IQWiG Reports – Commission No. A22-38

Dolutegravir (HIV in children and adolescents aged 6 to < 18 years) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Dolutegravir (HIV bei Kindern und Jugendlichen ab 6 bis < 18 Jahren) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 June 2022). 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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No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

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Table of contents

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
ACT	appropriate comparator therapy
AE	adverse event
ART	antiretroviral therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
WHO	World Health Organization
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

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. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 April 2022.

The present benefit assessment was performed because a reassessment was to be carried out on the basis of a data situation that corresponds to the currently generally recognized state of medical-scientific knowledge, including the ODYSSEY study. The entire available evidence on dolutegravir in children and adolescents aged 6 to < 18 years infected with human immunodeficiency virus type 1 (HIV-1) was to be considered for the reassessment.

Research question

The aim of this report was to assess the added benefit of dolutegravir in comparison with the appropriate comparator therapy (ACT) in children and adolescents from 6 to < 18 years of age infected with HIV-1.

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of dolutegravir

Research question	Therapeutic indication	ACT[a]
1	Treatment-naive adolescents aged 12 to < 18 years with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus emtricitabine or in combination with abacavir plus lamivudine
2	Treatment-experienced adolescents aged 12 to < 18 years with HIV-1[b]	Individual antiretroviral therapy[c]
3	Treatment-naive children aged 6 to < 12 years with HIV-1[b]	Atazanavir plus ritonavir in combination with abacavir plus emtricitabine or in combination with abacavir plus lamivudine
4	Treatment-experienced children aged 6 to < 12 years with HIV-1[b]	Individual antiretroviral therapy[c]

a. Presented is the respective ACT specified by the G-BA. The use of the drugs in accordance with the marketing authorisation must be observed. Here, in particular, the age-appropriate use of the medicinal products.
b. Which have no known or suspected resistances to the integrase inhibitor (INI) class.
c. Choosing from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

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 added benefit.

Research questions 1 and 3: treatment-naive adolescents and children.

In its dossier, the company did not present any data for the assessment of the added benefit of dolutegravir compared with the ACT in HIV-1 infected therapy-naive adolescents aged 12 to < 18 years and in HIV-1 infected therapy-naive children aged 6 to < 12 years. The ODYSSEY study is not relevant for the benefit assessment for treatment-naive adolescents and children, as the ACT was not implemented. This resulted in no hint of an added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

Research questions 2 and 4: treatment-experienced adolescents and children

The ODYSSEY study is potentially relevant for research question 2 (treatment-experienced adolescents aged 12 to < 18 years who are infected with HIV-1) and research question 4 (treatment-experienced children aged 6 to < 12 years who are infected with HIV-1).

ODYSSEY is an open-label RCT comparing dolutegravir-based antiretroviral therapy (ART) with non-dolutegravir-based ART. Patients were assigned to 2 cohorts. Treatment-naive children and adolescents were randomly assigned to cohort A, and pretreated children and adolescents for whom second-line ART was indicated because they had shown treatment failure on the first ART were randomly assigned to cohort B. Subpopulations potentially relevant for research question 2 (pretreated adolescents aged 12 to < 18 years who are infected with HIV-1) and research question 4 (pretreated children aged 6 to < 12 years who are infected with HIV-1) were included in cohort B.

The company did not use the ODYSSEY study for the benefit assessment. It justified its approach by stating that dolutegravir had not been administered in compliance with the current Summary of Product Characteristics (SPC) in a substantial proportion of the relevant study population. The company explained that the sponsor of the study was the Paediatric European Network for Treatment of AIDS (PENTA) foundation. In Module 4 A, the company states that it financially supports the study, but does not have access to the patient data and therefore cannot conduct its own analyses.

The company's approach is comprehensible with regard to the non-approval-compliant administration of dolutegravir. In the ODYSSEY study, only children and adolescents weighing 40 kg or more were dosed from the beginning according to the current approval. Therefore, only a subpopulation of unknown magnitude from the ODYSSEY study corresponds to the approved therapeutic indication and thus to the research questions of the present dossier assessment. However, it is conceivable that subpopulations of the ODYSSEY study relevant for research question 2 (pretreated adolescents aged 12 to < 18 years who are infected with HIV-1) and research question 4 (pretreated children aged 6 to < 12 years who are infected with HIV-1) can be operationalized. However, this requires access to the relevant patient data.

