon or other substances with a potential of interaction with the study medication over the entire study duration ▪ acetaminophen in patients with acute viral hepatitis during the study ▪ chronic application of systemic glucocorticoids during the study[c] ▪ at least 6 hours before and 2 hours after administration of DTG: polyvalent cation-containing antacids, dietary supplements containing calcium or iron ▪ drugs which could lower the DTG concentration (e.g: carbamazepine, St. John's Wort, oxcarbamazepine, phenobarbital, phenytoin, rifampicin, rifapentine) ≤ 30 days prior to and during the study ▪ dofetilide and pilsicainide **permitted concomitant treatment** ▪ chemoprophylaxis for HIV-associated diseases at the investigator's discretion	
GEMINI-2	DTG 50 mg + 3TC 300 mg once daily, orally	DTG 50 mg + TDF 300 mg/FTC 200 mg once daily, orally
	Pretreatment and concomitant treatment see information on GEMINI-1	

a: With regard to pretreatment, PrEP or PEP were excluded up to 1 year prior to screening if the last dose had been administered ≥ 1 year prior to HIV diagnosis or if seronegativity had been documented between the last prophylactic dose and HIV-1 diagnosis. Moreover, patients who had been treated with any antiretroviral therapy after diagnosis of an HIV-1 infection for ≤ 10 days before the start of the study were allowed to participate in the study.
b: Topical application of imiquimod was allowed.
c: Topical, inhalative and intranasal application as well as short-term oral treatment (≤ 14 days) with prednisone, prednisolone or methylprednisolone were allowed
3TC: lamivudine; DTG: dolutegravir; FTC: emtricitabine; HIV: human immunodeficiency virus; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; TDF: tenofovir disoproxil

The studies GEMINI-1 and GEMINI-2 were double-blind, randomized parallel-group studies on treatment-naive HIV-1 infected adults with identical design. The HIV-1 RNA viral load of the patients had to be 1000 to 500 000 copies/mL at screening.

According to the company, screening for resistances of the HI virus is based on the recommendations of the International Antiviral Society-USA Panel [3]. According to this, patients showing signs of resistances listed there at or prior to the time of screening were excluded from the study.

Both studies compare DTG + 3TC with treatment with the free combination of DTG and the fixed combination of TDF and FTC.

In GEMINI-1, a total of 719 patients were randomly allocated to treatment with the free combination of DTG + 3TC (N = 359) or treatment with DTG + TDF/FTC (N = 360) in a 1:1 ratio. In GEMINI-2, a total of 722 patients were randomly allocated to treatment with DTG + 3TC (N = 360) or DTG + TDF/FTC (N = 362) also in a 1:1 ratio. Stratification in both studies was by HIV-1 RNA viral load (≤ 100 000 copies/mL and > 100 000 copies/mL) and CD4+ cell count (≤ 200 cells/mm^3 and > 200 cells/mm^3).

In both studies, dosage was in compliance with the respective SPC [4-6].

Primary outcome of both studies was the virologic response (HIV-1 RNA viral load < 50 copies/mL) at week 48. Patient-relevant outcomes were “mortality”, “morbidity” and “AEs”.

Both studies are ongoing. Randomized treatment duration of each study was 148 weeks; after 96 weeks, the study was unblinded. However, at the date of the benefit assessment, results on the date of analysis of 48 weeks were available. These were used for the present assessment.

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations– RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Study Characteristics Category	GEMINI-1		GEMINI-2	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
	N[a] = 356	N[a] = 358	N[a] = 360	N[a] = 359
Age [years], median [min; max]	32 [18; 69]	33 [18; 66]	32 [18; 72]	33 [18; 70]
Sex [F/M], %	17/83	15/85	15/85	13/87
Family origin, n (%)				
white	243 (68)	248 (69)	237 (66)	249 (69)
black	44 (12)	36 (10)	55 (15)	40 (11)
Asian	37 (10)	42 (12)	34 (9)	30 (8)
other	32 (9)	32 (9)	34 (9)	40 (11)
HIV-1 RNA viral load at baseline, n (%)				
< 100 000 copies/mL	282 (79)[b]	282 (79)[b]	294 (82)[b]	282 (79)[b]
≥ 100 000 copies/mL	74 (21)[b]	76 (21)[b]	66 (18)[b]	77 (21)[b]
$CD4^+$ cell count/mm^3 at baseline, median [min; max]	427.0 [19; 1399]	435.5 [19; 1305]	427.5 [19; 1364]	442.0 [19; 1497]
$CD4^+$ cell count/mm^3 at baseline, n (%)				
< 350	123 (35)[b]	108 (30)[b]	119 (33)[b]	112 (31)[b]
≥ 350	233 (65)[b]	250 (70)[b]	241 (67)[b]	247 (69)[b]
HIV disease stage (CDC category)[c], n (%)				
A: Asymptomatic	128 (36)	126 (35)	129 (36)	137 (38)
B: Symptomatic	194 (54)	204 (57)	198 (55)	189 (53)
C: AIDS	33 (9)	28 (8)	33 (9)	32 (9)
Treatment discontinuation, n (%)	31 (9)	24 (7)	22 (6)	20 (6)
Study discontinuation, n (%)[d]	ND	ND	ND	ND

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: For 1 patient, allocation to one of the CDC categories A–C was impossible.
d: It is not clear whether a treatment discontinuation corresponds to a study discontinuation.
3TC: lamivudine; AIDS: acquired immunodeficiency syndrome; $CD4^+$: cluster of differentiation 4-positive; CDC: Centers for Disease Control and Prevention; DTG: dolutegravir; F: female; FTC: emtricitabine; HIV: human immunodeficiency virus; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; RNA: ribonucleic acid; TDF: tenofovir disoproxil; vs.: versus;

The demographic and clinical characteristics were essentially balanced, both between the individual study arms and between the two studies. Median age of the patients was 32 to 33 years, most of them were male (about 85%) and white (about 68%). Regarding their HIV disease stage, most of the patients were symptomatic (about 55%), less than 10% had AIDS.

