IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-48

Darunavir/cobicistat/ emtricitabine/tenofovir alafenamide (HIV infection) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Darunavir/Cobicistat/Emtricitabine/Tenofoviralafenamid (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
bPi	boosted protease inhibitor
DRV	darunavir
DRV/co	cobicistat-boosted darunavir
DRV/r	ritonavir-boosted darunavir
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LPV/r	ritonavir-boosted lopinavir
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil

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 darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 27 September 2017.

Research question

The aim of this report was to assess the added benefit of DRV/COBI/FTC/TAF in comparison with the appropriate comparator therapy (ACT) in adults and adolescents (12 years of age and older and with a body weight of at least 40 kg) infected with human immunodeficiency virus type 1 (HIV-1).

The G-BA's specification of the ACT resulted in 4 research questions, which are presented in the following Table 2.

Table 2: Research questions of the benefit assessment of DRV/COBI/FTC/TAF

Research question[a]	Subindication	ACT[b]
1	Treatment-naive adults	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TDF/TAF plus FTC or abacavir plus lamivudine)
2	Treatment-naive adolescents[c]	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TAF plus FTC or abacavir plus lamivudine)
3	Pretreated adults	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects[d]
4	Pretreated adolescents[c]	

a: Research questions 1, 2, 3 and 4 correspond to the respective subpopulations A1, A2, A3 and A4 of the company.
b: Presentation of the respective ACT specified by the G-BA.
c: Twelve years of age and older and with a body weight of at least 40 kg.
d: Non-drug treatment is not an option in the therapeutic indication "HIV infection".
ACT: appropriate comparator therapy; ART: antiretroviral therapy, COBI: cobicistat; DRV: darunavir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide; 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.

Results

Research questions 1, 2 and 4: Treatment-naive HIV-1 infected adults and adolescents as well as pretreated adolescents

The company presented no data for the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT in treatment-naive HIV-1 infected adults and adolescents as well as pretreated adolescents (research questions 1, 2 and 4). Hence, there was no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with the ACT for these research questions; an added benefit is therefore not proven.

Research question 3: pretreated adults

Study pool and study characteristics

The EMERALD study is included in the benefit assessment of DRV/COBI/FTC/TAF in pretreated adults. This study was conducted with patients without indication for a treatment switch. Studies for patients with an indication for a treatment switch are not available.

The EMERALD study is an open-label randomized parallel group trial with pretreated HIV-1 infected patients that compared DRV/COBI/FTC/TAF with continuation of ongoing treatment.

The study included virologically suppressed adults (HIV-1 ribonucleic acid [RNA] viral load of < 50 copies/mL) who had been treated with a therapy regimen of 1 boosted protease inhibitor (bPi) for at least 6 consecutive months (consisting of ritonavir-boosted darunavir [DRV/r], cobicistat-boosted darunavir [DRV/co], ritonavir-boosted atazanavir [ATV/r], cobicistat-boosted atazanavir [ATV/co] or ritonavir-boosted lopinavir [LPV/r]) and the drug combination emtricitabine/tenofovir disoproxil (FTC/TDF). The patients (N = 1149) were randomized in a 2:1 ratio either into the DRV/COBI/FTC/TAF arm (N = 766) or the arm with continuation of the ongoing treatment (N = 383).

Implementation of the ACT in the EMERALD study

The evaluation regarding content of the investigated patient population showed that mostly patients without medically required indication for a treatment switch (e.g. due to virologic failure or side effects) were enrolled in the EMERALD study [see Section 2.8.2.4.1 of the full dossier assessment].

For patients without indication for a treatment switch, the continuation of ongoing treatment in the control arm of the EMERALD study is considered to be an adequate implementation of the ACT specified by the G-BA.

Risk of bias

The risk of bias at study level was rated as low. At outcome level, the risk of bias was rated as low for the outcomes “all-cause mortality”, “AIDS-defining events”, “virologic response”, “CD4 cell count”, “Serious adverse events (SAEs) and severe adverse events (AEs)” (DAIDS grade 3–4). However, the risk of bias is considered to be high for the outcomes “discontinuation due to AEs” and the specific AEs.

Results

Mortality

- all-cause mortality

No deaths occurred in the EMERALD study. This resulted in no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; an added benefit is therefore not proven.

Morbidity

- AIDS-defining events (WHO class 4 events); supplementary consideration of the surrogate outcomes "virologic response" and "CD4 cell count"

An AIDS-defining event falling in WHO class 4 did not occur in the EMERALD study. No statistically significant difference between the treatment arms was shown for the two surrogate outcomes “virologic response” and “CD4 cell count” that were presented as supplementary information. Altogether, this resulted in no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; an added benefit is therefore not proven.

- Health-related quality of life

Outcomes of the outcome category “health-related quality of life” were not investigated in the EMERALD study. This resulted in no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; an added benefit is therefore not proven.