In its dossier, the company did not present any data for the assessment of the added benefit of dolutegravir versus the ACT in HIV-1 infected pretreated adolescents aged 12 to < 18 years and in HIV-1 infected pretreated children aged 6 to < 12 years. This resulted in no hint of an added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

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

On the basis of the results presented, the probability and extent of added benefit of the drug dolutegravir in comparison with the ACT are assessed as follows:

Table 3 presents a summary of the probability and extent of the added benefit of dolutegravir.

Table 3: Dolutegravir – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adolescents aged 12 to < 18 years with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus emtricitabine or in combination with abacavir plus lamivudine	Added benefit not proven
2	Treatment-experienced adolescents aged 12 to < 18 years with HIV-1[b]	Individual antiretroviral therapy[c]	Added benefit not proven
3	Treatment-naive children aged 6 to < 12 years with HIV-1[b]	Atazanavir plus ritonavir in combination with abacavir plus emtricitabine or in combination with abacavir plus lamivudine	Added benefit not proven
4	Treatment-naive children aged 6 to < 12 years with HIV-1[b]	Individual antiretroviral therapy[c]	Added benefit not proven

a. Presented is the respective ACT specified by the GBA. The use of the drugs in accordance with the marketing authorisation must be observed. Here, in particular, the age-appropriate use of the medicinal products.
b. Which have no known or suspected resistances to the INI class.
c. Choosing from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of this report was to assess the added benefit of dolutegravir in comparison with the ACT in children and adolescents from 6 to < 18 years of age infected with HIV.

The research questions shown in Table 4 were derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of dolutegravir

Research question	Therapeutic indication	ACT[a]
1	Treatment-naive adolescents aged 12 to < 18 years with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus emtricitabine or in combination with abacavir plus lamivudine
2	Treatment-experienced adolescents aged 12 to < 18 years with HIV-1[b]	Individual antiretroviral therapy[c]
3	Treatment-naive children aged 6 to < 12 years with HIV-1[b]	Atazanavir plus ritonavir in combination with abacavir plus emtricitabine or in combination with abacavir plus lamivudine
4	Treatment-experienced children aged 6 to < 12 years with HIV-1[b]	Individual antiretroviral therapy[c]

a. Presented is the respective ACT specified by the G-BA. The use of the drugs in accordance with the marketing authorisation must be observed. Here, in particular, the age-appropriate use of the medicinal products.
b. Which have no known or suspected resistances to the integrase inhibitor (INI) class.
c. Choosing from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

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 added benefit. This concurs with the company's inclusion criteria.

2.3 Research questions 1 and 3: treatment-naive adolescents and children

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 dolutegravir (status: 14 January 2022)
- bibliographical literature search on dolutegravir (last search on 20 January 2022)
- search in trial registries/trial results databases for studies on dolutegravir (last search on 20 January 2022)
- search on the G-A website for evolocumab (last search on 20 January 2022)

To check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 13 April 2022); for search strategies, see Appendix A of the full dossier assessment

No relevant RCT was identified from the check. This concurs with the company's assessment.

The RCT ODYSSEY [3-7], which was the basis for the limitation decision of the G-BA [8], is not relevant for answering research question 1 (HIV-1-infected treatment-naive adolescents aged 12 to < 18 years) and research question 3 (HIV-1-infected treatment-naive children aged 6 to < 12 years), as the ACT was not implemented in either case (a detailed description of the ODYSSEY study can be found in Section 2.4.1). The ACT for research question 1 (HIV-1-infected treatment-naive adolescents aged 12 to < 18 years) is an ART consisting of rilpivirine in combination with tenofovir alafenamide plus emtricitabine or abacavir plus lamivudine (see Table 4). The ACT for research question 3 (HIV-1-infected treatment-naive children aged 6 to < 12 years) is an ART consisting of atazanavir in combination with abacavir plus emtricitabine or abacavir plus lamivudine (see Table 4). However, in the ODYSSEY study, 145 of 157 (92%) of the treatment-naive children and adolescents in the control arm received an ART based on efavirenz. Only 2 children and adolescents received ART based on rilpivirine; atazanavir was not administered at all to treatment-naive children and adolescents (see Table 7).