Until week 48, less than 10% of the patients in both studies discontinued treatment with the study medication.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
GEMINI-1	yes	yes	yes	yes	yes	yes	low
GEMINI-2	yes	yes	yes	yes	yes	yes	low

3TC: lamivudine; DTG: dolutegravir; FTC: emtricitabine; RCT: randomized controlled trial; TDF: tenofovir disoproxil; vs.: versus

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.4.3.2 of the full dossier assessment):

- mortality
  - All-cause mortality
- morbidity
  - AIDS-defining events (CDC class C)
  - presented as supplementary information: virologic response, virologic failure and CD4+-positive cells as surrogate outcomes for the patient-relevant outcome "AIDS-defining diseases/death"
  - Health status (EQ-5D VAS)
- health-related quality of life
- side effects
  - SAEs

- severe AEs (DAIDS grade 3-4)
- discontinuation due to AEs
- gastrointestinal disorders (System Organ Class [SOC])
- skin and subcutaneous tissue disorders (SOC)
- nervous system disorders (SOC)
- psychiatric disorders (SOC)
- if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.8.4.3.2 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of the outcomes – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Study	Outcomes														
	All-cause mortality	AIDS-defining events (CDC class C)	Virologic response[a]	Virologic failure[a]	$CD4^+$ cell count[a]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs (DAIDS grade 3–4)	Discontinuation due to AEs	Gastrointestinal disorders (SOC)[b]	Skin and subcutaneous tissue disorders (SOC)[b]	Nervous system disorders (SOC)[b]	Psychiatric disorders (SOC)[b]	Further specific AEs
GEMINI-1	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GEMINI-2	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Virologic response and virologic failure (analysis according to FDA snapshot algorithm) and $CD4^{+-}$ cell count are presented as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" as supplementary information.
b: MedDRA coding
c: Outcome not recorded.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4+: cluster of differentiation 4-positive; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; FDA: Food and Drug Administration; FTC: emtricitabine; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Study		Outcomes														
	Study level	All-cause mortality	AIDS-defining events (CDC class C)	Virologic response[a]	Virologic failure[a]	$CD4^+$ cell count[a]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs (DAIDS grade 3–4)	Discontinuation due to AEs	Gastrointestinal disorders (SOC)[b]	Skin and subcutaneous tissue disorders (SOC)[b]	Nervous system disorders (SOC)[b]	Psychiatric disorders (SOC)[b]	Further specific AEs
GEMINI-1	L	L	L	L	L	L	L	-[c]	L	L	L	L	L	L	L	L
GEMINI-2	L	L	L	L	L	L	L	-[c]	L	L	L	L	L	L	L	L

a: Virologic response and virologic failure (analysis according to FDA snapshot algorithm) and $CD4^{+-}$ cell count are presented as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" as supplementary information.
b: MedDRA coding
c: Outcome not recorded.
3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4+: cluster of differentiation 4-positive; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; FDA: Food and Drug Administration; FTC: emtricitabine; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

The risk of bias for the results of the outcomes considered in both studies was rated as low. The outcome "health-related quality of life" was not recorded in the studies.

2.3.2.3 Results

Table 12 and Table 13 summarize the results of the comparison of DTG + 3TC with DTG + TDF/FTC in treatment-naive HIV-1 infected adults. Where necessary, calculations

conducted by the Institute are provided in addition to the data from the company's dossier. Forest plots of the meta-analysis calculated by the Institute can be found in Appendix A (of the full dossier assessment). Tables on common AEs, common SAEs and common discontinuations due to AEs are presented in Appendix B (of the full dossier assessment). Severe AEs (DAIDS grade 3–4) are not presented in Appendix B, because events with a frequency of > 5% did not occur in a study arm.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Outcome category Outcome Study	DTG + 3TC N	 Patients with event n (%)	DTG + TDF/FTC N	 Patients with event n (%)	DTG + 3TC vs. DTG + TDF/FTC RR [95% CI]; p-value[a, b]
Mortality					
All-cause mortality					
GEMINI-1	356	0 (0)	358	0 (0)	NC
GEMINI-2	360	2 (< 1)	359	0 (0)	4.99 [0.24; 103.49]; 0.299
Morbidity					
AIDS-defining events (CDC class C)					
GEMINI-1	356	4 (1)	358	2 (< 1)	1.97 [0.37; 10.60]; 0.430
GEMINI-2	360	2 (< 1)	359	1 (< 1)	1.93 [0.18; 21.23]; 0.590
Total					1.96 [0.50; 7.72]; 0.338
Additional information: surrogate outcome “virologic response” (HIV-1 RNA < 50 copies/mL)[c]					
GEMINI-1	356	320 (90)	358	332 (93)	0.97 [0.93; 1.02]; 0.210
GEMINI-2	360	335 (93)	359	337 (94)	1.00 [0.96; 1.05]; 0.904
Total					0.99 [0.96; 1.01]; 0.342
Additional information: surrogate outcome “virologic failure” (HIV-1 RNA ≥ 50 copies/mL)[c]					
GEMINI-1	356	13 (4)	358	6 (2)	2.13 [0.82; 5.53]; 0.118
GEMINI-2	360	7 (2)	359	7 (2)	0.99 [0.35; 2.77]; 0.978
Total					1.50 [0.74; 3.02]; 0.295
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)					
GEMINI-1	356	276 (78)	358	295 (82)	—
GEMINI-2	360	267 (74)	359	284 (79)	—
SAEs[d]					
GEMINI-1	356	21 (6)	358	22 (6)	0.96 [0.5[4]; 1.71]; 0.882
GEMINI-2	360	27 (8)	359	33 (9)	0.82 [0.50; 1.33]; 0.422
Total					0.88 [0.60; 1.27]; 0.486
Severe AEs (DAIDS grade 3–4)					
GEMINI-1	356	21 (6)	358	24 (7)	0.88 [0.50; 1.55]; 0.654
GEMINI-2	360	26 (7)	359	32 (9)	0.81 [0.49; 1.33]; 0.407
Total					0.84 [0.58; 1.22]; 0.361

(continued)

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults) (continued)

Outcome category Outcome Study	DTG + 3TC N	 Patients with event n (%)	DTG + TDF/FTC N	 Patients with event n (%)	DTG + 3TC vs. DTG + TDF/FTC RR [95% CI]; p-value[a, b]
Discontinuation due to AEs					
GEMINI-1	356	7 (2)	358	8 (2)	0.88 [0.32; 2.40]; 0.803
GEMINI-2	360	8 (2)	359	8 (2)	1.00 [0.38; 2.64]; 0.994
Total					0.94 [0.47; 1.89]; 0.863
Gastrointestinal disorders (SOC, AE)					
GEMINI-1	356	103 (29)	358	127 (35)	0.81 [0.66; 1.01]; 0.060
GEMINI-2	360	105 (29)	359	118 (33)	0.88 [0.71; 1.10]; 0.259
Total					0.84 [0.72; 0.98]; 0.029
Nausea (PT, AE)					
GEMINI-1	356	12 (3)	358	30 (8)	0.40 [0.21; 0.77]; 0.005
GEMINI-2	360	15 (4)	359	23 (6)	0.65 [0.35; 1.23]; 0.247
Total					0.51 [0.32; 0.80]; 0.004
Skin and subcutaneous tissue disorders (SOC, AE)					
GEMINI-1	356	51 (14)	358	52 (15)	0.99 [0.70; 1.42]; 0.970
GEMINI-2	360	42 (12)	359	48 (13)	0.87 [0.60; 1.28]; 0.479
Total					0.93 [0.72; 1.21]; 0.594
Nervous system disorders (SOC, AE)					
GEMINI-1	356	57 (16)	358	76 (21)	0.75 [0.55; 1.03]; 0.075
GEMINI-2	360	53 (15)	359	57 (16)	0.92 [0.65; 1.30]; 0.641
Total					0.82 [0.65; 1.04]; 0.099
Psychiatric disorders (SOC, AE)					
GEMINI-1	356	54 (15)	358	60 (17)	0.91 [0.65; 1.27]; 0.564
GEMINI-2	360	41 (11)	359	45 (13)	0.91 [0.61; 1.36]; 0.656
Total					0.91 [0.70; 1.18]; 0.472
Insomnia (PT, AE)					
GEMINI-1	356	16 (5)	358	29 (8)	0.55 [0.31; 1.00]; 0.048
GEMINI-2	360	11 (3)	359	16 (5)	0.69 [0.32; 1.46]; 0.530
Total					0.60 [0.38; 0.96]; 0.032

