IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-08

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Dolutegravir – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Dolutegravir – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
10 February 2014

Internal Commission No.:
A14-08

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Ingo Niemetz, diabetological practice, Kassel, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Ulrike Seay
- Wolfram Groß
- Ulrich Grouven
- Elke Hausner
- Thomas Kaiser
- Sarah Mostardt
- Stefanie Reken

Keywords: dolutegravir, HIV infections, benefit assessment

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

Table of contents

List of tables[3]

Page

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

List of abbreviations

Abbreviation	Meaning
3TC	lamivudine
ABC	abacavir
ACT	appropriate comparator therapy
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
DAIDS	Division of AIDS
DRV/r	ritonavir-boosted darunavir
EQ-5D	European Quality of Life-5 Dimensions
FTC	emtricitabine
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
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 reverse transcriptase inhibitor
PI	protease inhibitor
PT	Medical Dictionary for Regulatory Activities Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SDM	symptom distress module
SGB	Sozialgesetzbuch (Social Code Book)
SOC	Medical Dictionary for Regulatory Activities System Organ Class
SPC	Summary of Product Characteristics
TDF	tenofovir

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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 10 February 2014.

Research question

The aim of this report was to assess the added benefit of dolutegravir compared with the appropriate comparator therapy (ACT) in adults and adolescents above 12 years of age infected with human immunodeficiency virus type 1 (HIV-1).

Four research questions arose, for which the G-BA specified the ACTs presented in Table 2.

Table 2: Subindications and ACT for dolutegravir

Research question	Subindication	ACT specified by the G-BA
1	**Treatment-naive adults** adults without previous ART	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)
2	**Treatment-naive adolescents** adolescents above 12 years of age without previous ART	Efavirenz in combination with abacavir plus lamivudine
3	**Pretreated adults** adults with previous ART	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 AEs. The respective approval of the drugs is to be considered.
4	**Pretreated adolescents** adolescents above 12 years of age with previous ART	
ACT: appropriate comparator therapy; AE: adverse event; ART: antiretroviral therapy		

The company largely followed the G-BA's specification of the ACT, but separated the population of pretreated patients (research question 3 and research question 4) in patients with and without integrase inhibitor (INI) resistance. For the subpopulation without INI resistance, the company specified raltegravir as component of the individual treatment as ACT.

The assessment was conducted based on patient-relevant outcomes. Only direct comparative randomized controlled trials (RCTs) with a minimum duration of 48 weeks were included in the assessment.

Results for research question 1: treatment-naive adults

The 2 RCTs SPRING-1 and SINGLE were included in the assessment. The randomized study phase was 96 weeks in both studies, in each case followed by a still ongoing open-label phase. Analyses after 48 and after 96 weeks were available for each study. The benefit assessment was conducted based on the results after 96 weeks. Treatment-naive HIV-1 infected adults were included in both studies.

The SPRING-1 study is a phase 2b study. 103 patients were enrolled in the study. Dolutegravir was compared with efavirenz, each in addition to a backbone therapy of abacavir (ABC) and lamivudine (3TC) or tenofovir (TDF) and emtricitabine (FTC).

The SINGLE study was a phase 3 study, in which 844 patients were randomized to either dolutegravir or efavirenz. The patients in the dolutegravir arm received ABC/3TC as backbone therapy, the ones in the efavirenz arm received TDF/FTC.

The risk of bias of both studies was rated as low. However, the risk of bias at outcome level was rated as high for some outcomes of the SPRING-1 study due to its open-label design.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups in the meta-analysis of the 2 studies. An added benefit of dolutegravir compared with efavirenz for overall survival is therefore not proven.

Morbidity

AIDS-defining events (CDC class C events); surrogate outcomes "virologic response" and "cluster of differentiation 4 (CD4) cell count"

There was no statistically significant difference between the treatment groups in the outcome "AIDS-defining events (CDC class C events)" in the individual studies or in the meta-analysis. Only few events occurred, however. Both in the individual studies and in the meta-analysis, there was a statistically significant effect in favour of dolutegravir for virologic response. For the SPRING-1 study, there was no statistically significant difference between the treatment groups for CD4 cell count. In the SINGLE study and in the meta-analysis of both studies, in contrast, there was a statistically significant increase in CD4 cell count in favour of dolutegravir. As the direction of the effect in the outcome "AIDS-defining events (CDC class C events)", which is the outcome of actual interest, differed from the one in the surrogate outcomes, there is no proof of an added benefit of dolutegravir versus efavirenz in the overall assessment of the 3 outcomes. However, overall there is also no indication that dolutegravir achieves considerably worse results than efavirenz.

HIV symptoms (symptom distress module [SDM])

The outcome "SDM" was not recorded in the SPRING-1 study. There was no statistically significant difference between the treatment groups in the SINGLE study. An added benefit of dolutegravir compared with efavirenz for HIV symptoms is therefore not proven.

Health-related quality of life

European Quality of Life-5 Dimensions (EQ-5D)

The outcome "EQ-5D" was not recorded in the SPRING-1 study. There were no evaluable data on health-related quality of life for the SINGLE study. Hence an added benefit of dolutegravir compared with efavirenz for health-related quality of life is not proven.

Adverse events

Serious adverse events (SAEs)

There was no statistically significant difference between the treatment groups in the meta-analysis of the 2 studies. Greater/lesser harm from dolutegravir compared with efavirenz for SAEs is therefore not proven.

Discontinuation due to adverse events

The meta-analysis of the 2 studies showed a statistically significant difference in favour of dolutegravir. There was proof of lesser harm from dolutegravir versus efavirenz because of the discontinuation due to adverse events.

Grade 3-4 severe adverse events (Division of AIDS [DAIDS])

There was considerable heterogeneity between the studies for the outcome so that no common estimate was calculated. As the effects of both studies did not have the same direction, overall greater/lesser harm from dolutegravir in comparison with efavirenz for the outcome "grade 3-4 severe adverse events (DAIDS)" is not proven.

Nervous system disorders (System Organ Class [SOC])

The meta-analysis of the 2 studies showed a statistically significant difference in favour of dolutegravir. There was an effect modification by the characteristic "sex". The statistically significant result in favour of dolutegravir persisted in male patients, whereas it was no longer statistically significant for female patients. For men, this resulted in a proof of lesser harm from dolutegravir in nervous system disorders (SOC). For women, however, greater/lesser harm from dolutegravir than from efavirenz for this outcome is not proven.

Skin rash (Preferred Term [PT])

The meta-analysis of the 2 studies showed a statistically significant difference in favour of dolutegravir. There was proof of lesser harm from dolutegravir versus efavirenz for skin rash (PT).

Psychiatric disorders (SOC)

The meta-analysis of the 2 studies showed a statistically significant difference in favour of dolutegravir. However, as this was of only marginal effect size, greater/lesser harm from dolutegravir in comparison with efavirenz is not proven.

Musculoskeletal and connective tissue disorders (SOC)

There was no statistically significant difference between the treatment groups in the meta-analysis of the 2 studies. Greater/lesser harm from dolutegravir in comparison with efavirenz for musculoskeletal and connective tissue disorders (SOC) is therefore not proven.

Results for research question 2: treatment-naive adolescents

No data for a comparison of dolutegravir versus the ACT were available for treatment-naive adolescents above 12 years of age. Hence an added benefit of dolutegravir is not proven for treatment-naive adolescents.

Results for research question 3: pretreated adults

The RCT SINGLE was included in the assessment. The SAILING study is a phase 3 study with a study duration of 48 weeks. 724 pretreated adults were enrolled in the study. The study compared dolutegravir with raltegravir, in each case in addition to individual background therapy. Due to the fact that raltegravir was the comparator therapy, no conclusions could be derived from the SAILING study with regard to the total target population of pretreated patients, but only with regard to patients for whom an INI is an obligatory component of a new treatment regimen.

The risk of bias of the study was rated as low.

Mortality

All-cause mortality

The result of the SAILING study was not statistically significant. An added benefit of dolutegravir compared with raltegravir for overall survival is therefore not proven.

Morbidity

AIDS-defining events (CDC class C events); surrogate outcomes "virologic response" and "CD4 cell count"

There was no statistically significant difference between the treatment groups for the outcome "AIDS-defining events (CDC class C events)". Only few events occurred, however. For virologic response, there was a statistically significant difference in favour of dolutegravir. There was no statistically significant difference between the treatment groups for CD4 cell count. As the direction of the effect in the outcome "AIDS-defining events (CDC class C events)", which is the outcome of actual interest, differed from the one in the surrogate outcomes, there is no indication of an added benefit of dolutegravir versus raltegravir in the

overall assessment of the 3 outcomes. However, overall there is also no indication that dolutegravir achieves considerably worse results than raltegravir.

HIV symptoms (SDM)

The outcome "HIV symptoms" was not recorded in the SAILING study. An added benefit of dolutegravir compared with raltegravir for HIV symptoms is therefore not proven.

Health-related quality of life

EQ-5D

There were no evaluable data on health-related quality of life for the SAILING study. Hence an added benefit of dolutegravir compared with raltegravir for health-related quality of life is not proven.