Side effects

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

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "severe AEs (DAIDS grade 3-4)" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; greater or lesser harm for these outcomes is therefore not proven.

- Specific AEs (gastrointestinal disorders, skin and subcutaneous tissue disorders as well as nervous system disorders)

Statistically significant differences to the disadvantage of DRV/COBI/FTC/TAF in comparison with continuation of the ongoing treatment with 1 bPI + FTC/TDF were shown for each of the outcomes "gastrointestinal disorders", "skin and subcutaneous tissue disorders" as well as "nervous system disorders". The extent of the greater harm for each of the outcomes "gastrointestinal disorders" and "skin and subcutaneous tissue disorders" from the category of non-serious/non-severe side effects was no more than marginal. This results in no hint of greater or lesser harm of DRV/COBI/FTC/TAF in comparison with the continuation of the ongoing treatment with 1 bPI + FTC/TDF for the outcomes "gastrointestinal disorders" and "disorders of the skin and subcutaneous tissue disorders". However, there is a hint of greater harm from DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF for the outcome "nervous system disorders".

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

On the basis of the results presented, the probability and the extent of the added benefit of the drug DRV/COBI/FTC/TAF compared with the ACT is assessed as follows:

In the overall consideration, there remains a negative effect of DRV/COBI/FTC/TAF in comparison with continuation of the ongoing treatment with 1 bPI + FTC/TDF (nervous system disorders). In summary, there is a hint of greater harm with the extent "minor" from DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF in pretreated adults with HIV-1 infection without indication for a treatment switch.

The company presented no data for pretreated adults with HIV-1 infection and indication for a treatment switch, for pretreated adolescents as well as for treatment-naive adults and adolescents. For these patients, there was no hint of an added benefit; an added benefit is therefore not proven.

Table 3 presents a summary of probability and extent of the added benefit of DRV/COBI/ FTC/TAF.

[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 ess benefit). For further details see [1,2].

Table 3: DRV/COBI/FTC/TAF: Probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adults	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TDF/TAF plus FTC or abacavir plus lamivudine)	Added benefit not proven
2	Treatment-naive adolescents[b]	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TAF plus FTC or abacavir plus lamivudine)	Added benefit not proven
3	Pretreated adults (without indication for a treatment switch)	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possibly accompanying development of resistance, or due to side effects[c]	Hint of lesser benefit
	Pretreated adults (with indication for a treatment switch)		Added benefit not proven
4	Pretreated adolescents[b]		Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Twelve years of age and older and with a body weight of at least 40 kg.
c: Non-drug treatment is not an option in the therapeutic indication “HIV infection”.
ACT: appropriate comparator therapy; ART: antiretroviral therapy; COBI: cobicistat; DRV: darunavir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide

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 DRV/COBI/FTC/TAF 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 G-BA's specification of the ACT resulted in 4 research questions, which are presented in the following Table 4.

Table 4: Research questions of the benefit assessment of DRV/COBI/FTC/TAF

Research question[a]	Subindication	ACT[b]
1	Treatment-naive adults	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TDF/TAF plus FTC or abacavir plus lamivudine)
2	Treatment-naive adolescents[c]	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TAF plus FTC or abacavir plus lamivudine)
3	Pretreated adults	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects[d]
4	Pretreated adolescents[c]	

a: Research questions 1, 2, 3 and 4 correspond to the respective subpopulations A1, A2, A3 and A4 of the company.
b: Presentation of the respective ACT specified by the G-BA.
c: 12 years of age and older and with a body weight of at least 40 kg.
d: Non-drug treatment is not an option in the therapeutic indication "HIV infection".
ACT: appropriate comparator therapy; ART: antiretroviral therapy; COBI: cobicistat; DRV: darunavir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide

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. Randomized controlled trials (RCTs) with a minimum duration of 48 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

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 DRV/COBI/FTC/TAF (status: 7 August 2017)
- bibliographical literature search on DRV/COBI/FTC/TAF (last search on 2 August 2017)
- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 7 August 2017)

To check the completeness of the study pool:

- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 9 October 2017)

In its dossier, the pharmaceutical company had not presented a relevant study on research question 1. Nor was a relevant study identified from the check of the completeness.

2.3.2 Results on added benefit

The company presented no data for the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT in treatment-naive HIV-1 infected adults. Hence, there was no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT in treatment-naive HIV-1 infected adults, an added benefit of DRV/COBI/FTC/TAF is not proven for these patients.

2.3.4 List of included studies

Not applicable as the company presented no data for research question 1.

2.4 Research question 2: treatment-naive adolescents

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 DRV/COBI/FTC/TAF (status: 7 August 2017)
- bibliographical literature search on DRV/COBI/FTC/TAF (last search on 2 August 2017)
- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 7 August 2017)

To check the completeness of the study pool:

- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 9 October 2017)

In its dossier, the company had not presented a relevant study on research question 2. Nor was a relevant study identified from the check of the completeness.