(continued)

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults) (continued)

a: Unclear modelling, adjustment for $CD4^+$ cell count (≤ 200 vs. > 200 cells/mm^3) and viral load (≤ 100 000 vs. > 100 000 copies/mL) each at baseline; test statistics unclear
b: Overall effect (meta-analysis with fixed effect).
c: Analysis according to FDA snapshot algorithm.
d: without fatal SAEs

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; $CD4^+$: Cluster-of-Differentiation-4-positive; CDC: Centers for Disease Control and Prevention; CI: confidence interval; DAIDS: Division of AIDS; DTG: dolutegravir; FDA: Food and Drug Administration; FTC: emtricitabine; HIV: human immunodeficiency virus; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; PT: preferred term; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; SOC: system organ class; TDF: tenofovir disoproxil; vs.: versus

Table 13: Results (morbidity, continuous) – RCT, direct comparison: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Outcome category Outcome Study	DTG + 3TC N[a]	Values at baseline mean (SD)	Change at week 48 mean (SD)	DTG + TDF/FTC N[a]	Values at baseline mean (SD)	Change at week 48 mean (SD)	DTG + 3TC vs. DTG + TDF/FTC MD [95% CI]; p-value
Morbidity							
Health status (EQ-5D VAS)							
GEMINI-1	352	87.4 (11.61)	3.5 (11.64)	350[b]	84.6 (13.93)	3.7 (12.80)	1.5 [0.1; 2.8]; 0.031[c]
GEMINI-2	359[b]	85.6 (12.41)	4.0 (10.38)	358	85.7 (12.89)	4.5 (11.92)	−0.6 [−1.9; 0.6]; 0.328[c]
Total	heterogeneity: Q = 5.0; df = 1; p = 0.025; I^2 = 80.0%[d]						
Supplementary information: surrogate outcome $CD4^+$ cell count/mm^3							
GEMINI-1	324	464.2 (222.5)	223.8 (178.1)	334	453.6 (195.6)	217.3 (195.4)	4.55 [-23.94; 33.05]; 0.754[e]
GEMINI-2	337	459.8 (216.2)	224.3 (166.4)	340	469.0 (229.2)	216.9 (185.7)	8.55 [-17.70; 34.80]; 0.523[e]
Total							6.71 [-12.59; 26.02]; 0.496[d]

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b: Discrepancy between information in Module 4 and Module 5 of the dossier. The presented figures were taken from additional analyses in Module 5.
c: MMRM adjusted for treatment, visit, baseline plasma- HIV-1 RNA, baseline $CD4^+$-cell count, baseline EQ-5D VAS as well as interactions between treatment and visit, baseline EQ-5D VAS and visit.
d: Institute's calculation. Meta-analysis with fixed effect (inverse variance method).
e: MMRM adjusted for treatment, visit, baseline plasma HIV-1 RNA, baseline $CD4^+$ cell count as well as interactions between treatment and visit, baseline $CD4^+$ cell count and visit.

3TC: lamivudine; CD4+: cluster of differentiation 4-positive; CI: confidence interval; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; FTC: emtricitabine; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

Based on the available data, at most proof, e.g. of an added benefit, can be derived from the meta-analysis of the studies GEMINI-1 and GEMINI-2 (see Section 2.3.2.2). This concurs with the company's assessment.

Mortality

All-cause mortality

Up to week 48, no deaths occurred in the GEMINI-1 study. Two patients died in the intervention arm of GEMINI-2. There was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of DTG + 3TC in comparison

with DTG + TDF/FTC for the outcome "all-cause mortality"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

AIDS-defining events (CDC class C), supplementary consideration of the surrogate outcomes "virologic response", "virologic failure" and "CD4$^+$ cell count"

The meta-analysis shows no statistically significant difference between the treatment groups, neither for the outcome "CDC class C AIDS-defining events" nor for the outcomes "virologic response", "virologic failure" and "CD4$^+$ cell count" presented as supplementary information. This resulted in no hint of an added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for the outcome "AIDS-defining events (CDC class C)"; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

For the outcome "health status" recorded using the EQ-5D VAS, there was heterogeneity between GEMINI-1 and GEMINI-2 ($p < 0.05$) without effects in the same direction. Due to the heterogeneous evidence base, no pooled presentation of the results is provided. GEMINI-1 shows a statistically significant difference in favour of DTG/3TC versus DTG + TDF/FTC. In the GEMINI-2 study, there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for the outcome "health status"; an added benefit is therefore not proven.

This concurs with the assessment of the company, which allocated the outcome "health status (EQ-5D VAS)" to health-related quality of life, however.

Health-related quality of life

The outcome "health-related quality of life" was not investigated in the studies GEMINI-1 and GEMINI-2. This resulted in no hint of an added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for this outcome; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also derived no added benefit for "health-related quality of life", but used the results of the EQ-5D VAS and the EQ-5D utility score instead.

Side effects

SAEs, severe AEs (DAIDS grade 3–4) and discontinuation due to AEs

The meta-analysis showed no statistically significant difference between the treatment groups for the outcomes "SAEs", "severe AEs" (DAIDS grade 3–4) and "discontinuation due to AEs". Hence, for these outcomes, there was no hint of greater or lesser harm from DTG + 3TC in

comparison with DTG + TDF/FTC; greater or lesser harm is therefore not proven for these outcomes.

This concurs with the company's assessment.

Specific AEs

Gastrointestinal disorders, including: nausea

The meta-analysis showed a statistically significant difference in favour of DTG + 3TC versus DTG + TDF/FTC for the outcome "gastrointestinal disorders". However, the effect is no more than marginal. This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for the said outcome. Greater or lesser harm is therefore not proven.

For the outcome "nausea", the meta-analysis showed a statistically significant difference in favour of DTG + 3TC versus DTG + TDF/FTC. This resulted in a proof of lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for the outcome "nausea".

This assessment deviates from that of the company, which derived proof of minor added benefit for the outcome "gastrointestinal disorders" and did not include the PT "nausea" in its assessment.

Skin and subcutaneous tissue disorders, nervous system disorders

The meta-analysis showed no statistically significant difference between the treatment groups for each of the outcomes "skin and subcutaneous tissue disorders" and "nervous system disorders". Hence, there was no hint of greater or lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC; greater or lesser harm is therefore not proven for these outcomes.

This concurs with the company's assessment.