Adverse events

Serious adverse events

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "SAEs". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

Discontinuation due to adverse events

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "discontinuation due to adverse events". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

Grade 3-4 severe adverse events (DAIDS)

In the SAILING study there was a statistically significant effect in favour of dolutegravir for the outcome "grade 3-4 severe adverse events (DAIDS)". This led to an indication of lesser harm from dolutegravir versus raltegravir.

Nervous system disorders (SOC)

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "nervous system disorders (SOC)". However, there was an indication of an effect modification by the characteristic "age". There was a statistically significant result in favour of dolutegravir for people over 50 years of age, but not for people under 50 years of age. Hence there was an indication of lesser harm from dolutegravir in people over 50 years of age for the outcome "nervous system disorders (SOC)".

Skin rash (PT)

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "skin rash". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

Psychiatric disorders (SOC)

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "psychiatric disorders (SOC)". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

Musculoskeletal and connective tissue disorders (SOC)

There was a statistically significant effect in favour of dolutegravir for the outcome "musculoskeletal and connective tissue disorders (SOC)". However, as this was of only marginal effect size, greater/lesser harm from dolutegravir in comparison with raltegravir is not proven.

Results for research question 4: pretreated adolescents

No data for a comparison of dolutegravir versus the ACT were available for pretreated adolescents above 12 years of age. Hence an added benefit of dolutegravir is not proven for pretreated adolescents.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

Research question 1: treatment-naive adults

Overall, only positive effects remain in the outcome category "non-serious/non-severe adverse events" (extent: "considerable" in each case). The effect modification by the subgroup characteristic "sex" did not influence the overall conclusion on added benefit. It is to be noted that positive effects only occur in the area of adverse events. However, from the results on all-cause mortality and AIDS-defining events of CDC class C in combination with the results on the surrogate outcomes "virologic response" and "CD4 cell count" additionally presented, there is no indication that dolutegravir achieves considerably worse results than efavirenz with regard to these outcomes. Overall, there is therefore proof of an added benefit of dolutegravir in comparison with efavirenz with the extent "considerable" for treatment-naive adults.

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

Research question 2: treatment-naive adolescents

No data were available for treatment-naive adolescents. Hence an added benefit of dolutegravir is not proven for this population.

Research question 3: pretreated adults

Overall, only positive effects remain in the outcome categories "serious/severe adverse events" (extent: "minor") and "non-serious/non-severe adverse events" (extent: "minor"). The effect modification by the subgroup characteristic "age" did not influence the overall conclusion on added benefit. It is to be noted that positive effects only occur in the area of adverse events. However, from the results on all-cause mortality and AIDS-defining events of CDC class C in combination with the results on the surrogate outcomes "virologic response" and "CD4 cell count" additionally presented, there is no indication that dolutegravir achieves considerably worse results in comparison with raltegravir with regard to these outcomes. Overall, there is therefore an indication of an added benefit of dolutegravir in comparison with raltegravir with the extent "minor" for pretreated adult patients for whom an INI is a component of the optimized treatment.

Research question 4: pretreated adolescents

No data were available for pretreated adolescents. Hence an added benefit of dolutegravir is not proven for this population.

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

Table 3: Research questions, ACTs and extent and probability of the added benefit of dolutegravir

Research question	**Subindication**	**ACT**	**Extent and probability of added benefit**
1	Treatment-naive adults	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)	Proof of added benefit; extent: “considerable”
2	Treatment-naive adolescents above 12 years of age	Efavirenz in combination with abacavir plus lamivudine	Added benefit not proven
3	Pretreated adults ▪ a) INI treatment indicated ▪ a) INI treatment not indicated	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 AEs. The respective approval of the drugs is to be considered.	▪ a) indication of an added benefit, extent: “minor” ▪ b) added benefit not proven
4	Pretreated adolescents above 12 years of age		Added benefit not proven
ACT: appropriate comparator therapy; AE: adverse event; ART: antiretroviral therapy; INI: integrase inhibitor			

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

2.2 Research questions

The benefit assessment of dolutegravir was conducted according to the Summary of Product Characteristics (SPC) [3] for the treatment of HIV-1 infected adults and adolescents above 12 years of age.

Four research questions arose (see also Section 2.8.2.1 of the full dossier assessment), for which the G-BA specified the ACT presented in Table 4.

Table 4: ACT for the benefit assessment of dolutegravir

Research question	Subindication	ACT specified by the G-BA
1	**Treatment-naive adults** adults without previous ART	Efavirenz in combination with 2 nucleoside/nucleotide analogues (tenofovir plus emtricitabine or abacavir plus lamivudine)
2	**Treatment-naive adolescents** adolescents above 12 years of age without previous ART	Efavirenz in combination with abacavir plus lamivudine
3	**Pretreated adults** adults with previous ART	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 AEs. The respective approval of the drugs is to be considered.
4	**Pretreated adolescents** adolescents above 12 years of age with previous ART	
ACT: appropriate comparator therapy; AE: adverse event; ART: antiretroviral therapy; G-BA: Federal Joint Committee		

The company largely followed the G-BA's specification of the ACT, but separated the population of pretreated patients (research question 3 and research question 4) in patients with and without INI resistance. For the subpopulation without INI resistance, the company specified raltegravir as component of the individual treatment as ACT (see Sections 2.8.1 and 2.8.2.1 of the full dossier assessment).

The assessment was conducted based on patient-relevant outcomes. Only direct comparative RCTs were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.8.1 and 2.8.2.1 of the full dossier assessment.

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 lists on dolutegravir (studies completed up to 4 December 2013)

- bibliographical literature search on dolutegravir (last search on 4 December 2013)
- search in trial registries for studies on dolutegravir (last search on 27 November 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 26 February 2014)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.8.2.1 and 2.8.2.3 of the full dossier assessment.

2.3.1.1 Studies included

The SPRING-1 study and the SINGLE study listed in Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: dolutegravir vs. efavirenz

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ING112276 (SPRING-1)	Yes	Yes	No
ING114467 (SINGLE)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of dolutegravir corresponded to that of the company. It included the studies ING112276 (SPRING-1) and ING114467 (SINGLE), hereinafter referred to as "SPRING-1" and "SINGLE". In both studies, dolutegravir was directly compared with the G-BA's ACT (efavirenz in combination with TDF plus FCT or ABC plus 3TC).

Section 2.3.4 contains a reference list for the studies included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Section 2.8.2.3.1 of the full dossier assessment.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: dolutegravir vs. efavirenz

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SPRING-1	RCT, partially blinded (dose-ranging study: dolutegravir dosage double-blind; efavirenz open-label), parallel, multicentre	HIV-1 infected adult patients without previous antiretroviral treatment; baseline viral load at least 1,000 copies/mL	Dolutegravir 10 mg (N = 53)[b] dolutegravir 25 mg (N = 52)[b] dolutegravir 50 mg (N = 51) efavirenz 600 mg (N = 52) each in combination with either TDF + FTC or ABC + 3TC	Screening phase: up to 35 days treatment phase: 96 weeks[c] follow-up: 4 weeks	34 centres in France, Germany, Italy, Spain, Russia and United States since 7/2009 data cut-off at week 48: 11/2010 data cut-off at week 96: 9/2011	*Primary outcome:* virologic response at week 16 *Secondary outcomes:* AIDS-defining events (CDC class C), virologic response at week 96; change in CD4 cell count; mortality, AEs
SINGLE	RCT, double-blind, parallel, double-dummy, multicentre	HIV-1 infected adult patients without previous antiretroviral treatment; baseline viral load at least 1,000 copies/mL	Dolutegravir 50 mg (N = 422) efavirenz 600 mg (N = 422) dolutegravir in combination with ABC + 3TC, efavirenz in combination with TDF + FTC	Screening phase: up to 28 days treatment phase: 96 weeks followed by an open-label phase until 144 weeks	136 centres in Australia, Belgium, Canada, Denmark, France, Germany, Great Britain, Italy, the Netherlands, Romania, Spain and the United States since 2/2011 data cut-off at week 48: 5/2012 data cut-off at week 96: 5/2013	*Primary outcome:* virologic response at week 48 *Secondary outcomes:* AIDS-defining events (CDC class C events), virologic response at week 96; change in CD4 cell count; HIV symptoms, mortality, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for the present benefit assessment.
b: Dosage in this arm does not concur with the German approval. This arm is no longer presented in the following tables.
c: After week 96, patients from the dolutegravir arms of the study could switch to an open-label treatment with dolutegravir 50 mg daily until dolutegravir is commercially available or the development is ended. For patients in the efavirenz arm, the study ended after 96 weeks.