2.3.2 Results on added benefit

In its dossier, the company did not present any data for the assessment of the added benefit of dolutegravir compared with the ACT in HIV-1 infected therapy-naive adolescents aged 12 to < 18 years and in HIV-1 infected therapy-naive children aged 6 to < 12 years. This resulted in no hint of an added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Since the company did not present any data for the assessment of the added benefit of dolutegravir in comparison with the ACT in treatment-naive HIV-1-infected adolescents from 12 to < 18 years as well as in treatment-naive HIV-1-infected children from 6 to < 12 years, an added benefit of dolutegravir is not proven for these patients.

The assessment described above deviates from the assessment by the company, which claimed a hint of a non-quantifiable added benefit for both research questions.

2.4 Research questions 2 and 4: treatment-experienced adolescents and children

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 dolutegravir (status: 14 January 2022)
- bibliographical literature search on dolutegravir (last search on 20 January 2022)
- search in trial registries/trial results databases for studies on dolutegravir (last search on 20 January 2022)
- search on the G-A website for evolocumab (last search on 20 January 2022)

To check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 13 April 2022); for search strategies, see Appendix A of the full dossier assessment

By checking the completeness of the study pool, the RCT ODYSSEY was identified. This deviates from the company's approach, which did not include the ODYSSEY study in its assessment and presented no results.

The company justified its approach by stating that dolutegravir had not been administered in compliance with the current SPC in a substantial proportion of the relevant study population [9,10]. The company explained that the sponsor of the study was the PENTA foundation. In Module 4 A, the company states that it financially supports the study, but does not have access to the patient data and therefore cannot conduct its own analyses.

The company’s approach is comprehensible with regard to the non-approval-compliant administration of dolutegravir. In the ODYSSEY study, only children and adolescents weighing 40 kg or more were dosed from the beginning according to the current approval. Therefore, only a subpopulation of unknown magnitude from the ODYSSEY study corresponds to the approved therapeutic indication and thus to the research questions of the present dossier assessment. However, it is conceivable that subpopulations of the ODYSSEY study relevant for research question 2 (pretreated adolescents aged 12 to < 18 years who are infected with HIV-1) and research question 4 (pretreated children aged 6 to < 12 years who are infected with HIV-1) can be operationalized. However, this requires access to the relevant patient data.

The following sections present the characteristics of the ODYSSEY study.

Study design

Table 5 and Table 6 describe the ODYSEEY study.

Table 5: Characteristics of the ODYSSEY study – RCT, direct comparison: dolutegravir-based therapy vs. standard treatment

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period of study	Primary outcome; secondary outcomes[a]
ODYSSEY	RCT, open-label	Children and adolescents (< 18 years) with HIV-1 infection without resistance to integrase inhibitors with body weights ≥ 14 kg[b] cohort A: treatment-naive children and adolescents cohort B[c]: pretreated children and adolescents (second line)	Dolutegravir + 2 NRTI (N = 350) standard treatment (N = 357) subpopulations: **adolescents (12 to < 18 years)** 1. treatment-naive ▫ dolutegravir + 2 NRTI (N = 75) ▫ standard treatment (N = 68) 2. pretreated ▫ dolutegravir + 2 NRTI (N = 107) ▫ standard treatment (N = 114) children [6 to < 12 years] 3. treatment-naive ▫ dolutegravir + 2 NRTI (N = 72) ▫ standard treatment (N = 84) 4. pretreated ▫ dolutegravir + 2 NRTI (N = 81) ▫ standard treatment (N = 80)	Screening: < 4 weeks treatment and observation: 96 weeks until the last randomized patients was observed for 96 weeks extended treatment and observation: after the last study visit, patients were offered to continue the treatment	29 study centres in Germany, Portugal, South Africa, Spain, Thailand, Uganda, United Kingdom, Zimbabwe 09/2016–ongoing[d]	Primary: virologic or clinical failure[e] secondary: mortality, morbidity, health-related quality of life, health status, AEs

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes exclusively contain information on potentially relevant available outcomes for this benefit assessment.
b. Children with body weights from 3 to < 14 kg were randomized into a separate cohort. Since the children in this cohort were presumably < 6 years old, this cohort is not relevant for the present benefit assessment and is therefore not considered further.
c. The start of a second-line therapy had to be planned (change of at least 2 drugs due to treatment failure or change of the third drug if no NRTI resistance was detected). Within 4 weeks before screening, the viral load was to be ≥ 500 copies/mL.
d. Randomization had been completed by 22 June 2018 (for treatment-naive children and adolescents weighing 35 kg or more by July 2017). The last participant reached 96 weeks of observation on 24 April 2020.
e. The outcome was defined by insufficient virologic response (< 1 $\log_{10}$ reduction at week 24 and treatment switch), virologic failure (viral load ≥ 400 copies/mL at or after week 36 with confirmation at the following visit), AIDS-defining event (WHO grade 3 or 4) or death.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; HIV-1: human immunodeficiency virus (type 1); n: relevant subpopulation; N: number of randomized patients; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; RCT: randomized controlled trial; WHO: World Health Organization