Psychiatric disorders, including: insomnia

The meta-analysis showed no statistically significant difference between the treatment groups for the outcome "psychiatric disorders". For the outcome "insomnia", the meta-analysis showed a statistically significant difference in favour of DTG + 3TC versus DTG + TDF/FTC. However, the effect is no more than marginal. Overall, there was no hint of greater or lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for the two outcomes "psychiatric disorders" and "insomnia"; greater or lesser harm is thus not proven for these outcomes.

For the outcome "psychiatric disorders", this corresponds to the company's assessment. The company did not use the outcome "insomnia" for the derivation of the added benefit.

2.3.2.4 Subgroups and other effect modifiers

The following prespecified effect modifiers were considered in the present benefit assessment:

- Sex (female/male)

- Age (< 35 years/35 years to 50 years/≥ 50 years)
- Family origin (white/Afro-American or African family origin/Asian family origin/other)
- HIV-1 RNA viral load at start of study (≤ 100 000/> 100 000 copies/mL)

In both GEMINI-1 and GEMINI-2, the mentioned characteristics with the corresponding subgroups were prespecified only for the surrogate outcomes "CD4+ cell count" and "virologic response" presented as supplementary information. Interaction tests with the prespecified subgroups on all considered potential effect modifiers could only be performed for these outcomes. For the remaining outcomes included, results were only available for the prespecified subgroup characteristics "age" and "HIV-1 RNA viral load at baseline". In module 4 A, the company considered the post hoc subgroups "white" and "non-white" for the characteristic "family origin", and the post hoc subgroups "< 35 years" and "≥ 35 years" for the characteristic "age". The company did not provide sufficient justification for the use of these post hoc subgroups.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least 1 subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Effect modifications cannot be derived from the available subgroup results.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2 (see Table 14).

Determination of the outcome category for the outcomes on side effects

For all outcomes considered in the present benefit assessment, it cannot be inferred from the dossier whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Determination of the outcome category for the specific AEs "gastrointestinal disorders", "nausea" and "insomnia"

All occurring events of the specific AEs "nausea" and "insomnia" were non-serious/non-severe. For the specific AE "diseases of the gastrointestinal tract", the events that occurred were mostly non-serious/non-severe. The outcomes were therefore allocated to the category "non-serious/non-severe side effects". The company did not rate the severity level for the outcome "gastrointestinal tract diseases". The company did not include the outcomes "nausea" and "insomnia" in its assessment.

Table 14: Extent of added benefit at outcome level: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults)

Outcome category **Outcome**	**DTG + 3TC vs. DTG + TDF/FTC** **proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0-< 1% vs. 0%[c] RR: –	Lesser benefit/added benefit not proven
Morbidity		
AIDS-defining events (CDC class C)	< 1-1% vs. < 1%[c] RR: 1.96 [0.50; 7.72]; p = 0.338	Lesser benefit/added benefit not proven
Supplementary information:		
Virologic response[d]	90-93% vs. 93-94%[c] RR: 0.99 [0.96; 1.01]; p = 0.342	
Virologic failure[d]	2-4% vs. 2%[c] RR: 1.50 [0.74; 3.02]; p = 0.295	
$CD4^+$ cell count/mm^3	Change (mean): 223.8-224.3 vs. 216.9-217.3[c] MD: 6.71 [-12.59; 26.02]; p = 0.496	
Health status (EQ-5D VAS)	Change (mean): 3.5-4.0 vs. 3.7-4.5[c] MD: —[e]	lesser benefit/added benefit not proven
Health-related quality of life	Outcome not recorded	
Side effects		
SAEs	6-8% vs. 6-9%[c] RR: 0.88 [0.60; 1.27]; p = 0.486	Greater/lesser harm not proven
Severe AEs (DAIDS grade 3–4)	6-7% vs. 7-9%[c] RR: 0.84 [0.58; 1.22]; p = 0.361	Greater/lesser harm not proven
Discontinuation due to AEs	2% vs. 2%[c] RR: 0.94 [0.47; 1.89]; p = 0.863	Greater/lesser harm not proven
Gastrointestinal disorders (SOC, AE)	29% vs. 33-35%[c] RR: 0.84 [0.72; 0.98]; p = 0.029	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[f]

(continued)

Table 14: Extent of added benefit at outcome level: DTG + 3TC vs. DTG + TDF/FTC (treatment-naive adults) (continued)

Outcome category **Outcome**	**DTG + 3TC vs. DTG + TDF/FTC** **proportion of events (%) or MD** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Nausea (PT, AE)	3-4% vs. 6-8%[c] RR: 0.51 [0.32; 0.802]; p = 0.004 probability: "proof"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Skin and subcutaneous tissue disorders (SOC, AE)	12-14% vs. 13-15%[c] RR: 0.93 [0.72; 1.21]; p = 0.594	Greater/lesser harm not proven
Nervous system disorders (SOC, AE)	15-16% vs. 16-21%[c] RR: 0.82 [0.65; 1.04]; p = 0.099	Greater/lesser harm not proven
Psychiatric disorders (SOC, AE)	11-15% vs. 13-17%[c] RR: 0.91 [0.70; 1.18]; p = 0.472	Greater/lesser harm not proven
Insomnia (PT, AE)	3-5% vs. 5-8%[c] RR: 0.60 [0.38; 0.96]; p = 0.032	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ greater/lesser harm not proven[f]

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Minimum and maximum proportions of events or mean changes in each treatment arm in the included studies.
d: According to FDA snapshot algorithm.
e: No common effect estimation can be provided due to heterogeneous data. Since the effect estimations were not in the same direction, no added benefit was derived.
f: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; $CD4^+$: cluster of differentiation 4-positive; CI: confidence interval; CI_u: upper limit of confidence interval; DAIDS: Division of AIDS; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; FDA: Food and Drug Administration; FTC: emtricitabine; MD: mean difference; PT: Preferred Term; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; TDF: tenofovir disoproxil; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of DTG + 3TC versus DTG + TDF/FTC (treatment-naive adults)

Positive effects	Negative effects
Non-serious/non-severe side effects: ▪ nausea: proof of greater harm – extent: “minor”	–
3TC: lamivudine; DTG: dolutegravir; FTC: emtricitabine; TDF: tenofovir disoproxil; vs.: versus	

The overall consideration of the results shows proof of lesser harm from DTG + 3TC in comparison with DTG + TDF/FTC for treatment-naive HIV-1 infected adults. This positive effect with the extent “minor” was shown for the non-serious/non-severe side effects of the outcome “nausea”.

In summary, this resulted in a proof of minor added benefit of DTG + 3TC in comparison with DTG + TDF/FTC for treatment-naive HIV-1 infected[4] adults.

This concurs with the company’s assessment.

2.3.4 List of included studies

GEMINI-1

Cahn P, Madero JS, Arribas J, Antinori A, Ortiz R, Clarke AE et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovirdisoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019; 393(10167): 143-155.

ViiV Healthcare. An efficacy, safety, and tolerability study comparing dolutegravir plus lamivudine with dolutegravir plus tenofovir/emtricitabine in treatment naïve HIV infected subjects (Gemini 1): study details [online]. In: ClinicalTrials.gov. 18.04.2019 [Accessed: 23.07.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02831673.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults: clinical trial results [online]. In: EU Clinical Trials Register. 11.04.2019 [Accessed: 23.07.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-004418-95/results.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults [online]. In: EU Clinical Trials Register. [Accessed: 23.07.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004418-95.