3TC: lamivudine; ABC: abacavir; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; EFV: efavirenz; FTC: emtricitabine; HIV: human immunodeficiency virus; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; TDF: tenofovir; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: dolutegravir vs. efavirenz

Study	Intervention	Comparison	Concomitant medication
SPRING-1	Dolutegravir 50 mg once daily + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg[a]/200 mg each as fixed combination once daily	Efavirenz 600 mg once daily + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg[a]/200 mg each as fixed combination once daily	No other antiretroviral treatment allowed Other drugs that are not allowed: barbiturates, carbamezapines, glitazones, glucocorticoids, modafinil, phenytoin, rifabutin, rifampicin and St. John's Wort (dolutegravir arm); astemizole, bepridil, cisapride, midazolam, pimozide, triazolam and ergot alkaloids (efavirenz arm)
SINGLE	Dolutegravir 50 mg once daily + ABC/3TC 600 mg/300 mg as fixed combination once daily + placebo for EFV/TDF/FTC fixed combination once daily	Efavirenz 600 mg tenofovir 300 mg emtricitabine 200 mg/(EFV/TDF/FTC) as fixed combination once daily + placebo for dolutegravir + placebo for ABC/3TC fixed combination once daily	No other antiretroviral treatment allowed Other drugs that are not allowed: inducers of the CYP3A4 enzyme, inhibitors of the enzymes CYP2C9, CYP2C19, CYP3A4 and their isoenzymes and drugs lowering the serum level of dolutegravir

a: 300 mg tenofovir disoproxil fumarate is equivalent to 136 mg tenofovir or 245 mg tenofovir disoproxil.
3TC: lamivudine; ABC: abacavir; EFV: efavirenz; FTC: emtricitabine; RCT: randomized controlled trial; TDF: tenofovir; vs.: versus

SPRING-1 and SINGLE were multicentre studies conducted in Australia, Europe and America. The randomized study phase was 96 weeks in both studies, in each case followed by a still ongoing open-label phase. Analyses after 48 and after 96 weeks were available for each study. The benefit assessment was conducted based on the results after 96 weeks. Treatment-naive HIV-1 infected adults were included in the studies.

The SPRING-1 study is a partially blinded, randomized, active-controlled phase 2b study. Dolutegravir was administered at a dose of 10 mg/25 mg or 50 mg daily in 3 study arms. Only the patients from the study arm with approval-compliant treatment with 50 mg dolutegravir (N = 51) daily were included in the assessment. The patients in the comparator arm (N = 52) received efavirenz. The study was open-label with regard to the allocation of patients to dolutegravir or efavirenz, only the daily dose of dolutegravir was blinded. The patients received a backbone therapy of either TDF/FTC or ABC/3TC in addition to the study medication. The distribution of backbone therapies was balanced between the study arms, almost 70% of the patients in each study arm received TDF/FTC, and just over 30% received ABC/3TC. The randomization of the patients was stratified according to HIV-1 RNA ($\leq$ 100 000 copies/mL or > 100 000 copies/mL) and backbone therapy (TDF/FTC or ABC/3TC) in the study.

The SINGLE study is a double-blind, randomized, active-controlled phase 3 study. The patients were randomized to treatment with dolutegravir or efavirenz. The patients in the dolutegravir arm (N = 422) received ABC/3TC as backbone therapy, the ones in the efavirenz arm (N = 422) received TDF/FTC. As both treatments are part of the G-BA's ACT, the SINGLE study could be used for the benefit assessment despite the uneven distribution of the backbone therapies. Efavirenz was administered as fixed drug combination with TDF/FTC. The fixed combination is only approved for pretreated patients [4]. However, this was not a problem for the assessment because the respective individual substances are each approved for treatment-naive patients [5-7]. The randomization of the patients was stratified according to HIV-1 RNA (≤ 100 000 copies/mL or > 100 000 copies/mL) and CD4 cell count (≤ 200 cells/µL or > 200 cells/µL) in the study. The patients in the SINGLE study received daily placebo in addition to the study medication to maintain blinding.

Table 8 and Table 9 show the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations (demography) – RCT, direct comparison: dolutegravir vs. efavirenz (week 96)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Ethnicity %		Backbone therapy %		Treatment discon-tinuations n (%)
				Whites	Non-whites[a]	TDF+FTC	ABC+3TC	
SPRING-1								
dolutegravir	51	37 (9)	12/88	75	25	67	33	5 (9.8[b])
efavirenz	52	41 (11)	12/88	86	14	68	32	10 (19.2[b])
SINGLE								
dolutegravir	422	37 (11)	16/84	69	31	0	100	72 (17)
efavirenz	422	36 (10)	15/85	68	32	100	0	109 (26)

a: This group includes Asians, blacks/patients of African heritage, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.
b: Institute's calculation.
ABC+3TC: abacavir and lamivudine; F: female; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; TDF+FTC: tenofovir and emtricitabine; vs.: versus

Table 9: Characteristics of the study populations (severity of the disease at the start of the study) – RCT, direct comparison: dolutegravir vs. efavirenz (week 96)

Study group	N	Baseline viral load n (%)		CD4 cell count at start of study n (%)		HIV disease stage n (%)		
		≤ 100 000 HIV-1 RNA copies/mL	> 100 000 HIV-1 RNA copies/mL	< 350/µL	≥ 350/µL	Asymptomatic	Symptomatic	AIDS
SPRING-1								
dolutegravir	51	39 (76)	12 (24)	24[a] (47)	27[a] (53)	41 (80)	10 (20)	0 (0)
efavirenz	52	39 (78)	11 (22)	24[a] (48)	26[a] (52)	45 (90)	4 (8)	1 (2)
SINGLE								
dolutegravir	422	280 (68)	134 (32)	220[b] (53)	194[b] (47)	342 (83)	54 (13)	18 (4)
efavirenz	422	288 (69)	131 (31)	221[b] (53)	198[b] (47)	350 (84)	52 (12)	17 (4)

a: CD4 cell count categories: < 300/µL vs. ≥ 300/µL
b: Institute's calculation.
AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; HIV: human immunodeficiency virus; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; RNA: ribonucleic acid; vs.: versus

There were no important differences between the treatment groups with regard to age, sex and ethnicity. The patients were on average between 36 and 41 years old. Considerably more men than women were enrolled in both studies. The proportion of whites was considerably larger in both studies than the proportion of non-whites. With regard to disease severity, the vast majority of the patients was asymptomatic and only very few patients already had AIDS.

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: dolutegravir vs. efavirenz

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
SPRING-1	Yes	Yes	No	No	Yes	Yes	Low
SINGLE	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for both studies. This contradicts the company's assessment, which rated the risk of bias of the SPRING-1 study at study level as high. It justified this with the open-label design of the study.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-G of the dossier, and in Sections 2.8.2.4.1 and 2.8.2.4.2 of the full dossier assessment.

2.3.2 Results on added benefit

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

- Mortality
  - all-cause mortality
- Morbidity
  - AIDS-defining events (CDC class C events)
  - presented as additional information: virologic response and CD4 cell count as surrogate outcomes for the patient-relevant outcome “AIDS-defining illnesses/death”
  - HIV symptoms (HIV-SDM)
- Health-related quality of life
- Adverse events
  - overall rate of SAEs
  - discontinuation due to adverse events
  - grade 3-4 adverse events (DAIDS)
  - nervous system disorders (SOC)
  - skin rash (PT)
  - psychiatric disorders (SOC)
  - musculoskeletal and connective tissue disorders (SOC)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in its dossier (Module 4). In addition to the company’s dossier, the outcome “AIDS-defining events (CDC class C events)” was included in the benefit assessment because this outcome directly represents the AIDS-defining illnesses important in the therapeutic indication. Reasons for the choice of outcomes are given in Section 2.8.2.4.3 of the full dossier assessment.

Table 11 shows for which outcomes data were available in the studies included. Table 12 shows the risk of bias for these outcomes.

Table 11: Matrix of outcomes – RCT, direct comparison: dolutegravir vs. efavirenz

Study	Outcomes												
	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response[a]	CD4 cell count[a]	HIV symptoms (HIV-SDM)	Health-related quality of life	Serious adverse events	Discontinuation due to adverse events	Grade 3-4 adverse events (DAIDS)	Nervous system disorders (SOC)	Skin rash (PT)	Psychiatric disorders (SOC)	Musculoskeletal and connective tissue disorders (SOC)
SPRING-1	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y
SINGLE	Y	Y	Y	Y	Y	N[b]	Y	Y	Y	Y	Y	Y	Y

a: Virologic response and CD4 cell count as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" are presented as additional information.
b: Data not evaluable (see Section 2.8.2.4.3 of the full dossier assessment for reasons).
AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; HIV-SDM: HIV symptom distress module; MedDRA: Medical Dictionary for Regulatory Activities; N: no; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SOC: MedDRA System Organ Class; vs.: versus; Y: yes

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: dolutegravir vs. efavirenz

Study	Study level	Outcomes												
		All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response	CD4 cell count	HIV symptoms (HIV-SDM)	Health-related quality of life	Serious adverse events	Discontinuation due to adverse events	Grade 3-4 adverse events (DAIDS)	Nervous system disorders (SOC)	Skin rash (PT)	Psychiatric disorders (SOC)	Musculoskeletal and connective tissue disorders (SOC)
SPRING-1	L	L	L	L	H[a]	–[b]	–[b]	L	H[c]	L	H[c]	H[c]	H[c]	H[c]
SINGLE	L	L	L	L	L	H[d]	–[e]	L	L	L	L	L	L	L

a: ITT principle violated: proportion of missing values in the treatment groups 10% and 22%.
b: Outcome not recorded in the study.
c: Subjectively reported outcome in open-label study.
d: LOCF analysis highly biased; proportion of imputed values > 25%.
e: Data not evaluable (see Section 2.8.2.4.3 of the full dossier assessment for reasons).
AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; H: high; HIV: human immunodeficiency virus; HIV-SDM: HIV symptom distress module; ITT: intention to treat; L: low; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SOC: MedDRA System Organ Class; vs.: versus

The assessment of the risk of bias mainly concurs with that of the company. There is one deviation for the open-label SPRING-1 study in the risk of bias of the outcome "SAE", which the company rated as high. The risk of bias of SAEs and of the outcomes "AIDS-defining events (CDC class C events)" and "grade 3-4 severe adverse events (DAIDS)" additionally included in this assessment is rated as low. This is because the outcomes were not consistently recorded based on subjective reports. In subjectively reported outcomes (such as outcomes of quality of life or discontinuation due to adverse events) recorded in an open-label study, this leads to a high risk of bias. Moreover, in the SPRING-1 study the risk of bias for the outcome "CD4 cell count" was rated as high because of the high proportion of missing values; and in the SINGLE study the risk of bias for the outcome "HIV symptoms" was rated as high because of the high proportion of imputed values at week 96.

