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Elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide – Addendum to Commission A15-61[1]

Addendum

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[2] Due to legal data protection regulations, employees have the right not to be named.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
COBI	cobicistat
EVG	elvitegravir
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RNA	ribonucleic acid
SGB	Sozialgesetzbuch (Social Code Book)
TAF	tenofovir alafenamide

1 Background

On 9 May 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A15-61 (Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The pharmaceutical company (hereinafter referred to as "the company") had presented a one-arm study on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF) in adolescents 12 years of age and older (study GS-US-292-0106, hereinafter referred to as "study 292-0106") as additional information in its dossier [2]. It had excluded this study from the benefit assessment because it had considered it as unsuitable for methodological reasons (one-arm study design without data on the appropriate comparator therapy [ACT]). The 292-0106 study was not used for the benefit assessment [1].

To be able to make a decision on the added benefit of EVG/COBI/FTC/TAF, the G-BA commissioned IQWiG with the presentation and, if possible, assessment of the one-arm study 292-0106 presented by the company in the dossier.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Description of study 292-0106

The 292-0106 study [3-8] was a one-arm study on EVG/COBI/FTC/TAF. It included human immunodeficiency virus (HIV)-infected antiretroviral treatment-naive adolescents between ≥ 12 and < 18 years of age (cohort 1) and children between 6 and < 12 years of age with antiretroviral pretreatment (cohort 2).

The patients in cohort 1 (50 patients in total) reflected the population corresponding to the approval of EVG/COBI/FTC/TAF and research question 2 of benefit assessment A15-61 [1] (treatment-naive adolescents 12 years of age and older). Inclusion criteria for the patients in this cohort included body weight ≥ 35 kg, a ribonucleic acid (RNA) viral load of ≥ 1000 copies/mL, and a genotype report showing sensitivity to EVG, FTC, and tenofovir. The patients received 150 mg EVG, 150 mg COBI, 200 mg FTC, and 10 mg TAF daily. Further characteristics of the 292-0106 study and of the patients in cohort 1 are presented below in Table 1 to Table 4.

Based on the data from the one-arm study 292-0106, with missing information on the ACT and the corresponding lack of the investigation of effects, no conclusion on the added benefit was possible. The results of cohort 1 of the 292-0106 study are presented as additional information in Appendix A.

Table 1: Characteristics of the 292-0106 study – one-arm study, EVG/COBI/FTC/TAF

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
292-0106	Open-label, one-arm	HIV-1-infected children (6– < 12 years) with plasma HIV-1 RNA viral load < 50 copies/mL and antiretroviral treatment-naive adolescents (12– < 18 years and body weight ≥ 35 kg) with plasma HIV-1 RNA viral load ≥ 1000 copies/mL, eGFR ≥ 90 mL/min/1.73m^2	EVG/COBI/FTC/TAF (N = ND) cohort 1: adolescents (n = 50) cohort 2: children[b] (n = ND)	Screening: 35 days Treatment: 48 weeks with possible extension phase Follow-up: 30 days	9 centres in South Africa, Thailand, Uganda, USA 5/2013–ongoing Data cut-off at week 24: 8/2014 Data cut-off at week 48: 8/2015	Primary: virologic response at week 24 Secondary: AIDS-defining events (CDC class C), virologic response at week 48, change in CD4 cell count, mortality, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes.
b: Does not concur with the patient population approved for EVG/COBI/FTC/TAF [9] and is no longer presented in the following tables.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; COBI: cobicistat; eGFR: estimated glomerular filtration rate (according to Schwartz formula); EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus (type 1); n: relevant subpopulation; N: number of patients included; ND: no data; RNA: ribonucleic acid; TAF: tenofovir alafenamide

Table 2: Characteristics of the intervention of the 292-0106 study – one-arm study, EVG/COBI/FTC/TAF

Study	Intervention	Prior and concomitant medication
292-0106	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg once daily	**Non-permitted concomitant treatment:** ▪ contraceptives, orally or as patch ▪ immunosuppressant treatment or chemotherapy within 3 months before screening ▪ HMG-CoA reductase inhibitors (simvastatin, lovastatin, cerivastatin) ▪ systemic glucocorticoids, except short-term treatment (≤ 1 week) with prednisone as pulse therapy ▪ herbal (St. John's Wort, echinacea) and natural agents
COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; TAF: tenofovir alafenamide		