Table 6: Characteristics of the intervention – RCT, direct comparison: dolutegravir-based therapy vs. standard treatment

Study	Intervention	Comparison	Prior and concomitant treatment
ODYSSEY	Dolutegravir + 2 NRTI[a] dolutegravir dose once daily, orally, depending on body weight: <u>14 to < 20 kg BW</u>: 20 mg film-coated tablet[b] ▪ from May 2018: 25 mg film-coated tablet[b] or 25 mg tablet for the preparation of a suspension[c] ▪ from May 2019: 25 mg tablet for the preparation of a suspension[c] <u>20 to < 25 kg BW</u>: 25 mg film-coated tablet[b] ▪ from May 2018: 25 mg film-coated tablet[b] or 50 mg film-coated tablet[c] or 30 mg tablet for the preparation of a suspension[c] ▪ from May 2019: 50 mg film-coated tablet[c] <u>25 to < 30 kg BW</u>: 25 mg film-coated tablet[b] ▪ from April 2018: 25 mg film-coated tablet[b] or 50 mg film-coated tablet[c] ▪ from May 2019: 50 mg film-coated tablet[c] <u>30 to < 40 kg BW</u>: 35 mg film-coated tablet[b] ▪ from April 2018: 35 mg film-coated tablet[b] or 50 mg film-coated tablet[c] ▪ from May 2019: 50 mg film-coated tablet[c] from 40 kg BW: 50 mg film-coated tablet[c]	1 boosted protease inhibitor (PI/b) or NNRTI or INI (expect dolutegravir) + 2 NRTI[a]	**Pretreatment** <u>cohort A:</u> ▪ treatment-naive <u>cohort B:</u> ▪ 1 prior antiretroviral therapy[d] **non-permitted concomitant treatment** ▪ hepatitis C therapies

a. The treating physician specified the drugs taking into account international, national or local guidelines, prior treatments and resistance before randomization. The NRTI therapy should be maintained throughout the entire study period. Adjustments could be made in case of toxicities, intolerance or change of treatment due to treatment failure. Additional specification for cohort B: 1 new drug and at least 1 NRTI with maintained activity compared to prior therapy.
b. Dosage lower than specified in the current SPC.
c. Corresponds to the currently approved dosage.
d. Within 4 weeks before screening, the viral load was to be ≥ 500 copies/mL. Prior therapy of > 2 weeks with an INI was not allowed.

BW: body weight; INI: integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI/b: boosted protease inhibitor; RCT: randomized controlled trial

ODYSSEY is an open-label RCT comparing dolutegravir-based ART with non-dolutegravir-based ART. Patients were assigned to 2 cohorts. Treatment-naive children and adolescents were randomly assigned to cohort A, and pretreated children and adolescents for whom second-line

ART was indicated because they had shown treatment failure on first-line ART were randomly assigned to cohort B. Cohort A included 311 and cohort B included 396 children and adolescents. Cohort A is not relevant for research questions 2 + 4. Subpopulations of unknown magnitude potentially relevant for research question 2 (pretreated adolescents aged 12 to < 18 years who are infected with HIV-1) and research question 4 (pretreated children aged 6 to < 12 years who are infected with HIV-1) were included in cohort B.

Patients in the intervention arm received ART consisting of dolutegravir and 2 nucleoside or nucleotide reverse transcriptase inhibitors (NRTI). Patients in the comparator arm received ART consisting of 2 NRTIs and, as a third drug, 1 PI/b or 1 non-nucleoside reverse transcriptase inhibitor (NNRTI) or 1 integrase inhibitor (INI) except dolutegravir.

In both study arms, all drugs (except dolutegravir) were to be determined by the treating physician prior to randomization, taking into account international, national and local guidelines and under consideration of prior therapy and resistance.