2.4.2 Results on added benefit

The company presented no data for the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT in treatment-naive HIV-1 infected adolescents. Hence, there was no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT in treatment-naive HIV-1 infected adolescents, an added benefit of DRV/COBI/FTC/TAF is not proven for these patients.

2.4.4 List of included studies

Not applicable as the company presented no data for research question 2.

2.5 Research question 3: pretreated adults

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 DRV/COBI/FTC/TAF (status: 7 August 2017)
- bibliographical literature search on DRV/COBI/FTC/TAF (last search on 2 August 2017)
- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 7 August 2017)

To check the completeness of the study pool:

- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 9 October 2017)

The check identified no additional relevant study.

2.5.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (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)**
TMC114IFD3013 (EMERALD[c])	No	Yes	No

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
b: Study for which the company was sponsor.
c: In the following tables, the study is referred to with this designation.
ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; COBI: cobicistat; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; LPV/r: ritonavir-boosted lopinavir; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

The study pool for the benefit assessment of DRV/COBI/FTC/TAF in pretreated adults consists of the study EMERALD. This corresponded to the company's approach.

The study EMERALD included chiefly pretreated HIV-1 infected adults without indication for a treatment switch (e.g. due to virologic failure or side effects) and is used for conclusions on this patient group (see Section 2.8.2.4.1 of the full dossier assessment for detailed reasons). Studies for pretreated adult patients with an indication for a treatment switch are not available.

Section 2.5.4 contains a reference list for the study included.

2.5.1.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
EMERALD	RCT, open-label, parallel	HIV-1 infected adults with antiretroviral pretreatment[c, d] (≥ 18 years) with a stable ART for at least 6 consecutive months and an HIV-1 RNA viral load of < 50 copies/mL[e] prior to and at screening and an $eGFR_{CG}$ of ≥ 50 mL/min	▪ DRV/COBI/FTC/TAF (N = 766)[f] ▪ Continuation of ongoing treatment consisting of: 1 bPI[a] + FTC/TDF (N = 383)[f] The following number of patients received: ▫ DRV/r + FTC/TDF (n = 202) ▫ DRV/co + FTC/TDF (n = 64) ▫ ATV/r + FTC/TDF (n = 81) ▫ ATV/co + FTC/TDF (n = 1) ▫ LPV/r + FTC/TDF (n = 30)	▪ Screening: 30 days prior to the start of treatment ▪ Treatment: 48 weeks (followed by a one-arm extension phase) ▪ Observation: 30 days (± 7) in case of persistent AEs at the time point of the last study visit, 2 days in case of premature discontinuation of treatment without persistent AEs	106 study centres in Belgium, Canada, France, Poland, Spain, Sweden, Switzerland, United Kingdom, USA 04/2015–ongoing (Data cut-off at week 48: 24 February 2017)	Primary: virologic rebound at week 48 Secondary: mortality, morbidity, AEs

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
b: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
c: pretreated with 1 bPI (DRV/r, DRV/co, ATV/r, ATV/co or LPV/r) in combination with FTC/TDF for at least 6 consecutive month before screening.
d: Stratified by the bPI at screening and subdivided into 3 categories (DRV/r or DRV/co, ATV/r or ATV/co and LPV/r).
e: For at least 2 months before screening; one single outlying measurement between ≥ 50 and < 200 copies/mL was allowed, provided that a subsequent measurement was < 50 copies/ml before screening.
f: Both the DRV/COBI/FTC/TAF arm and the complete arm with continuation of the ongoing treatment were relevant for the assessment. In the next tables, the two arms are referred to as DRV/COBI/FTC/TAF vs. 1 bPI + FTC/TDF. Three of the 766 randomized patients in the DRV/COBI/FTC/TAF arm and 5 of the 383 randomized patients in the arm with continuation of the ongoing treatment discontinued the study before administration of their first study medication.

AE: adverse event; ART: antiretroviral therapy; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; COBI: cobicistat; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; $eGFR_{CG}$: glomerular filtration rate according to the Cockcroft-Gault equation; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; LPV/r: ritonavir-boosted lopinavir; N: number of randomized patients; n: number of treated patients; RCT: randomized controlled trial; RNA: ribonucleic acid; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study	Intervention	Comparison	Pretreatment and concomitant treatment
EMERALD	DRV 800 mg/ COBI 150 mg/ FTC 200 mg/ TAF 10 mg (fixed combination), orally, once daily at about the same time of the day	Continuation of ongoing treatment consisting of 1 bPI[a] + FTC/TDF, dosage and use in compliance with the respective local Summaries of Product Characteristics (SPCs)	**Pretreatment:** ▪ Pretreated with 1 bPI (DRV/r, DRV/co, ATV/r, ATV/co or LPV/r) in combination with FTC/TDF for at least 6 consecutive month before screening **Concomitant treatment:** ▪ According to the clinical specification and under consideration of the information provided in the local SPCs of the respective study medications **Non-permitted concomitant treatments:** ▪ No other HIV-1 antiretroviral (ARV) therapies ▪ The drugs listed as non-permitted concomitant medication in the current local SPCs of the respective study medication

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.