ViiV Healthcare. An efficacy, safety, and tolerability study comparing dolutegravir plus lamivudine with dolutegravir plus tenofovir/emtricitabine in treatment naïve HIV infected subjects (Gemini 1): study details [online]. In: ClinicalTrials.gov. 18.04.2019 [Accessed: 23.07.2019]. URL: https://ClinicalTrials.gov/show/NCT02831673.

ViiV Healthcare. A phase III, randomized, double-blind, multicentre, parallelgroup, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults; study 204861; clinical study protocol amendment 01 [unpublished]. 2017.

ViiV Healthcare. A phase III, randomized, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults: week 48; study 204861; clinical study report [unpublished]. 2018.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infectedtreatment-naïve adults: study 204861; reporting and analysis plan [unpublished]. 2018.

ViiV Healthcare. A phase III, randomized, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults: study 204861; Zusatzanalysen [unpublished]. 2019.

GEMINI-2

Cahn P, Madero JS, Arribas J, Antinori A, Ortiz R, Clarke AE et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovirdisoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019; 393(10167): 143-155.

ViiV Healthcare. An efficacy, safety, and tolerability study comparing dolutegravir (DTG) plus lamivudine (3TC) with dolutegravir plus tenofovir/emtricitabine in treatment naïve HIV infected subjects (Gemini 2): study results [online]. In: ClinicalTrials.gov. 22.04.2019 [Accessed: 23.07.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02831764.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults: clinical trial results [online]. In: EU Clinical Trials Register. 13.04.2019 [Accessed: 23.07.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000459-28/results.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults [online]. In: EU Clinical Trials Register. [Accessed: 23.07.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000459-28.

ViiV Healthcare. An efficacy, safety, and tolerability study comparing dolutegravir (DTG) plus lamivudine (3TC) with dolutegravir plus tenofovir/emtricitabine in treatment naïve HIV infected subjects (Gemini 2): study details [online]. In: ClinicalTrials.gov. 22.04.2019 [Accessed: 23.07.2019]. URL: https://ClinicalTrials.gov/show/NCT02831764.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults [online]. In: Clinical Trials Peruvian Registry. [Accessed: 23.07.2019]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=030-16.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults: study 205543; clinical study protocol [unpublished]. 2016.

ViiV Healthcare. A phase III, randomized, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults: week 48; study 205543; clinical study report [unpublished]. 2018.

ViiV Healthcare. A phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infectedtreatment-naïve adults: study 205543; reporting and analysis plan [unpublished]. 2018.

ViiV Healthcare. A phase III, randomized, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults: study 205543; Zusatzanalysen [unpublished]. 2019.

2.4 Research question 2: pretreated adults

2.4.1 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 DTG/3TC (status: 2 May 2019)
- bibliographical literature search on DTG/3TC (last search on 2 May 2019)
- search in trial registries for studies on DTG/3TC (last search on 2 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/3TC (last search on 15 July 2019)

The check identified no additional relevant study.

2.4.1.1 Studies included

The study listed in the following Table 16 was included in the benefit assessment.

Table 16: Study pool – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)
ASPIRE	No	No	Yes
a: Continuation of ongoing treatment. b: Study sponsored by the company. 3TC: lamivudine; DTG: dolutegravir; RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of DTG/3TC in pretreated HIV-1 infected adults consists of the ASPIRE study. In the study, DTG and 3TC were administered as free combination (DTG +3TC). This concurs with the company's study pool.

Section 2.4.4 contains a reference list for the study included.

2.4.1.2 Study characteristics

Table 17 and Table 18 describe the study used for the benefit assessment.

Table 17: Characteristics of the study included – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
ASPIRE	RCT, open-label, parallel	HIV-1 infected adults (≥ 18 years) with antiretroviral pretreatment[c] with an HIV-1 RNA viral load of < 50 copies/mL before[d] and < 20 copies/mL at screening as well as a $CD4^+$ cell count > 200/µl	▪ DTG + 3TC (N = 45[e]) ▪ continuation of ongoing treatment: ART[c] (N = 45)	▪ Screening: up to 45 days ▪ treatment: 48 weeks ▪ observation period: ND	Centres in the USA 12/2014–07/2017	Primary: virologic failure at week 24 Secondary: morbidity, AEs

a: Continuation of ongoing treatment.
b: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c: ART recommended by the DHHS or alternative ART consisting of 2 NRTIs in combination with a third drug of the drug class of the NNRTIs, PIs or INIs.
d: Measured on at least two time points over 48 weeks before screening.
e: 1 of the 45 randomized patients received no study mediation and were excluded from the analyses.

3TC: lamivudine; AE: adverse event; ART: antiretroviral therapy; CD4+: cluster of differentiation 4-positive; DHHS: Department of Health and Human Services; DTG: dolutegravir; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; N: number of randomized patients; ND: no data; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; RCT: randomized controlled trial; vs.: versus

Table 18: Characteristics of the intervention – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study	Intervention	Comparison
ASPIRE	DTG 50 mg + 3TC 300 mg once daily, orally	Continuation of an ongoing ART[a]
	Pretreatment ▪ according to the inclusion criteria at screening, treatment with a drug recommended by the DHHS or an alternative ART from 3 drugs for at least 48 weeks **non-permitted pretreatment** ▪ treatment with immunomodulators ≤ 30 days before start of the study ▪ systemic therapy for the treatment of a severe disease or AIDS-associated complications ≤ 21 days before screening ▪ vaccines ≤ 7 days before screening ▪ current hepatitis C treatment **non-permitted concomitant treatment** ▪ hepatitis C treatment	

a: Continuation of ongoing treatment.
3TC: lamivudine; AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; DHHS: Department of Health and Human Services; DTG: dolutegravir; RCT: randomized controlled trial; vs.: versus

The ASPIRE study was an open-label, randomized parallel-group study on pretreated and virologically suppressed HIV-1 infected adults. The HIV-1 RNA viral load of the patients had to be < 50 copies/mL for at least 48 weeks before the start of the study and < 20 copies/mL at screening. According to the inclusion criteria, patients were not allowed to have documented mutation in protease or reverse transcriptase genes or any known resistance to INIs. A $CD4^+$ cell count of > 200/µl was an additional inclusion criterion. The study compared DTG + 3TC with a continuation of the ongoing treatment.

In the ASPIRE study, a total of 90 patients were randomly allocated to treatment with DTG + 3TC (N = 45) or continuation of their ongoing ART (N = 45) in a 1:1 ratio. For patients in the comparator arm, ART consisted in the continuation of the ongoing treatment with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third drug from the drug class of non-nucleoside reverse transcriptase inhibitor (NNRTIs), protease inhibitors (PIs) or INIs.

Primary outcome of the study was “virologic failure” at week 24. Patient-relevant outcomes were “morbidity” and “AEs”. Treatment duration was 48 weeks.