Table 3: Characteristics of the study population (demography and renal function) of the 292-0106 study – one-arm study, EVG/COBI/FTC/TAF

Study Group	N[a]	Age [years] mean (SD)	Sex [F/M] %	Ethnicity Caucasian/Asian/black %	eGFR (mL/min) median (Q1; Q2	Treatment discontinuation n (%)	Study discontinuation n (%)
292-0106							
EVG/COBI/FTC/ TAF	50	15 (2)	56/44	0/12/88	156.0 (129.0; 185.0)	2 (4.0)[b]	2 (4.0)

a: Number of patients in the safety population, which includes all patients who received at least one dose of the study treatment.
b: According to the information provided by the company in Module 4A, the patients discontinued treatment and the study.

COBI: cobicistat; eGFR: estimated glomerular filtration rate (according to Schwartz formula); EVG: elvitegravir; F: female; FTC: emtricitabine; M: male; n: number of patients with event; N: number of patients included; Q: quartile; SD: standard deviation; TAF: tenofovir alafenamide

Table 4: Characteristics of the study population (disease severity at baseline) of the 292-0106 study – one-arm study, EVG/COBI/FTC/TAF

Study Group	N[a]	Viral load (log_{10} copies/mL) median (Q1; Q3)	Baseline viral load HIV-1 RNA copies/mL n (%)		CD4 cell count/µL median (Q1; Q3)	CD4 cell count/µL n (%)		HIV disease stage n (%)		
			≤ 100 000	> 100 000		< 350	≥ 350	Asymptomatic	Symptomatic	AIDS
292-0106										
EVG/COBI/ FTC/TAF	50	4.65 (4.25; 4.94)	39 (78.0)	11 (22.0)	456 (332; 574)	13 (26.0)[b]	37 (74.0)[b]	42 (84.0)	8 (16.0)	0

a: Number of patients in the safety population, which includes all patients who received at least one dose of the study treatment.
b: Institute's calculation.

AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus (type 1); n: number of patients with event; N: number of patients included; Q: quartile; RNA: ribonucleic acid; TAF: tenofovir alafenamide

2.2 Summary

Based on the data from the one-arm study 292-0106, with missing information on the ACT and the corresponding lack of the investigation of effects, no conclusion on the added benefit of EVG/COBI/FTC/TAF in comparison with the ACT was possible. The assessment of dossier assessment A15-61 for research question 2 (treatment-naive adolescents 12 years of age and older) has not been changed: No data for the assessment of the added benefit were available for treatment-naive adolescents. Hence an added benefit of EVG/COBI/FTC/TAF in comparison with the ACT for this population is not proven.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Elvitegravir/Cobicistat/ Emtricitabin/ Tenofoviralafenamid: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A15-61 [online]. 30.03.2016 [Accessed: 08.04.2016]. (IQWiG-Berichte; Volume 380). URL: https://www.iqwig.de/download/A15-61_Elvitegravir-CobicistatEmtricitabin-Tenofoviralafenamid_Nutzenbewertung-35a-SGB-V.pdf.

2. Gilead Sciences. Elvitegravir/ Cobicistat/ Emtricitabin/ Tenofoviralafenamid (Genvoya): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4A; zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg), die mit dem humanen Immundefizienzvirus 1 (HIV-1) infiziert sind; die HI-Viren dieser Patienten dürfen keine bekanntermaßen mit Resistenzen gegen die Klasse der Integrase-Inhibitoren, Emtricitabin oder Tenofovir verbundenen Mutationen aufweisen; medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 01.01.2016 [Accessed: 23.05.2016]. URL: https://www.g-ba.de/downloads/92-975-1318/2016-01-01_Modul4A_Elvitegravir-Cobicistat-Emtricitabin-Tenofoviralafenamid.pdf.

3. Gilead. A phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents: study GS-US-292-0106; interim clinical study report [unpublished]. 2014.