Primary outcome of the study was the virologic or clinical treatment failure. This composite outcome is reached by the occurrence of one of the following criteria:

- insufficient virologic response defined by < 1 $\log_{10}$ reduction in viral load at week 24 (or a viral load of ≥ 50 copies/mL at week 24 in participants with a viral load of < 500 copies/mL at baseline) and switch to a second-line or third-line ART
- virologic failure defined by a viral load of ≥ 400 copies/mL at or after week 36 with confirmation at the following visit
- New or recurrent AIDS-defining event (World Health Organization [WHO] grade 3 or 4) (confirmed by an outcome review committee)
- Death from any cause

Patient-relevant secondary outcomes were “mortality”, “morbidity”, “health-related quality of life”, “health status” and adverse events (AEs).

The children and adolescents were treated and observed until the last included patient had been observed for 96 weeks. This was the case on 24 April 2020. The median observation period in the study was 142 weeks. After this, all children and adolescents were subsequently offered prolonged treatment and observation.

Dosage of dolutegravir in the ODYSSEY study

The dolutegravir dosage at the start of the ODYSSEY study in September 2016 (see Table 6) corresponded to the approval valid at the time [11,12]. During the course of the study, both the dosage in the study (see Table 6) and the approval were adjusted based on current data on pharmacokinetics [9,10]. Consequently, in the study, only children and adolescents weighing 40 kg or more were dosed from the beginning according to the current approval. For children

and adolescents in the lower weight classes, the dosage at baseline was clearly lower than specified in the current approval. From April 2018 at the earliest, the dosage in the weight classes < 40 kg was adjusted according to the currently approved dosage. Since recruitment in the weight classes of ≥ 35 kg ended in July 2017, all children and adolescents in the 35 kg to < 40 kg weight class initially received dosed that were too low. In the weight classes from 14 kg to < 35 kg, recruitment continued until June 2018. In these weight classes, only participants enrolled in the study in April, May or June 2018 may have been dosed correctly from the start. However, there is no information available on how many children and adolescents in which age class received a dosage that was too low and for how long.

Despite the fact that the majority of the study participants received too low a dose over a long period of time, usable analyses from the data of the ODYSSEY study are conceivable for subpopulations of research question 2 (HIV-1 infected pretreated adolescents aged 12 to < 18 years) and research question 4 (HIV-1 infected pretreated children aged 6 to < 12 years). For example, 125 pretreated children and adolescents in the weight class of 40 kg and more were included in the study (N = 66 in the dolutegravir arm and N = 59 in the comparator arm). In the dolutegravir arm, these children and adolescents received doses according to the current approval for the entire study period. The study population in this weight class (> 40 kg) thus meets all requirements for the present research questions 2 and 4, although due to the weight they would possibly rather be assigned to research question 2 (HIV-1 infected pretreated adolescents aged 12 to < 18 years). However, information on the age structure in the weight class of 40 kg and more is not available. In addition, it is possible that data from pretreated children and adolescents from the lower weight classes can also be meaningfully analysed, provided that they were dosed largely in accordance with the current approval due to late study inclusion and an overall long treatment duration. Corresponding analyses were not available, however.

Characteristics of the patients in the ODYSSEY study

Table 7 shows the characteristics of the children and adolescents in the ODYSSEY study.

Table 7: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: dolutegravir-based therapy vs. standard treatment (multipage table)