The available study documents show that the patient population consisted of patients without indication for a treatment switch. There are no indications implying that treatment switch was indicated, for instance, due to side effects. Moreover, continuation of the ongoing treatment in

patients with indication for a treatment switch would make no sense and would not correspond to the ACT.

For adults without indication for a treatment switch, continuation of ongoing individual treatment in the control arm of the ASPIRE study is thus considered an adequate implementation of the ACT specified by the G-BA (an ART depending on the prior therapy/therapies and under consideration of the reason for the treatment switch, particularly treatment failure due to virologic failure and possible accompanying development of resistance or because of side effects).

Table 19 shows the characteristics of the patients in the study included.

Table 19: Characteristics of the study population – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study Characteristics Category	**DTG + 3TC**	**Comparator therapy[a]**
ASPIRE	N[b] = 45	N[b] = 45
Age [years], median [Q1; Q3]	46 [37; 56]	50 [41; 53]
Sex [F/M], %	11/89	13/87
Family origin, n (%)		
white	23 (52.3)	29 (64.4)
black	19 (43.2)	15 (33.3)
Asian	2 (4.5)	1 (2.2)
HIV-1 RNA viral load at baseline, n (%)		
< 50 copies/mL	ND	ND
≥ 50 copies/mL	ND	ND
$CD4^+$ cell count/mm^3 at baseline, Median [Q1; Q3]	694 [533; 1034]	646 [380; 819]
$CD4^+$ cell count/mm^3 at baseline, n (%)		
< 350	ND	ND
≥ 350	ND	ND
HIV disease stage (CDC category), n (%)		
A: asymptomatic	ND	ND
B: symptomatic	ND	ND
C: AIDS	ND	ND
Prior ART therapy, n (%)		
INI + 2 NRTI	18 (40.9)	15 (33.3)
PI + 2 NRTI	14 (31.8)	15 (33.3)
NNRTI + 2 NRTI	12 (27.3)	15 (33.3)
Treatment duration with current ART before the start of the study, median [Q1; Q3]	5.3 [3.8; 7.5]	6.0 [3.7; 7.4]
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	1 (2.3[c])	1 (2.2[c])

a: Continuation of ongoing treatment.
b: Number of randomized patients of whom 1 had not been treated in the intervention arm; information on the intervention arm refers to 44 patients.
c: Institute's calculation.

3TC: lamivudine; AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CD4+: cluster of differentiation 4-positive; CDC: Centers for Disease Control and Prevention; DTG: dolutegravir; F: female; INI: integrase inhibitors; HIV: human immunodeficiency virus; M: male; n: number of patients in the category; N: number of randomized patients; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; RNA: ribonucleic acid; vs.: versus

Patient characteristics were largely balanced between the two treatment arms. On average, the patients were mostly male (about 88%) and white (about 58%). The median age of the patients was 46 and 50 years. Median treatment duration with the ART before the start of the study was approx. 5 years in the intervention arm and approx. 6 years in the comparator arm. Information on the HIV disease stage are lacking.

Risk of bias across outcomes (study level)

Table 20 shows the risk of bias across outcomes (risk of bias at study level).

Table 20: Risk of bias across outcomes (study level) – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
ASPIRE	Unclear	Unclear	No	No	No[b]	Yes	High

a: Continuation of ongoing treatment.
b: An adequate predefined analysis strategy cannot be inferred from the study documents.
RCT: randomized controlled trial; vs.: versus

The data available for the ASPIRE study provide no information on how the randomization sequence was generated, whether allocation was concealed and to what extent the evaluation of the outcomes was prespecified. Therefore, the risk of bias across outcomes is assessed as high. This contradicts the company's assessment, which assessed the risk of bias for this study as low.

Limitations resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.4.2.2.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - AIDS-defining events (CDC class C)

  - presented as additional information: virologic response, virologic failure and CD4 cell count as surrogate outcomes for the patient-relevant outcome “AIDS-defining illnesses/death”
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (DAIDS grade 3–4)
  - gastrointestinal disorders (SOC)
  - skin and subcutaneous tissue disorders (SOC)
  - nervous system disorders (SOC)
  - psychiatric disorders (SOC)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.8.4.3 of the full dossier assessment).

Table 21 shows for which outcomes data were available in the study included.

Table 21: Matrix of outcomes – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study	Outcomes									
	All-cause mortality	AIDS-defining events (CDC class C)	Virologic response[b]	Virologic failure[b]	$CD4^+$ cell count[b]	Health-related quality of life	SAEs	Severe AEs (DAIDS grade 3–4)	Discontinuation due to AEs	Specific AEs[c]
ASPIRE	yes	no[d]	yes	no[e]	yes	no[f]	yes	no[g]	yes	no[d]

a: Continuation of ongoing treatment.
b: Virologic response, virologic failure (analysis according to FDA snapshot algorithm) and $CD4^{+-}$ cell count are presented as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" as supplementary information.
c: Gastrointestinal disorders (SOC), skin and subcutaneous tissue disorders (SOC), nervous system disorders (SOC), psychiatric disorders (SOC).
d: No data available.
e: No data available at week 48.
f: Outcome not recorded.
g: No usable data available since multiple answers per patient cannot be ruled out.
3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4+: cluster of differentiation 4-positive; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS ;DTG: dolutegravir; FDA: Food and Drug Administration; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2.2 Risk of bias

Table 22 describes the risk of bias for the results of the relevant outcomes.

Table 22: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study	Study level	Outcomes									
		All-cause mortality	AIDS-defining events (CDC class C)	Virologic response[b]	Virologic failure[b]	$CD4^+$ cell count[b]	Health-related quality of life	SAEs	Severe AEs (DAIDS grade 3–4)	Discontinuation due to AEs	Specific AEs[c]
ASPIRE	H	H[d]	-[e]	H[d]	-[f]	H[d, g]	–[h]	H[d]	-[i]	H[d, j]	-[e]

a: Continuation of ongoing treatment.
b: Virologic response, virologic failure (analysis according to FDA snapshot algorithm) and CD4 cell count are presented as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" as supplementary information.
c: Gastrointestinal disorders (SOC), skin and subcutaneous tissue disorders (SOC), nervous system disorders (SOC), psychiatric disorders (SOC).
d: High risk of bias at study level.
e: No data available.
f: No data available at week 48.
g: Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
h: Outcome not recorded.
i: Data not usable due to possible multiple answers per patient.
j: Lack of blinding in subjective recording of outcomes.
3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4+: cluster of differentiation 4-positive; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; DTG: dolutegravir; FDA: Food and Drug Administration; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Due to the high risk of bias at study level, the results of all considered outcomes were rated as potentially high. Moreover, relevant proportions of patients (> 5 percentage points) are lacking in the analysis of the outcome "CD4+ cell count". It cannot be ruled out that the outcome "discontinuation due to AEs" had been recorded subjectively due to lack of blinding.