ARV: antiretroviral; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; COBI: cobicistat; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; LPV/r: ritonavir-boosted lopinavir; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

The EMERALD study is an open-label randomized parallel-group study with pretreated HIV-RNA viral load of < 50 copies/mL) who had been treated with a therapy regimen of 1 bPi for at least 6 consecutive months (consisting of DRV/r, DRV/co, ATV/r, ATV/co or LPV/r) and the drug combination FTC/TDF.

The patients (N = 1149) were randomized in a 2:1 ratio either into the DRV/COBI/FTC/TAF arm (N = 766) or into the arm with continuation of the ongoing treatment (N = 383). Randomization was stratified by the bPI (DRV, ATV or LPV) administered within the ongoing treatment.

106 study centres in 9 countries were involved in the conduction of the study, about half of these centres were located in the USA (about 43%) or Canada (about 6%), the other half were situated in Europe. Treatment duration of the comparative phase was 48 weeks. The patients of the control arm could then switch to treatment with DRV/COBI/FTC/TAF in the extension phase.

The study medication was applied in compliance with the respective local SPCs. Dosage and use were in compliance with the German approval status. According to the SPCs of the drugs administered in the study, there should be no resistances against the study medication. Since almost all patients (98%) had been virologically suppressed for at least 2 months at the start of the study (HIV-1 RNA viral load of < 50 copies/mL) and this suppression persisted over the entire period of the study, it must be expected that they had not developed any relevant resistances to one of the drugs (see Section 2.8.2.4.1 of the full dossier assessment).

"Virologic rebound" was the primary outcome of the study. Patient-relevant outcomes were "overall survival", "morbidity" and "AEs". Data on health-related quality of life were not recorded in this study.

Based on the evaluation regarding content of the investigated patient population it could be found out that mostly patients without medically required indication for a treatment switch (e.g. due to virologic failure or side effects) were enrolled in the EMERALD study [see Section 2.8.2.4.1 of the full dossier assessment]. It is unclear whether a small proportion of patients with necessary treatment switch due to side effects was also included in the study. Continuation of the ongoing treatment with 1 bPI + FTC/TDF would not have been reasonable for these patients, and would not have concurred with the ACT. However, the possible proportion of these patients is considered to be too low to question the informative value of the EMERALD study for patients without indication for a treatment switch.

For patients without indication for a treatment switch, the continuation of ongoing treatment in the control arm of the EMERALD study is considered to be an adequate implementation of the ACT specified by the G-BA (an individual 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 possibly accompanying development of resistance or because of side effects).

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

Table 8: Characteristics of the study population – RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study **Characteristics** **Category**	**DRV/COBI/FTC/TAF**	**bPI[a] + FTC/TDF**
EMERALD	N[b] = 766	N[b] = 383
Age [years], mean (SD)	45 (11)	45 (11)
Sex [F/M], %	18/82	17/83
Time since HIV diagnosis [years], mean (SD)	11.8 (8.4)	11.3 (8.2)
Time since first ARV therapy [years], mean (SD)	8.8 (6.8)	8.5 (6.5)
HIV disease status according to the WHO classification[c], n (%)		
1 (asymptomatic)	522 (68.4)	255 (67.5)
2 (mild symptoms)	96 (12.6)	51 (13.5)
3 (advanced symptoms)	66 (8.7)	36 (9.5)
4 (severe symptoms/AIDS)	79 (10.4)	36 (9.5)
HIV-1 RNA viral load at baseline, n (%)		
< 50 copies/mL	747 (97.9)	371 (98.1)
≥ 50 copies/mL[d]	16 (2.1)	7 (1.9)
CD4 cell count/mm^3 at baseline, n (%)		
< 350 cells/mm^3	70 (9.2)	46 (12.2)
≥ 350 cells/mm^3	693 (90.8)	332 (87.8)
Ethnicity, n (%)		
White	573 (75.1)	282 (74.6)
Other	184 (24.1)	94 (24.9)
Unknown	6 (0.8)	2 (0.5)
$eGFR_{CG}$ [mL/min], mean (SD)	107.5 (30.6)	107.0 (30.3)
Treatment discontinuation, n (%)	34 (4.5)	20 (5.3)
Study discontinuation, n (%)	32 (4.2)	18 (4.8)