Study characteristic category	Treatment-naive children and adolescents (cohort A)		Treatment-experienced children and adolescents (cohort B)	
	dolutegravir N[a] = 154	standard treatment N[a] = 157	dolutegravir N[a] = 196	standard treatment N[a] = 200
ODYSSEY study				
Age [years], mean (SD)	12 (4)	12 (4)	12 (4)	12 (3)
2 - < 6 years, n (%)	7 (5)	5 (3)	8 (4)	6 (3)
6 - < 12 years, n (%)	72 (47)	84 (54)	81 (41)	80 (40)
12 - < 18 years, n (%)	75 (49)	68 (43)	107 (55)	114 (57)
Sex [f/m], %	56/44	49/51	44/56	47/53
Body weight [kg], mean (SD)	34.5 (14.5)	34.2 (14.5)	33.7 (12.1)	33.6 (12.0)
14 - < 20, n (%)	18 (12)	20 (13)	21 (11)	23 (12)
20 - < 25, n (%)	33 (21)	29 (18)	38 (19)	35 (18)
25 - < 30, n (%)	26 (17)	32 (20)	32 (16)	27 (14)
30 - < 35, n (%)	16 (10)	17 (11)	22 (11)	34 (17)
35 - < 40, n (%)	12 (8)	10 (6)	17 (9)	22 (11)
≥ 40, n (%)	49 (32)	49 (31)	66 (34)	59 (30)
Region, n (%)				
Germany	5 (2)	2 (1)	0 (0)	1 (1)
Portugal	1 (1)	0 (0)	0 (0)	0 (0)
Spain	1 (1)	3 (2)	2 (1)	2 (1)
United Kingdom	2 (1)	4 (3)	1 (1)	1 (1)
Thailand	24 (16)	26 (17)	124 (63)	108 (54)
South Africa	36 (23)	41 (26)	25 (13)	42 (21)
Uganda	46 (30)	53 (34)	124 (63)	108 (54)
Zimbabwe	39 (25)	28 (18)	40 (20)	39 (20)
Viral load at baseline, n (%)				
< 400 copies/mL	5 (3)	10 (6)	0 (0)	0 (0)
400 - < 1000 copies/mL	7 (5)	4 (3)	4 (2)	2 (1)
1000 - < 10000 copies/mL	28 (18)	34 (22)	49 (25)	73 (37)
10000 - < 50000 copies/mL	41 (27)	36 (23)	74 (38)	77 (39)
50000 - < 100000 copies/mL	23 (15)	21 (13)	21 (11)	24 (12)
100000 - < 500000 copies/mL	40 (26)	42 (27)	42 (21)	19 (10)
500000 - < 1000000 copies/mL	6 (4)	6 (4)	4 (2)	4 (2)
≥ 1000000 copies/mL	4 (3)	3 (2)	2 (1)	1 (1)
Not recorded	0 (0)	1 (1[b])	0 (0)	0 (0)
Treatment at start of study, n (%)				
Nucleoside reverse transcriptase inhibitor (NRTI)				
Abacavir + lamivudine	126 (82)	122 (78)	106 (54)	109 (55)
Zidovudine + lamivudine	0 (0)	3 (2)	37 (19)	37 (19)

Table 7: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: dolutegravir-based therapy vs. standard treatment (multipage table)

Study characteristic category	Treatment-naive children and adolescents (cohort A)		Treatment-experienced children and adolescents (cohort B)	
	dolutegravir N[a] = 154	standard treatment N[a] = 157	dolutegravir N[a] = 196	standard treatment N[a] = 200
Tenofovir/tenofovir alafenamide + lamivudine/emtricitabine	28 (18)	32 (20)	52 (27)	52 (26)
Abacavir + tenofovir	0 (0)	0 (0)	1 (1)	2 (1)
3. Drug class				
Integrase inhibitor (INI)	154 (100)	1 (1)	196 (100)	0 (0)
NNRTI	0 (0)	149 (95)	0 (0)	5 (3)
Protease inhibitor (PI)	0 (0)	7 (4)	0 (0)	195 (98)
3. Drug				
Atazanavir	0 (0)	0 (0)	0 (0)	49 (25)
Darunavir	0 (0)	4 (3)	0 (0)	2 (1)
Dolutegravir	154 (100)	0 (0)	196 (100)	0 (0)
Efavirenz	0 (0)	145 (92)	0 (0)	5 (3)
Elvitegravir	0 (0)	1 (1)	0 (0)	0 (0)
Lopinavir	0 (0)	3 (2)	0 (0)	144 (72)
Nevirapine	0 (0)	2 (1)	0 (0)	0 (0)
Rilpivirine	0 (0)	2 (1)	0 (0)	0 (0)
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)	15 (9.7)[b]	23 (14.6)[b]	6 (3.1)[b]	13 (6.5)[b]

a. Number of randomized patients.
b. Institute's calculation.

F: female; INI: integrase inhibitor; M: male; n: number of patients in the category, 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; SD: standard deviation

The characteristics of the patients are not available separately for research questions 2 and 4. However, the table shows that 221 adolescents aged 12 to < 18 years can be assigned to research question 2 and 161 children aged 6 to < 12 years can be assigned to research question 4.

Most of the children and adolescents were recruited in Africa. Overall, only 4% of the participating children and adolescents were included in the study in Europe.

2.4.2 Results on added benefit

In its dossier, the company did not present any data for the assessment of the added benefit of dolutegravir versus the ACT in HIV-1 infected pretreated adolescents aged 12 to < 18 years and in HIV-1 infected pretreated children aged 6 to < 12 years. This resulted in no hint of an

added benefit of dolutegravir in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company did not present any data for the assessment of the added benefit of dolutegravir in comparison with the ACT in pretreated HIV-1-infected adolescents aged 12 to < 18 years as well as in pretreated HIV-1-infected children aged 6 to < 12 years, an added benefit of dolutegravir is not proven for these patients.