2.3.2.1 Results

Table 13 summarizes the results on the comparison of dolutegravir with efavirenz in treatment-naive adults infected with HIV-1. Where necessary, the data from the company's

dossier were supplemented by the Institute's own calculations. The results at the analysis date of 96 weeks were used in the benefit assessment. The figures of the meta-analyses can be found in Appendix A of the full dossier assessment. In principle, it is possible to derive proof, e.g. of an added benefit of dolutegravir, from the meta-analysis of 2 studies with a low risk of bias. This assessment corresponds to that of the company. Any possible weakening of the results by outcome-specific aspects will be noted separately for individual outcomes in the following presentation of the results.

Table 13: Results (dichotomous outcomes) – RCT, direct comparison: dolutegravir vs. efavirenz (week 96), treatment-naive adults

Outcome category outcome study	Dolutegravir N	Dolutegravir Patients with events n (%)	Efavirenz N	Efavirenz Patients with events n (%)	Dolutegravir vs. efavirenz RR [95% CI]; p-value
Mortality					
All-cause mortality					
SPRING-1	51	1 (2.0)	50	0 (0)	2.94 [0.12; 70.56]; 0.506
SINGLE	414	0 (0)	419	2 (0.5)	0.20 [0.01; 4.20]; 0.302
total					0.74 [0.05; 10.22]; 0.822[a,b]
Morbidity					
AIDS-defining events (CDC class C events)					
SPRING-1	51	1 (2)	50	0 (0)	2.94 [0.12; 70.56]; 0.522[c]
SINGLE	414	5 (1.2)[a]	419	5 (1.2)[a]	1.01 [0.30; 3.47]; >0.999[c]
total					1.16 [0.37; 3.67]; 0.796[a,b]
Additional information: surrogate outcome "virologic response" (< 50 RNA copies/mL)					
SPRING-1[i]	51	45 (88.2)	50	36 (72.0)	1.23 [1.00; 1.50]; 0.046
SINGLE[j]	414	319 (77.1)	419	293 (69.9)	1.10 [1.02; 1.20]; 0.020
total					1.12 [1.04; 1.21]; 0.004[a,b]
Additional information: surrogate outcome "CD4 cell count" (number/µL)					
SPRING-1	51[d]	327[e] (122.3) 338[f] (162.6)	50[d]	328[e] (106.5) 321[f] (218.9)	17.0 [-65.5; 99.5]; 0.680[a]
SINGLE	414[d]	349[e] (158.2) 324[f] (205.7)	419[d]	351[e] (157.5) 286[f] (196.0)	43.95[g] [14.34; 73.55]; 0.004
total					40.79 [12.98; 68.61]; 0.004[a,b]
Symptoms					
SPRING-1	Outcome not recorded				
SINGLE					
symptom bother score	391[d]	12.9[e] (12.03) −1.07[h] (0.48)	391[d]	12.8[e] (12.30) -2.00[h] (0.48)	0.94 [-0.40; 2.27]; 0.168
Health-related quality of life					
Study					
SPRING-1	Outcome not recorded				
SINGLE	No evaluable data				
Adverse events					
AEs					
SPRING-1	51	46 (90.2)	50	46 (92.0)	
SINGLE	414	376 (90.8)	419	394 (94.0)	

(continued)

Table 13: Results (dichotomous outcomes) – RCT, direct comparison: dolutegravir vs. efavirenz (week 96), treatment-naive adults (continued)

Outcome category outcome Study	Dolutegravir		Efavirenz		Dolutegravir vs. efavirenz
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
SAEs					
SPRING-1	51	7 (13.7)	50	7 (14.0)	0.98 [0.37; 2.59]; 0.968
SINGLE	414	44 (10.6)	419	51 (12.2[a])	0.87 [0.60; 1.28]; 0.497[c]
total					0.89 [0.62; 1.26]; 0.505[a,b]
Discontinuation due to AEs					
SPRING-1	51	2 (3.9)	50	5 (10.0)	0.39 [0.08; 1.93]; 0.249
SINGLE	414	14 (3.4[a])	419	52 (12.4)	0.27 [0.15; 0.48]; < 0.001
total					0.28 [0.17; 0.49]; < 0.001[a,b]
Severity grade 3-4 AEs (DAIDS)					
SPRING-1	51	9 (17.6)	50	3 (6)	2.94 [0.85; 10.24]; 0.074[c]
SINGLE	414	57[a] (13.8[a])	419	83[a] (19.8[a])	0.70 [0.51; 0.95]; 0.020[c]
total				heterogeneity: Q = 4.87; df = 1; p = 0.027; I^2 = 79.5%[a,b]	
Nervous system disorders (SOC)					
SPRING-1	51	14 (27)	50	21 (42.0)	0.65 [0.38; 1.14]; 0.131[c]
SINGLE	414	121 (29.2)	419	225 (53.7)	0.54 [0.46; 0.65]; < 0.001
total					0.55 [0.47; 0.65]; < 0.001[a,b]
Skin rash (PT)					
SPRING-1	51	3 (6)	50	6 (12)	0.49 [0.13; 1.85]; 0.320[c]
SINGLE	414	19 (5)	419	60 (14)	0.32 [0.19; 0.53]; < 0.001[c]
total					0.34 [0.21; 0.54]; < 0.001[a,b]
Psychiatric disorders (SOC)					
SPRING-1	51	10 (19.6)	50	19 (38.0)	0.52 [0.27; 1.00]; 0.049
SINGLE	414	144 (34.8)	419	178 (42.5)	0.82 [0.69; 0.97]; 0.023
total					0.79 [0.67; 0.94]; 0.007[a,b,k]
Musculoskeletal and connective tissue disorders (SOC)					
SPRING-1	51	14 (27)	50	12 (24.0)	1.14 [0.59; 2.22]; 0.767[c]
SINGLE	414	109 (26.3)	419	93 (22.2)	1.12 [0.88; 1.43]; 0.362
total					1.18 [0.94; 1.48]; 0.150[a,b]

(continued)

Table 13: Results (dichotomous outcomes) – RCT, direct comparison: dolutegravir vs. efavirenz (week 96), treatment-naive adults (continued)

a: Institute's calculation.
b: Calculated from meta-analysis.
d: Institute's calculation, unconditional exact test (CSZ method according to [8]).
d: Number of patients analysed at 96 weeks. The values at the start of the study can be based on other patient numbers.
e: Values at the start of the study (mean [SD]).
f: Values at the end of the study (mean [SD]).
g: Difference adjusted mean values (95% CI, p-value) from repeated measures mixed model analysis of the ITT population. The adjusted mean value is the mean change in CD4 cell count from baseline to week 96 in each study arm with the following covariables: treatment, visit, baseline plasma HIV-1 RNA level, baseline CD4 cell count, treatment*visit interaction, baseline plasma HIV-1 RNA level*visit interaction and baseline CD4 cell count*visit interaction; unstructured covariance matrix.
h: Change at the end of study (mean [SD]); unless stated otherwise, LOCF analysis of the ITT population.
i: Analysed with the TLOVR algorithm.
j: Analysed with the MSDF algorithm.
k: Fixed effects model (FEM).

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CSZ: convexity, symmetry, z score; DAIDS: Division of AIDS; HIV: human immunodeficiency virus; ITT: intention to treat; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; MSDF: missing, switch or discontinuation = failure; N: number of analysed patients; n: number of patients with event; PT: MedDRA Preferred Term; RR: relative risk; SAE: serious adverse event; SD: standard deviation; SOC: MedDRA System Organ Class; TLOVR: time to loss of virologic response; vs.: versus

Mortality

All-cause mortality

Only few events occurred in all-cause mortality and there was no statistically significant difference of the results between the treatment groups in the individual studies or in the meta-analysis. An added benefit of dolutegravir compared with efavirenz for overall survival is therefore not proven.

This concurs with the company's assessment.