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
b: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: These data reflect the most severe disease stage ever occurred and not necessarily the disease stage at the start of the study.
D: Twenty-three patients with a HIV-1 RNA viral load of < 50 copies/mL in the screening had a viral load of ≥ 50 copies/ml at the start of the study.
AIDS: acquired immunodeficiency syndrome; ARV: antiretroviral; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; CD4: cluster of differentiation 4; COBI: cobicistat; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; $eGFR_{CG}$: glomerular filtration rate according to the Cockcroft-Gault equation; F: female; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; LPV/r: ritonavir-boosted lopinavir; M: male; n: number of patients in the category; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus; WHO: World Health Organization

The characteristics of the study population were comparable between the both arms DRV/COBI/FTC/TAF and bPI + FTC/TDF. The average age of the patients was about 45 years, the great majority of them were male (about 82%) and white (about 75%). At the start of the study, the average period since the HIV-1 diagnosis had been made was about 12 years, whereas the patients had received their first ART about 9 years before the start of the study. Almost all patients were virologically suppressed at the start of the study (HIV-1 RNA viral load of < 50 copies/mL). Patients with indications of a liver disease including hepatitis B coinfection were not included in the study.

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
EMERALD	Yes	Yes	No	No	Yes	Yes	Low

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.

ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; COBI: cobicistat; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; LPV/r: ritonavir-boosted lopinavir; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

The risk of bias at study level was rated as low for the included EMERALD study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described with the outcome-specific risk of bias in Section 2.5.2.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - AIDS-defining events (class 4 WHO events)

  - Presented as additional information: virologic response 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 (System Organ Class [SOC])
  - Skin and subcutaneous tissue disorders (SOC)
  - Nervous system disorders (SOC)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.8.2.4.3 of the full dossier assessment). However, the company did not include the specific AEs “gastrointestinal disorders”, “disorders of the skin and subcutaneous tissue disorders” as well as “nervous system disorders” in its assessment.

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

Table 10: Matrix of the outcomes – RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study	Outcomes										
	All-cause mortality	AIDS-defining events (Class 4 WHO events)	Virologic response (snapshot)[b]	CD4 cell count[b]	Health-related quality of life	SAE	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Gastrointestinal disorders	Skin and subcutaneous tissue disorders	Nervous system disorders
EMERALD	Yes	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
b: Virologic response and CD4 cell count are presented as additional information as surrogate outcomes for the composite outcome "AIDS-defining illnesses/death".
c: Outcomes of this outcome category were not recorded.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; CD4: cluster of differentiation 4; COBI: cobicistat; DAIDS: Division of AIDS; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; LPV/r: ritonavir-boosted lopinavir; RCT: randomized controlled trial; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus; WHO: World Health Organization

2.5.2.2 Risk of bias

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

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study		Outcomes										
	Study level	All-cause mortality	AIDS-defining events (Class 4 WHO events)	Virologic response (snapshot)[b]	CD4 cell count[b]	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Gastrointestinal disorders	Skin and subcutaneous tissue disorders	Nervous system disorders
EMERALD	L	L	L	L	L	-[c]	L	H[d]	L	H[d]	H[d]	H[d]

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
b: Virologic response and CD4 cell count are presented as additional information as surrogate outcomes for the composite outcome "AIDS-defining illnesses/death".
c: Outcomes of this outcome category were not recorded.
d: Lack of blinding in subjective recording of outcomes.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; CD4: cluster of differentiation 4; COBI: cobicistat; DAIDS: Division of AIDS; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; LPV/r: ritonavir-boosted lopinavir; RCT: randomized controlled trial; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus; WHO: World Health Organization

The risk of bias for the outcomes “all-cause mortality”, “AIDS-defining events” (class 4 WHO events), “virologic response”, “CD4 cell count”, “SAEs and severe AEs” (DAIDS grade 3–4) was rated as low. This concurs with the company's assessment.

Due to a lack of blinding in subjective recording, the risk of bias was rated as high for the outcomes “discontinuation due to AEs” as well as for the specific AEs “gastrointestinal disorders”, “disorders of the skin and subcutaneous tissue disorders” as well as “nervous system disorders”. For the outcome “discontinuation due to AEs”, this concurs with the assessment of the company. The company did not include the outcomes on the specific AEs in its assessment and therefore presented no information on the risk of bias.

2.5.2.3 Results

The results on the comparison of DRV/COBI/FTC/TAF with continuation of ongoing treatment with 1 bPI + FTC/TDF in pretreated adults with HIV-1 infection without indication for a treatment switch are summarized in Table 12 and Table 13. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations.