This deviates from the assessment of the company, which assumed a low risk of bias for the outcomes "mortality", "virologic response", "$CD4^+$ cell count" and "discontinuation due to AEs" included by it. For the results on the harm outcomes SAEs and severe AEs (DAIDS grade 3–4), the company also assumed a high risk of bias.

2.4.2.3 Results

The results on the comparison of DTG + 3TC with continuation of ongoing treatment in pretreated HIV-1 infected adults without indication for a treatment switch are summarized in Table 23 and Table 24. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 23: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study Outcome category Outcome	DTG + 3TC		Comparator therapy[a]		DTG + 3TC vs. comparator therapy[a]
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
ASPIRE					
Mortality					
All-cause mortality	44	0 (0)	45	0 (0)	—
Morbidity					
AIDS-defining events (CDC class C)				ND	
Supplementary information: surrogate outcome "virologic response" (HIV-1 RNA < 50 copies/mL)[b]	44	40 (91)	45	40 (89)	1.02 [0.89; 1.18]; 0.752
Supplementary information: surrogate outcome "virologic failure" (HIV-1 RNA ≥ 50 copies/mL)[b]				ND	
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)				ND	
SAEs	44	1 (2)	45	2 (4)	0.51 [0.05; 5.44]; 0.578
Severe AEs (DAIDS grade 3–4)				Data not evaluable[c]	
Discontinuation due to AEs	44	1 (2)	45	0 (0)	3.07 [0.13; 73.31]; 0.489
Specific AEs				ND	

a: Continuation of ongoing treatment.
b: Analysis according to FDA snapshot algorithm.
c: Data not usable due to possible multiple answers per patient.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; DAIDS: Division of AIDS; DTG: dolutegravir; FDA: Food and Drug Administration; HIV: human immunodeficiency virus; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 24: Results (morbidity, continuous) – RCT, direct comparison: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Study Outcome category Outcome	DTG + 3TC			Comparator therapy[a]			DTG + 3TC vs. comparator therapy[a]
	N[b]	Values at baseline median [Q1; Q3]	Change at end of study median [Q1; Q3]	N[b]	Values at baseline median [Q1; Q3]	Change at end of study median [Q1; Q3]	Group difference; p-value
ASPIRE							
Morbidity							
Supplementary information: Surrogate outcome $CD4^+$ cell count/mm^3	40	694 [533; 1034]	39 [−71; 188]	43	646 [380; 819]	28 [−36; 83]	ND; 0.866[c]

a: Continuation of ongoing treatment.
b: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
c: Wilcoxon (Mann-Whitney) test
3TC: lamivudine; $CD4^+$: cluster of differentiation 4-positive; DTG: dolutegravir; ND: no data; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; vs.: versus

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes. This deviates from the approach of the company, which assumed a high certainty of results for some outcomes on the basis of its assessment on the risk of bias across outcomes (see Section 2.4.2.2), however, without making a statement on probability.

Mortality

All-cause mortality

Until week 48, no deaths occurred in the ASPIRE study. This resulted in no hint of an added benefit of DTG + 3TC in comparison with continuation of ongoing treatment for the outcome "overall survival". An added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

AIDS-defining events (CDC class C), supplementary consideration of the surrogate outcomes "virologic response", "virologic failure" and "$CD4^+$ cell count"

There are no results for the outcome "AIDS-defining events (CDC class C)". No statistically significant difference between the treatment groups was shown for the outcomes "virologic response" and "CD4+ cell count" presented as supplementary information. At week 48, there were no results for the outcome "virologic failure" presented as supplementary information. This resulted in no hint of an added benefit of DTG + 3TC in comparison with continuation of

the ongoing treatment for the outcome “AIDS-defining events (CDC class C)”. An added benefit is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life

Health-related quality of life was not investigated in the ASPIRE study. This resulted in no hint of an added benefit of DTG + 3TC in comparison with continuation of ongoing treatment for the outcome “health-related quality of life”. An added benefit is therefore not proven.

This concurs with the company’s assessment.

Side effects

SAEs, discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcomes “SAEs” and “discontinuation due to AEs”. This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with continuation of ongoing treatment for these outcomes. Hence, greater or lesser harm is not proven for these outcomes.

This concurs with the company’s assessment.

Severe AEs (DAIDS grade 3–4)

There are no usable data for the outcome “severe AEs (DAIDS grade 3−4)” due to possible multiple answers per patient. This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with continuation of ongoing treatment for this outcome. Hence, greater or lesser harm is not proven for this outcome.

This deviates from the assessment of the company insofar as the company considered the results on this outcome in the benefit assessment, but also derived no greater or lesser harm.

Specific AEs

The ASPIRE study yielded no results on the outcomes “gastrointestinal disorders”, “skin and subcutaneous tissue disorders”, “nervous system disorders” or “psychiatric disorders”. This resulted in no hint of greater or lesser harm from DTG + 3TC in comparison with continuation of ongoing treatment for these outcomes. Hence, greater or lesser harm is not proven for these outcomes.

This concurs with the company’s assessment.

2.4.2.4 Subgroups and other effect modifiers

No subgroup analyses available for the ASPIRE study.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2 (see Table 25).

Table 25: Extent of added benefit at outcome level: DTG + 3TC vs. comparator therapy[a] (pretreated adults)

Outcome category **Outcome**	**DTG + 3TC vs. comparator therapy[a]** **Proportion of events (%) or group difference** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit/added benefit not proven
Morbidity		
AIDS-defining events (CDC class C)	ND	Lesser benefit/added benefit not proven
Supplementary information:		
Virologic response[d]	91% vs. 89% RR: 1.02 [0.89; 1.18]; p = 0.752	Lesser benefit/added benefit not proven
Virologic failure[d]	ND	
$CD4^+$ cell count/mm^3	Change: 39 vs. 28 group difference: ND; p > 0.866	
Health-related quality of life	Outcome not recorded	
Side effects		
SAEs	2% vs. 4% RR: 0.51 [0.05; 5.44]; p = 0.578	Greater/lesser harm not proven
Severe AEs (DAIDS grade 3–4)	Data not evaluable[e]	Greater/lesser harm not proven
Discontinuation due to AEs	2% vs. 0% RR: 3.07 [0.13; 73.31]; p = 0.489	Greater/lesser harm not proven
Specific AEs[f]	ND	Greater/lesser harm not proven

a: Continuation of ongoing treatment.
b: Probability provided if there is a statistically significant and relevant effect.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: According to FDA snapshot algorithm.
e: Data not usable due to possible multiple answers per patient.
f: Gastrointestinal disorders (SOC), skin and subcutaneous tissue disorders (SOC), nervous system disorders (SOC), psychiatric disorders (SOC).

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; $CD4^+$: cluster of differentiation 4-positive; CDC: Centers for Disease Control and Prevention; CI: confidence interval; DAIDS: Division of AIDS; DTG: dolutegravir; FDA: Food and Drug Administration; ND: no data;RR: relative risk; SAE: serious adverse event; SOC: system organ class; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 26 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 26: Positive and negative effects from the assessment of DTG + 3TC versus comparator therapy[a] (pretreated adults)

Positive effects	Negative effects
–	–
a: Continuation of ongoing treatment. 3TC: lamivudine; DTG: dolutegravir; vs.: versus	

The overall consideration of the results revealed neither positive nor negative effects of DTG + 3TC in comparison with continuation of ongoing treatment.