4. Gilead. A phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents: study GS-US-292-0106; clinical study protocol [unpublished]. 2013.

5. Gilead. A phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents: study GS-US-292-0106; clinical study protocol amendment 1 [unpublished]. 2013.

6. Gilead. A phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents: study GS-US-292-0106; statistical analysis plan [unpublished]. 2014.

7. Gilead. A phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents and virologically suppressed children: study GS-US-292-0106; second interim clinical study report [unpublished]. 2015.

8. Gilead. A phase 2/3, open-label study of the pharmacokinetics, safety, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) single tablet regimen (STR) in HIV-1 infected antiretroviral treatment-naive adolescents and virologically suppressed children: study GS-US-292-0106; clinical study protocol amendment 2 [unpublished]. 2015.

9. Gilead. Genvoya 150 mg / 150 mg / 200 mg / 10 mg Filmtabletten: Fachinformation [online]. 11.2015 [Accessed: 22.01.2016]. URL: http://www.fachinfo.de/.

10. Food and Drug Administration. Guidance for industry: human immunodeficiency virus-1 infection; developing antiretroviral drugs for treatment [online]. 11.2015 [Accessed: 29.02.2016]. URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf.

Appendix A – Supplementary presentation of the results of the 292-0106 study (cohort 1)

Table 5: Results (mortality and morbidity) of the 292-0106 study – one-arm study, EVG/COBI/FTC/TAF (week 48)

Study	**EVG/COBI/FTC/TAF**		
Outcome category **Outcome**	**N**	**Patients with event** **n (%)**	
292-0106			
Mortality			
All-cause mortality	50	0 (0)	
Morbidity			
AIDS-defining events (CDC class C)	50	0 (0)	
Additional information: surrogate outcome "virologic response" snapshot (HIV-1 RNA < 50 copies/mL)			
Snapshot[a]	50	46 (92.0)	
Sensitivity analysis: missing = failure[b]	*50*	*46 (92.0)*	
Sensitivity analysis: missing = excluded[b]	*48*[c]	*46 (95.8)*	
	N[d]	**Baseline values mean (SD)**	**Change at end of study mean (SD)**
Additional information: surrogate outcome "CD4 cell count/µL"	47	471 (212.2)	224 (170.3)

a: Calculated with FDA snapshot algorithm, primary analysis of the company. Time window for the analysis: day 308 up to and including day 377; if results from several samples are available within the time window, the last measurement is relevant [10].
b: No information on the analysis time window for the analysis in the study documents.
c: Patients without missing values at all dates of analysis up to week 48.
d: Number of patients considered in the analysis; the values at the start of the study may be based on other patient numbers.

CDC: Centers for Disease Control and Prevention; COBI: cobicistat; EVG: elvitegravir; FDA: Food and Drug Administration; FTC: emtricitabine; HIV-1: human immunodeficiency virus (type 1); n: number of patients with event; N: number of analysed patients; SD: standard deviation; TAF: tenofovir alafenamide

Table 6: Results (side effects) of the 292-0106 study – one-arm study, EVG/COBI/FTC/TAF (week 48)

Study	**EVG/COBI/FTC/TAF**	
Outcome category **Outcome**	**N**	**Patients with event** **n (%)**
292-0106		
Side effects		
AEs (supplementary information)	50	42 (84.0)
SAEs	50	6 (12.0)
Severe adverse events (grade 3-4)	50	6 (12.0)
Discontinuation due to AEs	50	0 (0)
Nervous system disorders[a]	50	17 (34.0)
Psychiatric disorders[a]	50	6 (12.0)
Skin and subcutaneous tissue disorders[a]	50	15 (30.0)
Gastrointestinal disorders[a]	50	27 (54.0)
Renal and urinary disorders[a]	50	2 (4.0)
Bone fractures[b]	50	2 (4.0)

a: SOC.
b: SMQ defined on the basis of osteopenia/osteoporosis.
AE: adverse event; COBI: cobicistat; EVG: elvitegravir; FTC: emtricitabine; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; SMQ: standardized MedDRA Query; SAE: serious adverse event; SOC: System Organ Class; TAF: tenofovir alafenamide