Table 12: Results (mortality, morbidity, side effects, dichotomous) - RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study Outcome category Outcome	DRV/COBI/FTC/TAF		bPI[a] + FTC/TDF		DRV/COBI/FTC/TAF vs. bPI[a] + FTC/TDF
	L	Patients with event n (%)	L	Patients with event n (%)	RR [95% CI]; p-value
EMERALD					
Mortality					
All-cause mortality	763	0 (0)	378	0 (0)	NC
Morbidity					
AIDS-defining events (WHO class 4)	763	0 (0)	378	0 (0)	NC
Additional information: surrogate outcome "virologic response" (HIV-1 RNA < 50 copies/mL)[b]					
Snapshot	763	724 (94.9)	378	354 (93.7)	1.01 [0.98; 1.05]; 0.420[c]
Time to Loss of Virologic Response (TLOVR) (sensitivity analysis)	763	715 (93.7)	378	351 (92.9)	1.01 [0.98; 1.04][d] 0.625[c]
Side effects					
AEs (supplementary information)	763	624 (81.8)	378	310 (82.0)	–
SAE	763	34 (4.5)	378	18 (4.8)	0.94 [0.54; 1.63]; 0.866[c]
Severe AEs (CTCAE grade 3–4):	763	51 (6.7)	378	30 (7.9)	0.84 [0.55; 1.30]; 0.454[c]
Discontinuation due to AEs	763	10 (1.3)	378	4 (1.1)[e]	1.24 [0.39; 3.92]; 0.745[c]
Gastrointestinal disorders	763	204 (26.7)	378	75 (19.8)	1.35 [1.07; 1.70]; 0.011[c]
Skin and subcutaneous tissue disorders	763	116 (15.2)	378	38 (10.1)	1.51 [1.07; 2.14]; 0.017[c]
Nervous system disorders	763	116 (15.2)	378	35 (9.3)	1.64 [1.15; 2.35]; 0.005[c]

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
b: Analysis according to FDA snapshot algorithm and Time to Loss of Virologic Response (TLOVR) analysis.
c: Institute's calculation, unconditional exact test (CSZ method according to [3]).
a: Institute's calculation; effect and CI (asymptotic).
e: There is a discrepancy regarding the information in Module 4 A of the company stating that 5 patients discontinued treatment due to AEs.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; CI: confidence interval, COBI: cobicistat; DAIDS: Division of AIDS; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FDA: Food and Drug Administration; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; LPV/r: ritonavir-boosted lopinavir; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; TLOVR: Time to Loss of Virologic Response; vs.: versus; WHO: World Health Organization

Table 13: Results (morbidity, continuous) - RCT, direct comparison: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Study Outcome category Outcome	DRV/COBI/FTC/TAF			bPI[a] + FTC/TDF			DRV/COBI/FTC/TAF vs. bPI[a] + FTC/TDF
	N[b]	Values at start of study mean (SD)	Change at week 48 mean[c] (SE)	N[b]	Values at start of study mean (SD)	Change at week 48 mean[c] (SE)	MD[c] [95% CI]; p-value
EMERALD							
Morbidity							
Supplementary information: Surrogate outcome "CD4 cell count" (cells/mm^3)	763	653.3 (251.78)	18.69 (7.22)	378	641.7 (255.59)	4.91 (9.07)	13.78 [−4.89/32.45]; 0.148

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
b: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
c: Change from the baseline value; ANCOVA with the covariables baseline value CD4 cell count, bPI at screening and treatment; missing values due to discontinuation by baseline value, intermittent values were replaced with the last observation carried forward (LOCF); longitudinal model (MMRM) provides comparable results (MD: 13.69; 95% CI: [−4.98; 32.36]; p = 0.150).

ANCOVA: analysis of covariance; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; CD4: cluster of differentiation 4; CI: confidence interval; COBI: cobicistat; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; LOCF: last observation carried forward; LPV/r: ritonavir-boosted lopinavir; MD: mean difference; MMRM: mixed effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcomes "all-cause mortality", "AIDS-defining events", SAEs and severe AEs (DAIDS grade 3–4), and at most hints can be derived for the outcome "discontinuation due to AEs" as well as for the specific AEs "gastrointestinal disorders", "disorders of the skin and subcutaneous tissue disorders" as well as "nervous system disorders" due to the high risk of bias.

Mortality

all-cause mortality

No deaths occurred in the EMERALD study. This resulted in no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

AIDS-defining events (WHO class 4 events), supplementary consideration of the surrogate outcomes "virologic response" and "CD4 cell count"

No WHO class 4 AIDS-defining event occurred in the EMERALD study. No statistically significant difference between the treatment arms was shown for the two outcomes “virologic response” and “CD4 cell count” that were presented as supplementary information. Altogether, this resulted in no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Health-related quality of life

Outcomes of the outcome category “health-related quality of life” were not investigated in the EMERALD study. This resulted in no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Side effects

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

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs", "severe AEs” (DAIDS grade 3-4) and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF; greater or lesser harm for these outcomes is therefore not proven.

This concurs with the company’s assessment.