Morbidity

AIDS-defining events (CDC class C events); surrogate outcomes "virologic response" and "CD4 cell count"

There was no statistically significant difference between the treatment groups in the outcome **"AIDS-defining events (CDC class C events)"** in the individual studies or in the meta-analysis. Only few events occurred, however. Both in the individual studies and in the meta-analysis, there was a statistically significant effect in favour of dolutegravir for **virologic response**. For the SPRING-1 study, there was no statistically significant difference between the treatment groups for **CD4 cell count**. In the SINGLE study and in the meta-analysis of both studies, in contrast, there was a statistically significant increase in CD4 cell count in favour of dolutegravir. As the direction of the effect in the outcome "AIDS-defining events (CDC class C events)", which is the outcome of actual interest, differed from the one in the

surrogate outcomes, there is no proof of an added benefit of dolutegravir versus efavirenz in the overall assessment of the 3 outcomes. However, overall there is also no indication that dolutegravir achieves considerably worse results than efavirenz.

This contradicts the company's assessment, which derived proof of added benefit of dolutegravir from the virologic response. The company did not present the outcomes "AIDS-defining events (CDC class C events)" and "CD4 cell count" in Module 4 of its dossier.

HIV symptoms (SDM)

The outcome "SDM" was not recorded in the SPRING-1 study. There was no statistically significant difference between the treatment groups in the SINGLE study. An added benefit of dolutegravir compared with efavirenz for HIV symptoms is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

EQ-5D

The outcome "EQ-5D" was not recorded in the SPRING-1 study. There were no evaluable data on health-related quality of life for the SINGLE study (for reasons see Section 2.8.2.4.3 of the full dossier assessment). Hence an added benefit of dolutegravir compared with efavirenz for health-related quality of life is not proven.

This concurs with the company's assessment.

Adverse events

The adverse events, SAEs, discontinuations due to adverse events and grade 3-4 severe adverse events (DAIDS) that most commonly occurred in the studies are presented in Appendix B of the full dossier assessment.

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs" in the individual studies or in the meta-analysis. Greater/lesser harm from dolutegravir in comparison with efavirenz is therefore not proven for this outcome.

This concurs with the company's assessment.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to adverse events" in the SPRING-1 study. For the SINGLE study and the meta-analysis of both studies, in contrast, there was a statistically significant difference in favour of dolutegravir. The risk of bias of the outcome in the SPRING-1 study was rated as high. This had no consequence on the assessment, however, because the meta-analysis

showed a statistically significant effect. Overall, there was proof of lesser harm from dolutegravir than from efavirenz.

This concurs with the company's assessment.

Grade 3-4 severe adverse events (Division of AIDS [DAIDS])

In the SPRING-1 study, there was no statistically significant difference between the treatment groups for the outcome "grade 3-4 severe adverse events (DAIDS)". For the SINGLE study, in contrast, there was a statistically significant difference in favour of dolutegravir. However, there was considerable heterogeneity between the studies ($p < 0.2$) for the outcome so that no common estimate was calculated. As, moreover, the effects of both studies did not have the same direction, overall greater/lesser harm from dolutegravir in comparison with efavirenz for this outcome is not proven.

The company did not present this outcome in Module 4 of its dossier.

Nervous system disorders (SOC)

There was no statistically significant difference between the treatment groups for the outcome "nervous system disorders (SOC)" in the SPRING-1 study. For the SINGLE study and the meta-analysis of both studies, in contrast, there was a statistically significant difference in favour of dolutegravir. The risk of bias of the outcome in the SPRING-1 study was rated as high. This had no consequence on the assessment, however, because the meta-analysis showed a statistically significant effect. Overall, there was proof of lesser harm from dolutegravir than from efavirenz.

This concurs with the company's assessment, which derived proof of added benefit in men based on the subgroup analyses. The assessment of the subgroups can be found in Section 2.3.2.2.

Skin rash (PT)

There was no statistically significant difference between the treatment groups for the outcome "skin rash (PT)" in the SPRING-1 study. For the SINGLE study and the meta-analysis of both studies, in contrast, there was a statistically significant difference in favour of dolutegravir. The risk of bias of the outcome in the SPRING-1 study was rated as high. This had no consequence on the assessment, however, because the meta-analysis showed a statistically significant effect. Overall, there was proof of lesser harm from dolutegravir than from efavirenz.

The company also derived proof of an added benefit for this outcome. However, it used deviating operationalizations (see Section 2.8.2.4.3 of the full dossier assessment).

Psychiatric disorders (SOC))

For the outcome "psychiatric disorders (SOC)", there was a statistically significant difference between the treatment groups in favour of dolutegravir both for the SPRING-1 study and for the SINGLE study. The heterogeneity test showed a significant result ($p < 0.2$). Due to the specific data situation (the confidence interval of the highly biased imprecise study (SPRING-1) completely covers the confidence interval of the more precise study with low bias (SINGLE)), the pooling of the results with the fixed effects model was considered to be adequate. Both the individual studies and the result of the meta-analysis only showed a marginal effect size (the upper confidence interval is above the threshold of 0.9; outcome category "non-severe/non-serious adverse events [1]) so that greater/lesser harm from dolutegravir is not proven.

This concurs with the company's assessment.

Musculoskeletal and connective tissue disorders (SOC)

There was no statistically significant difference between the treatment groups for the outcome "musculoskeletal and connective tissue disorders (SOC)" in the individual studies or in the meta-analysis. Greater/lesser harm from dolutegravir than from efavirenz is therefore not proven for this outcome.

This concurs with the company's assessment.

2.3.2.2 Subgroup analyses

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company presented the corresponding analyses for the outcomes it rated as relevant. Hence there were no subgroup analyses for the outcomes "AIDS-defining events (CDC class C events)" and "grade 3-4 severe adverse events (DAIDS)", which were additionally rated as relevant, and on the surrogate outcome "CD4 cells" presented as additional information, and they could also not be subsequently calculated from the available documents. The subgroup results on virologic response are also not presented because this additional surrogate outcome cannot be interpreted in isolation.

Subgroup analyses for the following characteristics were considered:

- age (< / ≥ 36 years)
- sex
- ethnicity (whites/non-whites)
- baseline viral load (≤ 100 000/> 100 000 HIV-1 RNA copies/mL)

The subgroup characteristics presented by the company and the cut-off values were specified a priori in the studies.

Only the results on subgroups and outcomes with at least indications of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one subgroup are presented below. The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification.

Table 14 shows the results regarding the subgroup analyses.

Table 14: Subgroups with at least indications of interaction – RCT, direct comparison: dolutegravir vs. efavirenz (week 96), treatment-naive adults

Outcome characteristic study subgroup	Dolutegravir		Efavirenz		Dolutegravir vs. efavirenz	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value[a]
Discontinuation due to AEs						
Ethnicity						
SPRING-1						
white	38	2 (5)	43	4 (9)	0.57 [0.11; 2.92]	
non-white	13	0 (0)	7	1 (14)	0.19 [0.01; 4.15]	
SINGLE						
white	284	13 (5)	285	35 (12)	0.37 [0.20; 0.69]	
non-white	130	1 (0.8)	133	17 (13)	0.06 [0.01; 0.45]	
total					interaction:	0.091[b]
white					0.39 [0.22; 0.70][b]	0.001[b]
non-white					0.08 [0.02; 0.45][b]	0.004[b]
Nervous system disorders (SOC)						
Sex						
SPRING-1						
men	45	11 (24)	44	18 (41)	0.60 [0.32; 1.12]	
women	6	2 (33)	6	3 (50)	0.67 [0.17; 2.67]	
SINGLE						
men	347	94 (27)	356	202 (57)	0.48 [0.39; 0.58]	
women	67	27 (40)	63	23 (37)	1.10 [0.71; 1.71]	
total					interaction:	< 0.001[b]
men					0.49 [0.40; 0.59][b]	< 0.001[b]
women					1.05 [0.70; 1.60][b]	0.803[b]
Psychiatric disorders (SOC)						
age						
SPRING-1						
< 36 years	23	6 (26)	16	7 (44)	0.60 [0.25; 1.44]	
≥ 36 years	28	4 (14)	34	12 (35)	0.40 [0.15; 1.12]	
SINGLE						
< 36 years	202	76 (38)	215	87 (40)	0.93 [0.73; 1.18]	
≥ 36 years	212	68 (32)	204	91 (38)	0.72 [0.56; 0.92]	
total					interaction:	0.184[b]
< 36 years					0.90 [0.72; 1.14][b]	0.382[b]
≥ 36 years					0.67 [0.46; 0.97][b]	0.035[b]

a: Institute's calculation.
b: Calculated from meta-analysis.
AE: adverse event; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: MedDRA System Organ Class; vs.: versus

Discontinuation due to adverse events

There was an indication of an effect modification by the characteristic "ethnicity" for the outcome "discontinuation due to adverse events".

The result of the meta-analysis showed a statistically significant result in favour of dolutegravir both for the group of non-whites and for the group of whites. Proof of lesser harm from dolutegravir can still be assumed for both groups. As there are no differing conclusions on added benefit for the 2 groups, and this is only an indication of an interaction, the result of this subgroup analysis has no consequences on the assessment and is not considered further.