In summary, there was no hint of an added benefit of DTG + 3TC in comparison with continuation of ongoing treatment for pretreated HIV-1 infected[4] adults without an indication for treatment switch.

No data for the assessment of the added benefit were available for pretreated HIV-1 infected[4] adults with indication for a treatment switch. This resulted in no hint of an added benefit for this population; an added benefit is therefore not proven.

This concurs with the company's assessment.

2.4.4 List of included studies

Taiwo B. Dolutegravir antiretroviral strategy to promote improvement and reduce drug exposure (ASPIRE): study results [online]. In: ClinicalTrials.gov. 19.03.2019 [Accessed: 23.07.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02263326.

Taiwo B. Dolutegravir antiretroviral strategy to promote improvement and reduce drug exposure (ASPIRE): study details [online]. In: ClinicalTrials.gov. 19.03.2019 [Accessed: 23.07.2019]. URL: https://ClinicalTrials.gov/show/NCT02263326.

Taiwo B. Dolutegravir Antiretroviral Strategy to Promote Improvement and Reduce drug Exposure (ASPIRE) study: study protocol, statistical analysis plan, and informed consent form [online]. 25.06.2015 [Accessed: 01.08.2019]. URL: https://clinicaltrials.gov/ProvidedDocs/26/NCT02263326/Prot_SAP_ICF_000.pdf.

Taiwo BO, Marconi VC, Berzins B, Moser CB, Nyaku AN, Fichtenbaum CJ et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through week 48 in a pilot randomized trial. Clin Infect Dis 2018; 66(11): 1794-1797.

2.5 Research question 3: treatment-naive adolescents

2.5.1 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 DTG/3TC (status: 2 May 2019)
- bibliographical literature search on DTG/3TC (last search on 2 May 2019)
- search in trial registries for studies on DTG/3TC (last search on 2 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/3TC (last search on 15 July 2019)

Concurring with the company, the check of the completeness of the study pool did not produce any RCTs with treatment-naive HIV-1 infected adolescents as target population on the direct comparison of DTG/3TC versus the ACT or on a corresponding indirect comparison based on RCTs.

For the derivation of an added benefit, the company transferred the results of GEMINI-1 and GEMINI-2 in treatment-naive HIV-1 infected adults to the target population of treatment-naive HIV-1 infected adolescents (see also Section 2.8.8.2 of the full dossier assessment). The company's approach to transfer study results for adults to adolescents is comprehensible as there are no comparative data for adolescents; however, the concrete implementation was inadequate:

- The company presented no data for treatment-naive adolescents.
- With the GEMINI-1 and GEMINI-2 studies, the company additionally used RCTs in which patients in the comparator arm were treated with the ACT "DTG + TDF/FTC" specified for treatment-naive adults. However, this does not correspond to the ACT for treatment-naive HIV-1-infected adolescents. TDF is thus explicitly not part of the ACT for treatment-naive HIV-1-infected adolescents.

2.5.2 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of DTG/3TC in comparison with the ACT in treatment-naive HIV-1 infected adolescents. This resulted in no hint of an added benefit of DTG/3TC in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

An added benefit is not proven because the company presented no suitable data for the assessment of the added benefit of DTG/3TC in comparison with the ACT in treatment-naive HIV-1 infected adolescents[5].

This deviates from the company's assessment, which transferred the results of the studies GEMINI-1 and GEMINI-2 with treatment-naive adults to treatment-naive adolescents and derived an indication of minor added benefit.

2.5.4 List of included studies

Not applicable as the company presented no relevant data for research question 3.

2.6 Research question 4: pretreated adolescents

2.6.1 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 DTG/3TC (status: 2 May 2019)
- bibliographical literature search on DTG/3TC (last search on 2 May 2019)
- search in trial registries for studies on DTG/3TC (last search on 2 May 2019)

To check the completeness of the study pool:

- search in trial registries for studies on DTG/3TC (last search on 15 July 2019)

Concurring with the company, the check of the completeness of the study pool did not produce any RCTs with pretreated HIV-1 infected adolescents as target population on the direct comparison of DTG/3TC versus the ACT or on a corresponding indirect comparison based on RCTs.

2.6.2 Results on added benefit

In its dossier, the company presented no suitable data for the assessment of the added benefit of DTG/3TC in comparison with the ACT in pretreated HIV-1 infected adolescents. This resulted in no hint of an added benefit of DTG + 3TC in comparison with the ACT; an added benefit is therefore not proven.

2.6.3 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of DTG/3TC in comparison with the ACT in pretreated HIV-1 infected adolescents[5], an added benefit is not proven.

This concurs with the company's assessment.

2.6.4 List of included studies

Not applicable as the company presented no relevant data for research question 4.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of DTG/3TC in comparison with the ACT is summarized in Table 27.

Table 27: DTG/3TC – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adults infected with HIV-1[b]	Rilpivirine in combination with TDF /tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or **DTG in combination with TDF**/tenofovir alafenamide **plus FTC** or in combination with abacavir plus lamivudine	Proof of minor added benefit
2	Pretreated adults infected with HIV-1[b]	Individual ART depending 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	
	With indication for a treatment switch		Added benefit not proven
	Without indication for a treatment switch		Added benefit not proven
3	Treatment-naive adolescents[c] infected with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus 3TC or DTG in combination with tenofovir alafenamide plus FTC or in combination with abacavir plus lamivudine	Added benefit not proven
4	Pretreated adolescents[c] infected with HIV-1[b]	Individual ART depending 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

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The HI virus was not to have any known or suspected resistances to the INI class or 3TC.
c: Twelve years of age and older and with a body weight of at least 40 kg.
3TC: lamivudine; ACT: appropriate comparator therapy; ART: antiretroviral therapy; DTG: dolutegravir; FTC: emtricitabine; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitors; TDF: tenofovir disoproxil

The approach for deriving a conclusion on the added benefit is a proposal by IQWiG. 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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Günthard HF, Saag MS, Benson CA, Del Rio C, Eron JJ, Gallant JE et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society–USA Panel. JAMA 2016; 316(2): 191-210.

4. ViiV Healthcare. Dovato 50 mg/300 mg Filmtabletten: Fachinformation [online]. 07.2019 [Accessed: 17.07.2019]. URL: https://www.fachinfo.de.

5. ViiV Healthcare. Tivicay 10 mg/25 mg/50 mg Filmtabletten: Fachinformation [online]. 03.2019 [Accessed: 17.07.2019]. URL: https://www.fachinfo.de.

6. Gilead. Truvada 200 mg/245 mg Filmtabletten: Fachinformation [online]. 12.2018 [Accessed: 25.07.2019]. URL: https://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-55-dolutegravir-lamivudine-hiv-infection-benefit-assessment-according-to-35a-social-code-book-v.12493.html