Specific AEs

Gastrointestinal disorders as well as skin and subcutaneous tissue disorders

Statistically significant differences to the disadvantage of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF were shown for each of the outcomes “gastrointestinal disorders” and “disorders of the skin and subcutaneous tissue disorders”. The extent of the greater harm from DRV/COBI/FTC/TAF was no more than marginal for these non-serious/non-severe side effects. This resulted in no hint of greater or lesser harm of DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF for these outcomes; greater or lesser harm is therefore not proven for these outcomes.

Nervous system disorders

A statistically significant difference to the disadvantage of DRV/COBI/FTC/TAF in comparison with continuation of the ongoing therapy with 1 bPI + FTC/TDF was shown for the outcome "nervous system disorders". This resulted in a hint of greater harm from DRV/COBI/FTC/TAF in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF.

This deviates from the assessment of the company, which did not use these specific AEs for the derivation of the added benefit.

2.5.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- age (< 50 years/≥ 50 years)
- sex (men/women)
- region (Europe, North America)

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.

Based on this method, the EMERALD study provided no relevant subgroup results.

2.5.3 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 are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.3.1 Assessment of the added benefit at outcome level

The data situation presented in Section 2.5.2 results in a hint of greater harm from DRV/COBI/FTC/TAF in comparison with continuation of the ongoing therapy with 1 bPI + FTC/TDF for the outcome “nervous system disorders”. This outcome is assigned to the category “non-serious/non-severe side effects”, because the AEs included in this outcome are mostly rated as non-serious in comparison with the frequent AEs. The extent of the respective added benefit at outcome level was estimated from this result (see Table 14).

Table 14: Extent of added benefit at outcome level: DRV/COBI/FTC/TAF vs. bPIa + FTC/TDF (pretreated adults)

Outcome category **Outcome**	**DRV/COBI/FTC/TAF vs. bPI[a] + FTC/TDF** **Proportion of events or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
All-cause mortality	0% vs. 0% RR: NC	Lesser benefit/added benefit not proven
Morbidity		
AIDS-defining events Additional information: "virologic response" Snapshot CD4 cell count (cells/mm^3)	0% vs. 0% RR: NC 94.9% vs. 93.7% RR: 1.01 [0.98; 1.05]; p = 0.420 18.69 vs. 4.91 MD: 13.78 [-4.89; 32.45]; p = 0.148	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes of this outcome category were not investigated in the study included.		
Side effects		
SAEs	4.5% vs. 4.8% RR: 0.94 [0.54; 1.63]; p = 0.866	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	6.7% vs. 7.9% RR: 0.84 [0.55; 1.30]; p = 0.454	Greater/lesser harm not proven
Discontinuation due to AEs	1.3% vs. 1.1% RR: 1.24 [0.39; 3.92]; p = 0.745	Greater/lesser harm not proven
Gastrointestinal disorders	26.7% vs. 19.8% RR: 1.35 [1.07; 1.70]; RR: 0.74 [0.59; 0.93][d]; p = 0.011	Outcome category: “non-serious/non-severe symptoms/late complications” $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]
Skin and subcutaneous tissue disorders	15.2% vs. 10.1% RR: 1.51 [1.07; 2.14]; RR: 0.66 [0.47; 0.93][d]; p = 0.017	Outcome category: “non-serious/non-severe symptoms/late complications” $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]

(continued)

Table 14: Extent of added benefit at outcome level: DRV/COBI/FTC/TAF vs. bPI[a] + FTC/TDF (pretreated adults) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**DRV/COBI/FTC/TAF vs. bPI[a] + FTC/TDF** **Proportion of events or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Nervous system disorders	15.2% vs. 9.3% RR: 1.64 [1.15; 2.35]; RR: 0.61 [0.43; 0.87][d]; p = 0.005 Probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Greater harm, extent: "minor"

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
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: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
AE: adverse event; AIDS: acquired immunodeficiency syndrome; ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; CD4: cluster of differentiation 4; CI: confidence interval, CI_u: upper limit of confidence interval; COBI: cobicistat; DAIDS: Division of AIDS; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; LPV/r: ritonavir-boosted lopinavir; MD: mean difference (change between start of study and week 48); NC: not calculable; RR: relative risk; SAE: serious adverse event; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; TLOVR: Time to Loss of Virologic Response; vs.: versus

2.5.3.2 Overall conclusion on added benefit

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

Table 15: Positive and negative effects from the assessment of DRV/COBI/FTC/TAF in comparison with bPIa + FTC/TDF (pretreated adults)

Positive effects	**Negative effects**
–	Non-serious/non-severe side effects ▪ Nervous system disorders: hint of greater harm – extent: "minor"
There were no results on the outcome "health-related quality of life". Outcomes of this outcome category were not investigated in the included EMERALD study.	