Nervous system disorders (SOC)

There was proof of an effect modification by the characteristic "sex" for the outcome "nervous system disorders (SOC)".

The statistically significant result in favour of dolutegravir persisted in male patients, whereas it was no longer statistically significant for female patients. Hence for men, proof of lesser harm from dolutegravir can still be derived. For women, however, greater/lesser harm from dolutegravir than from efavirenz for this outcome is not proven.

Psychiatric disorders (SOC)

There was an indication of an effect modification by the characteristic "age" for the outcome "psychiatric disorders". In the meta-analysis, the result is no longer statistically significant for people under 36 years of age. In the group of people over 36 years of age, the meta-analysis showed a statistically significant result in favour of dolutegravir, but the effect size is only marginal (the upper confidence interval is above the threshold of 0.9; outcome category "non-severe/non-serious adverse events [1]) so that greater/lesser harm from dolutegravir is not proven. As there are no differing conclusions on added benefit for the 2 groups, and this is only an indication of an interaction, the result of this subgroup analysis has no consequences on the assessment and is not considered further.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of the Institute [1].

2.3.3.1 Evaluation of added benefit at outcome level

The available data presented in Section 2.3.2 results in proof of lesser harm from dolutegravir than from efavirenz for the outcomes "discontinuation due to adverse events", "nervous system disorders (SOC)" and "skin rash (PT)".

There are effect modifications by the subgroup characteristic "sex".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 15). In the overall assessment, it was then investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 15: Extent of added benefit at outcome level: dolutegravir vs. efavirenz (week 96), treatment-naive adults

Outcome category **outcome**	**Dolutegravir vs. efavirenz** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0.2% vs. 0.4% RR: 0.74 [0.05; 10.22] p = 0.822[c,d]	Added benefit not proven
Morbidity		
AIDS-defining events (CDC class C events) *Additional information: surrogate outcome "virologic response"* *Additional information: surrogate outcome "CD4 cell count"*	1.3% vs. 1.3% RR: 1.16 [0.37; 3.67] p = 0.796[c] 78.3% vs. 70.1% RR: 1.12 [1.04; 1.21] p = 0.004 MD: 40.79 [12.98; 68.61] p = 0.004	Added benefit not proven
HIV symptoms (SDM) symptom bother score	-1.0 vs. -2.0 MD: 0.94 [-0.40; 2.27] p = 0.168	Added benefit not proven
Health-related quality of life		
No evaluable data		
Adverse events		
SAEs	11.0% vs. 12.4% RR: 0.89 [0.62; 1.26] p = 0.505[c]	Greater/lesser harm not proven
Discontinuation due to AEs	3.4% vs. 12.2% RR: 0.28 [0.17; 0.49] p < 0.001[c,d] probability: "proof"	Outcome category: non-serious/non-severe AEs CI_u < 0.80 lesser harm extent: "considerable"
Grade 3-4 AEs (DAIDS)	Heterogeneous results[e]	Greater/lesser harm not proven

(continued)

Table 15: Extent of added benefit at outcome level: dolutegravir vs. efavirenz (week 96), treatment-naive adults (continued)

Outcome category outcome	**Dolutegravir vs. efavirenz effect estimate [95% CI] p-value probability[a]**	**Derivation of extent[b]**
Nervous system disorders (SOC)	29.0% vs. 52.5% RR: 0.55 [0.47; 0.65] $p < 0.001$[c,d]	
Men	26.8% vs. 55.0% RR: 0.49 [0.40; 0.59][c] $p < 0.001$[c] probability: "proof"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ lesser harm extent: "considerable"
Women	39.7% vs. 37.7% RR: 1.05 [0.70; 1.60][c] $p = 0.803$[c]	Greater/lesser harm not proven
Skin rash (PT)	4.7% vs. 14.1% 0.34 [0.21; 0.54] $p < 0.001$[c,d] probability: "proof"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ lesser harm extent: "considerable"
Psychiatric disorders (SOC)	33.1% vs. 42.0% RR: 0.79 [0.67; 0.94] $p = 0.007$[c,d]	Outcome category: non-serious/non-severe AEs $CI_u > 0.90$ greater/lesser harm not proven
Musculoskeletal and connective tissue disorders (SOC)	26.5% vs. 22.4% RR: 1.18 [0.94; 1.48][c] $p = 0.150$	Greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation.
d: Calculated from meta-analysis.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CI_u: upper limit of CI; HIV: human immunodeficiency virus; DAIDS: Division of AIDS; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RR: relative risk; SAE: serious adverse event; SDM: symptom distress module; SOC: MedDRA System Organ Class; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 16: Positive and negative effects from the assessment of dolutegravir compared with efavirenz, treatment-naive adults

Positive effects	Negative effects
Non-serious/non-severe adverse events ▪ discontinuation due to adverse events: proof of lesser harm – extent: "considerable" ▪ skin rash (PT): proof of lesser harm – extent: "considerable" ▪ nervous system disorders (SOC) ▫ men: proof of lesser harm – extent: "considerable"	–
MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; SOC: MedDRA System Organ Class	

Overall, only positive effects remain in the outcome category "non-serious/non-severe adverse events" (extent: "considerable" in each case). The effect modification by the subgroup characteristic "sex" did not influence the overall conclusion on added benefit.

It is to be noted that positive effects only occur in the area of adverse events. However, from the results on all-cause mortality and AIDS-defining events of CDC class C in combination with the results on the surrogate outcomes "virologic response" and "CD4 cell count" additionally presented, there is no indication that dolutegravir achieves considerably worse results than efavirenz with regard to these outcomes.

Overall, there is therefore proof of an added benefit of dolutegravir in comparison with efavirenz with the extent "considerable" for treatment-naive adults.

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

2.3.4 List of included studies

SPRING-1

Rockstroh J, Felizarta F, Maggiolo F, Pulido F, Stellbrink HJ, Tsybakova O et al. Once-daily S/GSK1349572 combination therapy in antiretroviral-naive adults: rapid and potent 24- week antiviral responses in SPRING-1 (ING112276). J Int AIDS Soc 2010; 13(Suppl 4): O50.

Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS 2013; 27(11): 1771-1778.

Van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis 2012; 12(2): 111-118.

ViiV Healthcare. A dose ranging trial of GSK1349572 and 2 NRTI in HIV-1 infected, therapy naive subjects (ING112276): study results [online]. In: ClinicalTrials.gov. 22 August 2013 [accessed: 27 November 2013]. URL: http://ClinicalTrials.gov/show/NCT00951015.

ViiV Healthcare. A phase IIb study to select a once daily dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antiretroviral therapy naive adult subjects: protocol summary [online]. In: GlaxoSmithKline Clinical Study Register. 25 April 2013 [accessed: 27 November 2013]. URL: http://www.gsk-clinicalstudyregister.com/study/112276#ps.

ViiV Healthcare. A phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antiretroviral therapy naïve adult subjects [online]. In: Pharmnet.Bund Klinische Prüfungen. [Accessed: 27 November 2013]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

ViiV Healthcare. A phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antiretroviral therapy naïve adult subjects [online]. In: EU Clinical Trials Register. 9 April 2009 [accessed: 27 November 2013]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-010269-21/DE.

ViiV Healthcare. A phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antriretroviral therapy naive adult subjects (week 48): study no ING112276; clinical study report [unpublished]. 2011.

ViiV Healthcare. A phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antriretroviral therapy naïve adult subjects: study no ING112276; clinical study report [unpublished]. 2012.

ViiV Healthcare. ING112276 (SPRING-1 study): post-hoc subgroup analyses [unpublished]. 2013.

SINGLE

Eron J Jr, Rockstroh J, Pozniak A, Elliott J, Small C, Johnson M et al. Dolutegravir treatment response by baseline viral load and NRTI backbone in treatment-naive HIV-infected individuals. J Int AIDS Soc 2012; 15(Suppl 4): 121.

ViiV Healthcare. A phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects [online]. In: Pharmnet.Bund Klinische Prüfungen. [Accessed: 27 November 2013]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

ViiV Healthcare. A phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects [online]. In: EU Clinical Trials Register. 11 November 2010 [accessed: 27 November 2013]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-020983-39/DE.

ViiV Healthcare. A phase III, randomized, double-blind study of the safety and efficacy of dolutegravir plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects: study no ING114467; clinical study report [unpublished]. 2012.

ViiV Healthcare. A phase III, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects: study no ING114467; clinical study report [unpublished]. 2013.

ViiV Healthcare. A randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects: result summary [online]. In: GlaxoSmithKline Clinical Study Register. [Accessed: 27 November 2013]. URL: http://www.gsk-clinicalstudyregister.com/study/114467#rs.

ViiV Healthcare. A trial comparing GSK1349572 50mg plus abacavir/lamivudine once daily to atripla (also called the SINGLE trial): full text view [online]. In: ClinicalTrials.gov. 11 July 2013 [accessed: 27 November 2013]. URL: http://ClinicalTrials.gov/show/NCT01263015.