The assessment described above deviates from the assessment by the company, which claimed a hint of a non-quantifiable added benefit for both research questions.

2.5 Probability and extent of added benefit – summary

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

Table 8: Dolutegravir – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adolescents aged 12 to < 18 years with HIV-1[b]	Rilpivirine in combination with tenofovir alafenamide plus emtricitabine or in combination with abacavir plus lamivudine	Added benefit not proven
2	Treatment-experienced adolescents aged 12 to < 18 years with HIV-1[b]	Individual antiretroviral therapy[c]	Added benefit not proven
3	Treatment-naive children aged 6 to < 12 years with HIV-1[b]	Atazanavir plus ritonavir in combination with abacavir plus emtricitabine or in combination with abacavir plus lamivudine	Added benefit not proven
4	Treatment-naive children aged 6 to < 12 years with HIV-1[b]	Individual antiretroviral therapy[c]	Added benefit not proven

a. Presented is the respective ACT specified by the GBA. The use of the drugs in accordance with the marketing authorisation must be observed. Here, in particular, the age-appropriate use of the medicinal products.
b. Which have no known or suspected resistances to the integrase inhibitor (INI) class.
c. Choosing from the approved drugs; under consideration of prior treatment(s) and the reason for the switch of treatment, particularly treatment failure due to virologic failure and possible accompanying development of resistance, or due to side effects.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1

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 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. The PENTA Foundation. A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART [online]. 2021 [Accessed: 29.04.2022]. URL: https://www.isrctn.com/ISRCTN91737921.

4. PENTA Foundation. A Randomised Trial of Dolutegravir (DTG)-Based Antiretroviral Therapy vs. Standard of Care (SOC) in Children With HIV Infection Starting First-line or Switching to Second-line ART [online]. 2021 [Accessed: 29.04.2022]. URL: https://ClinicalTrials.gov/show/NCT02259127.

5. Fondazione PENTA ONLUS. A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART [online]. [Accessed: 29.04.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-002632-14.

6. Moore CL, Turkova A, Mujuru H et al. ODYSSEY clinical trial design: a randomised global study to evaluate the efficacy and safety of dolutegravir-based antiretroviral therapy in HIV-positive children, with nested pharmacokinetic sub-studies to evaluate pragmatic WHO-weight-band based dolutegravir dosing. BMC Infect Dis 2021; 21(1): 5. https://dx.doi.org/10.1186/s12879-020-05672-6.

7. Turkova A, White E, Mujuru HA et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. N Engl J Med 2021; 385(27): 2531-2543. https://dx.doi.org/10.1056/NEJMoa2108793.

8. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über die Veranlassung einer erneuten Nutzenbewertung nach § 35a Abs. 1 SGB V i.V.m. § 3 Abs. 1 Nr. 4 AM-NutzenV und 5. Kapitel § 13 VerfO: Anlage XII –Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Dolutegravir [online]. 2020 [Accessed: 04.05.2022]. URL: https://www.g-ba.de/downloads/39-261-4435/2020-08-20_AM-RL-XII_Dolutegravir_Veranlassung-erneute-NB.pdf.

9. ViiV Healthcare. Tivicay 5 mg Tabletten zur Herstellung einer Suspension zum Einnehmen [online]. 2022 [Accessed: 05.05.2022]. URL: https://www.fachinfo.de.

10. ViiV Healthcare. Tivicay 10 mg/25 mg/50 mg Filmtabletten [online]. 2022 [Accessed: 05.05.2022]. URL: https://www.fachinfo.de.

11. European Medicines Agency. European Public Assessment Report (EPAR): Tivicay (intenational non-proprietary name. dolutegravir). Procedure No. EMEA/H/C/002753/0000 [online]. 2013. URL: https://www.ema.europa.eu/en/documents/assessment-report/tivicay-epar-public-assessment-report_en.pdf.

12. European Medicines Agency. European Public Assessment Report (EPAR) - Extension. Tivicay (intenational non-proprietary name. dolutegravir). Procedure No. EMEA/H/C/002753/X/0018/G [online]. 2016. URL: https://www.ema.europa.eu/en/documents/variation-report/tivicay-h-c-002753-x-0018-g-epar-assessment-report-extension_en.pdf.

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