a: Consisting of one of the following drug combinations: DRV/co, DRV/r, ATV/co, ATV/r or LPV/r.
ATV/co: cobicistat-boosted atazanavir; ATV/r: ritonavir-boosted atazanavir; bPI: boosted protease inhibitor; COBI: cobicistat; DRV: darunavir; DRV/co: cobicistat-boosted darunavir; DRV/r: ritonavir-boosted darunavir; FTC: emtricitabine; LPV/r: ritonavir-boosted lopinavir; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil

Overall, a negative effect remains for DRV/COBI/FTC/TAF in comparison with the continuation of the ongoing treatment with 1 bPI + FTC/TDF. In summary, there is a hint of greater harm from DRV/COBI/FTC/TAF with the extent "minor" in comparison with continuation of ongoing treatment with 1 bPI + FTC/TDF in pretreated adults with HIV-1 infection without indication for a treatment switch.

The company presented no data for pretreated HIV-1 infected patients with indication for a treatment switch. For this population, there was no hint of an added benefit; an added benefit is therefore not proven.

2.5.4 List of included studies

TMC114IFD3013 (EMERALD)

Janssen R&D Ireland. A Phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a bPI combined with FTC/TDF fumarate in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects [online]. In: EU Clinical Trials Register. [Accessed: 13.10.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-003052-31.

Janssen R&D Ireland. Study to evaluate efficacy and safety of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) regimen versus bPI along with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) regimen in virologically-suppressed, HIV-1 infected participants: full text view [online]. In: ClinicalTrials.gov. 10.10.2017 [Accessed: 13.10.2017]. URL: https://ClinicalTrials.gov/show/NCT02269917.

Janssen Reseach & Development. A Phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor (bPI) combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects: study TMC114IFD3013 (EMERALD); clinical study report [unpublished]. 2017.

Janssen Reseach & Development. A Phase 3, randomized, active-controlled, open-label study to evaluate the efficacy, safety and tolerability of switching to a darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) once-daily single-tablet regimen versus continuing the current regimen consisting of a bPI combined with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in virologically-suppressed, human immunodeficiency virus type 1 (HIV-1) infected subjects: study TMC114IFD3013 (EMERALD); Zusatzanalysen [unpublished]. 2017.

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 DRV/COBI/FTC/TAF (status: 7 August 2017)
- bibliographical literature search on DRV/COBI/FTC/TAF (last search on 2 August 2017)
- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 7 August 2017)

To check the completeness of the study pool:

- search in trial registries for studies on DRV/COBI/FTC/TAF (last search on 9 October 2017)

In its dossier, the pharmaceutical company presented no relevant study on research question 4. Nor was a relevant study identified from the check of the completeness.

2.6.2 Results on added benefit

The company presented no data for the assessment of the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT in pretreated HIV-1 infected adolescents. Hence, there was no hint of an added benefit of DRV/COBI/FTC/TAF in comparison with the ACT; an added benefit is therefore not proven.

2.6.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT in pretreated HIV-1 infected adolescents, an added benefit of DRV/COBI/FTC/TAF is not proven for these patients.

2.6.4 List of included studies

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

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of DRV/COBI/FTC/TAF in comparison with the ACT is summarized in Table 16.

Table 16: DRV/COBI/FTC/TAF: probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
1	Treatment-naive adults	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TDF/TAF plus FTC or abacavir plus lamivudine)	Added benefit not proven
2	Treatment-naive adolescents[b]	Rilpivirine or dolutegravir, each in combination with 2 nucleoside/nucleotide analogues (TAF plus FTC or abacavir plus lamivudine)	Added benefit not proven
3	Pretreated adults (without indication for a treatment switch)	Individual ART based on prior treatment(s) and under consideration of the reason for the switch of treatment, particularly treatment failure due to virologic failure and possibly accompanying development of resistance, or due to side effects[c]	Hint of lesser benefit
	Pretreated adults (with indication for a treatment switch)		Added benefit not proven
4	Pretreated adolescents[b]		Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Twelve years of age and older and with a body weight of at least 40 kg.
c: Non-drug treatment is not an option in the therapeutic indication “HIV infection”.
ACT: appropriate comparator therapy; ART: antiretroviral therapy; COBI: cobicistat; DRV: darunavir; FTC: emtricitabine; G-BA: Federal Joint Committee; TAF: tenofovir alafenamide; TDF: tenovofir disoproxil

The assessment described above deviates from that of the company, which considered an added benefit or greater harm as not proven for all 4 research questions. Moreover, the company does not distinguish between pretreated HIV-1 infected adults with and without indication for a treatment switch.

The approach for deriving an overall 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.

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. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-48-darunavir-cobicistat-emtricitabine-tenofovir-alafenamide-hiv-infection-benefit-assessment-according-to-35a-social-code-book-v.8195.html.