ViiV Healthcare. ING114467 (SINGLE study): post-hoc subgroup analyses [unpublished]. 2013.

Walmsley S, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F et al. Dolutegravir (DTG; S/GSK1349572) + abacavir/lamivudine once daily statistically superior to tenofovir/emtricitabine/efavirenz: 48-week results; SINGLE (ING114467) [online]. In: 52nd ICAAC Interscience Conference on Antimicrobial Agents and Chemotherapy; 9-12 September 2012; San Francisco, USA. [Accessed: 16 April 2014]. URL: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=e1c18d5b-830f-4b4e-8671-35bcfb20eed5&cKey=af219b7d-2171-46b2-91ef-b8049552c9e5&mKey=%7b6B114A1D-85A4-4054-A83B-04D8B9B8749F%7d.

Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013; 369(19): 1807-1818.

2.4 Research question 2: treatment-naive adolescents above 12 years of age

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 lists on dolutegravir (studies completed up to 4 December 2013)
- bibliographical literature search on dolutegravir (last search on 4 December 2013)
- search in trial registries for studies on dolutegravir (last search on 27 November 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 26 February 2014)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.8.2.1 and 2.8.2.3 of the full dossier assessment.

2.4.2 Results on added benefit

No data were available for treatment-naive adolescents. An added benefit of dolutegravir versus the ACT is therefore not proven for this subpopulation.

2.4.3 Extent and probability of added benefit

As the company presented no data for treatment-naive adolescents, an added benefit of dolutegravir is not proven for this subpopulation.

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 lists on dolutegravir (studies completed up to 4 December 2013)
- bibliographical literature search on dolutegravir (last search on 4 December 2013)
- search in trial registries for studies on dolutegravir (last search on 27 November 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 26 February 2014)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.8.2.1 and 2.8.2.3 of the full dossier assessment.

2.5.1.1 Studies included

The SAILING study listed in Table 17 was included in the benefit assessment.

Table 17: Study pool – RCT, direct comparison: dolutegravir vs. raltegravir

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ING111762 (SAILING)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of dolutegravir corresponded to that of the company. It included the ING111762 study (SAILING), hereinafter referred to as "SAILING". Dolutegravir was directly compared with raltegravir in the study. The patients additionally received individual antiretroviral background therapy in both study arms.

Section 2.5.4 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier, and in Sections 2.8.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.5.1.2 Study characteristics

Table 18 and Table 19 describe the SAILING study.

Table 18: Characteristics of the studies included – RCT, direct comparison: dolutegravir vs. raltegravir

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SAILING	RCT, double-blind, parallel, double-dummy, multicentre	HIV-1 infected adult patients with previous ART, without previous INI treatment and baseline viral load of > 400 copies/mL. Moreover, they had to have resistance to at least 2 ART drug classes.	Dolutegravir 50 mg[b] (N = 360) raltegravir 800 mg[b] (N = 364) in each case in addition to optimized individual antiretroviral background therapy	Screening phase: up to 42 days treatment phase: 48 weeks[b] follow-up: 4 weeks	156 centres in Australia, Europe, North and South America, Russia, South Africa and Taiwan since 10/2010 data cut-off at week 48: 2/2013	*Primary outcome:* virologic response at week 48 *Secondary outcomes:* AIDS-defining events (CDC class C), virologic response at week 96; change in CD4 cell count; mortality, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for the present benefit assessment.
b: After week 48, the patients from the dolutegravir arm could switch to an open-label phase.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CDC: Centers for Disease Control and Prevention; CD4: cluster of differentiation 4; HIV: human immunodeficiency virus; INI: integrase inhibitor; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 19: Characteristics of the interventions – RCT, direct comparison: dolutegravir vs. raltegravir

Study	Intervention	Comparison	Concomitant medication
SAILING	Dolutegravir 50 mg once daily + placebo for raltegravir twice daily	400 mg raltegravir twice daily + placebo for dolutegravir once daily	Other antiretroviral therapies than the ones specified for the background regimen were not permitted. Other non-permitted medications: cytotoxic chemotherapy or radiotherapy, HIV vaccine, nevirapine, barbiturates, oxcarbamazepine, phenytoin, phenobarbital, carbamazepine, St. John's Wort, long-term treatment with oral glucocorticoids, HCV therapy, dofetilide Restricted medication: etravirine, systemic immunomodulators (e.g. interleukin and interferons) were prohibited until week 48.
	Individual background therapy: The background therapy was already defined and documented for the individual patient under consideration of primary resistance before randomization. It consisted of at least 1 and no more than 2 active drugs. During the study it was allowed to switch one drug of the background therapy, but only within the respective drug class. The number of patients without primary PI resistance at the start of the study who were allowed to receive DRV/r was limited to 170.		

DRV/r: darunavir/ritonavir; HCV: hepatitis C virus; HIV: human immunodeficiency virus; PI: protease inhibitor; RCT: randomized controlled trial; vs.: versus

The SAILING study is a double-blind, parallel, double-dummy active-controlled phase 3 study. It is a multicentre study conducted in countries in America, Australia and Europe, as well as in Russia, South Africa and Taiwan. The randomized study phase was 48 weeks, followed by a still ongoing open-label phase. The assessment was conducted based on the results after 48 weeks. HIV-1 positive pretreated adult patients were enrolled in the study.

The patients in the SAILING study were not allowed to be pretreated with INIs and had to have resistance to at least 2 drugs from 2 different antiretroviral therapy (ART) drug classes (nucleoside reverse transcriptase inhibitor [NRTI], non-NRTI [NNRTI], protease inhibitors (PIs), fusion inhibitors or chemokine receptor antagonists). Dolutegravir (N = 360) was compared with raltegravir (N = 364) in the study. Like dolutegravir, raltegravir is a drug from the INI class. Each patient received an individual background therapy in addition to the study medication. The individual background therapy was defined by the doctors before randomization. It was selected based on the patient's resistances and had to consist of at least 1 and no more than 2 fully active antiretroviral agents. During the study it was allowed to switch one drug of the background therapy due to intolerance, but only within the drug class. Regarding the patients without primary PI resistance, the number of patients who received the PI darunavir (DRV/r) as part of their background therapy was limited a priori to 170. However, this did not have any consequences for the present assessment (see Section 2.8.2.4.3 of the full dossier assessment). Due to the existing multiple resistances to antiretroviral drugs from different drug classes it can be assumed that an INI was an obligatory component of the new treatment regimen in the patients investigated. The approach

chosen in the SAILING study can therefore be regarded as an adequate approximation to an optimized individual treatment for this patient group. Due to this specification, however, no conclusions could be derived from the SAILING study with regard to the total target population of pretreated patients, but only with regard to patients for whom an INI is an obligatory component of a new treatment regimen.

The patients in the study were stratified by

- HIV-1 RNA (≤ 50 000 copies/mL or > 50 000 copies/mL)
- patients without PI resistance and with DRV/r as part of their background therapy versus patients without DRV/r as part of their background therapy or with PI resistance
- number of active drugs in their background therapy (2 versus < 2)

The patients received daily placebo in addition to the study medication to maintain blinding.

Table 20, Table 21 and Table 22 show the characteristics of the patients in the studies included.

Table 20: Characteristics of the study population – RCT, direct comparison: dolutegravir vs. raltegravir (week 48)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Ethnicity %		Treatment discon-tinuations n (%)
				Whites	Non-whites[a]	
SAILING						
dolutegravir	360	43 (11)	30/70	50	49	68 (19)
raltegravir	364	43 (10)	34/66	48	51	82 (23)

a: This group includes Asians, blacks/patients of African heritage, native Americans/native Alaskans, Hawaiians/Pacific Islanders, and others.

F: female; M: male; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 21: Characteristics of the study population (severity of the disease at the start of the study) – RCT, direct comparison: dolutegravir vs. raltegravir (week 48)

Study group	N	Baseline viral load n (%)		CD4 cell count at start of study n (%)		HIV disease stage n (%)		
		≤ 100 000 HIV-1 RNA copies/mL	> 100 000 HIV-1 RNA copies/mL	< 350/µL	≥ 350/µL	Asymptomatic	Symptomatic	AIDS
SAILING								
dolutegravir	360	287[a] (81)	67 (19)	255[a] (72)	99[a] (28)	111 (31)	70 (20)	173 (49)
raltegravir	364	288[a] (80)	73 (20)	263[a] (73)	98[a] (27)	114 (32)	89 (25)	158 (44)

a: Institute's calculation.

AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; HIV: human immunodeficiency virus; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; RNA: ribonucleic acid; vs.: versus

Table 22: Characteristics of the study population (extent of pretreatment) – RCT, direct comparison: dolutegravir vs. raltegravir (week 48)

Study	Dolutegravir N = 354 n (%)	Raltegravir N = 361 n (%)
SAILING		
Previous ART		
Any previous ART	354 (100)	360 (> 99)
1 regimen	0	1 (< 1)
2 regimens	4 (1)	4 (1)
3 regimens	119 (34)	103 (29)
4 regimens	43 (12)	51 (14)
5 regimens	37 (10)	43 (12)
≥ 6 regimens	151 (43)	158 (44)
Primary resistance at baseline		
1 drug class	0	0
2 drug classes	186 (53)	178 (49)
3 drug classes	124 (35)	150 (42)
4 drug classes	40 (11)	30 (8)
5 drug classes	4 (1)	3 (< 1)

ART: antiretroviral therapy; N: number of randomized patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus

There were no important differences between the treatment arms with regard to age, sex and ethnicity. The average age of the patients was 43 years. More men than women and about the same number of white and non-white patients were enrolled in the 2 study arms. Almost half of the patients already had AIDS. The patients in the study had already received several previous ARTs and already had resistances to several drug classes.

Table 23 shows the risk of bias at study level.

Table 23: Risk of bias at study level – RCT, direct comparison: dolutegravir vs. raltegravir

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

RCT: randomized controlled trial; vs.: versus

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

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-G of the dossier, and in Sections 2.8.2.4.1 and 2.8.2.4.2 of the full dossier assessment.

2.5.2 Results on added benefit

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

- Mortality
  - all-cause mortality
- Morbidity
  - AIDS-defining events (CDC class C events)
  - presented as additional information: virologic response and CD4 cell count as surrogate outcomes for the patient-relevant outcome "AIDS-defining illnesses/death"
  - HIV symptoms (HIV-SDM)
- Health-related quality of life
- Adverse events
  - overall rate of SAEs
  - discontinuation due to adverse events
  - grade 3-4 adverse events (DAIDS)
  - nervous system disorders (SOC)
  - skin rash (PT)
  - psychiatric disorders (SOC)
  - musculoskeletal and connective tissue disorders (SOC)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in its dossier (Module 4). In addition to the company's dossier, the outcome "AIDS-defining events (CDC class C events)" was included in the benefit assessment because this outcome directly represents the AIDS-defining illnesses important in the therapeutic indication. Reasons for the choice of outcomes are given in Section 2.8.2.4.3 of the full dossier assessment.

Table 24 shows for which outcomes data were available in the studies included. Table 25 shows the risk of bias for these outcomes.

Table 24: Matrix of outcomes – RCT, direct comparison: dolutegravir vs. raltegravir

Study	Outcomes												
	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response[a]	CD4 cell count[a]	HIV symptoms (HIV-SDM)	Health-related quality of life	Serious adverse events	Discontinuation due to adverse events	Grade 3-4 adverse events (DAIDS)	Nervous system disorders (SOC)	Skin rash (PT)	Psychiatric disorders (SOC)	Musculoskeletal and connective tissue disorders (SOC)
SAILING	Y	Y	Y	Y	N	N[b]	Y	Y	Y	Y	Y	Y	Y

a: Virologic response and CD4 cell count as surrogate outcomes for the combined outcome "AIDS-defining illnesses/death" are presented as additional information.
b: Data not evaluable (see Section 2.8.2.4.3 of the full dossier assessment for reasons).

AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; HIV: human immunodeficiency virus; HIV-SDM: HIV symptom distress module; MedDRA: Medical Dictionary for Regulatory Activities; N: no; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SOC: MedDRA System Organ Class; vs.: versus; Y: yes

Table 25: Risk of bias at study and outcome level – RCT, direct comparison: dolutegravir vs. raltegravir

Study		Outcomes												
	Study level	All-cause mortality	AIDS-defining events (CDC class C events)	Virologic response	CD4 cell count	HIV symptoms (HIV-SDM)	Health-related quality of life	Serious adverse events	Discontinuation due to adverse events	Grade 3-4 adverse events (DAIDS)	Nervous system disorders (SOC)	Skin rash (PT)	Psychiatric disorders (SOC)	Musculoskeletal and connective tissue disorders (SOC)
SAILING	L	L	L	L	H[a]	–[b]	–[c]	L	L	L	L	L	L	L

a: ITT principle violated: proportion of missing values in the treatment groups 17% and 22%.
b: Outcome was not recorded.
c: Data not evaluable (see Section 2.8.2.4.3 of the full dossier assessment for reasons).

AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; DAIDS: Division of AIDS; H: high; HIV: human immunodeficiency virus; HIV-SDM: HIV symptom distress module; ITT: intention to treat; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; SOC: MedDRA System Organ Class; vs.: versus

The assessment of the risk of bias is largely consistent with the one of the company. The risk of bias of the outcome "CD4 cell count" not presented by the company in the dossier was rated as high because of missing values.

2.5.2.1 Results

Table 26 shows the results on the comparison of dolutegravir with raltegravir in pretreated adults infected with HIV-1. Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations. In principle, it is possible to derive indications, e.g. of an added benefit of dolutegravir, from one study with a low risk of bias. This assessment corresponds to that of the company. Any possible weakening of the results by outcome-specific aspects will be noted separately for individual outcomes in the following presentation of the results.

Table 26: Results (dichotomous outcomes) – RCT, direct comparison: dolutegravir vs. raltegravir (week 48), pretreated adults

Study outcome category outcome	Dolutegravir		Raltegravir		Dolutegravir vs. raltegravir
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
SAILING					
Mortality					
All-cause mortality	354	0 (0)	361	3 (0.8)	0.15 [0.01; 2.80]; 0.088[a]
Morbidity					
AIDS-defining events (CDC class C events)	354	10 (2.8)	361	5 (1.4%)	2.04 [0.70; 5.91]; 0.195[a]
Additional information: surrogate outcome "virologic response"[b] (< 50 RNA copies/mL)	354	251 (70.9)	361	230 (63.7)	1.14 [1.04; 1.24]; 0.003
Additional information: surrogate outcome "CD4 cell count" (number/µL)	294[c]	254 (207.8)[d] 162 (151.4)[e]	283[c]	246 (199.0)[d] 153 (143.9)[e]	9.0 [-15.2; 33.2]; 0.470[a]
Health-related quality of life					
No evaluable data					
Adverse events					
AEs	357	280 (78.4)	362	286 (79.0)	
SAEs	357	33 (9.2)	362	42 (11.6)	0.80 [0.52; 1.23]; 0.302
Discontinuation due to AEs	357	7 (2.0)	362	13 (3.6)	0.55 [0.22; 1.35]; 0.191
Severity grade 3-4 AEs (DAIDS)	357	35 (9.8)[f]	362	53 (14.6)[f]	0.67 [0.45; 1.00]; 0.049[a]
Nervous system disorders (SOC)	357	57 (16.0)	362	71 (19.6)	0.81 [0.59; 1.12]; 0.203
Skin rash (PT)	357	19 (5.3)	362	18 (5.0)	1.07 [0.57; 2.01]; 0.879[a]
Psychiatric disorders (SOC)	357	40 (11.2)	362	32 (8.8)	1.27 [0.82; 1.97]; 0.292
Musculoskeletal and connective tissue disorders (SOC)	357	51 (14.3)	362	72 (19.9)	0.72 [0.52; 1.00]; 0.048

a: Institute's calculation, unconditional exact test (CSZ method according to [8]).
b: Analysed with the MSDF.
c: Number of patients analysed at 48 weeks. The values at the start of the study can be based on other patient numbers.
d: Values at the start of the study (mean [SD]).
e: Change at the end of the study (mean [SD]).
f: Institute's calculation.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CD4: cluster of differentiation 4; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CSZ: convexity, symmetry, z score; DAIDS: Division of AIDS; MedDRA: Medical Dictionary for Regulatory Activities; MSDF: missing, switch or discontinuation = failure; N: number of analysed patients; n: number of patients with event; PT: MedDRA Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SD: standard deviation; SOC: MedDRA System Organ Class; vs.: versus

Mortality

All-cause mortality

Only few events occurred in all-cause mortality, the result of the SAILING study was not statistically significant. An added benefit of dolutegravir compared with raltegravir for overall survival is therefore not proven.

This concurs with the company's assessment.

Morbidity

AIDS-defining events (CDC class C events); surrogate outcomes "virologic response" and "CD4 cell count"

There was no statistically significant difference between the treatment groups for the outcome **"AIDS-defining events (CDC class C events)"**. Only few events occurred, however. For **virologic response**, there was a statistically significant effect in favour of dolutegravir. There was no statistically significant difference between the treatment groups for **CD4 cell count**. As the direction of the effect in the outcome "AIDS-defining events (CDC class C events)", which is the outcome of actual interest, differed from the one in the surrogate outcomes, there is no indication of an added benefit of dolutegravir versus raltegravir in the overall assessment of the 3 outcomes. However, overall there is also no indication that dolutegravir achieves considerably worse results than raltegravir. This contradicts the company's assessment, which derived an indication of added benefit of dolutegravir from the virologic response. The company did not present the outcomes "AIDS-defining events (CDC class C events)" and "CD4 cell count" in Module 4 of its dossier.

HIV symptoms (SDM)

The outcome "HIV symptoms", measured with the SDM, was not recorded in the SAILING study.

An added benefit of dolutegravir compared with raltegravir for HIV symptoms is therefore not proven.

Health-related quality of life

EQ-5D

There were no evaluable data on health-related quality of life for the SAILING study. For reasons, see Section 2.8.2.4.3 of the full dossier assessment. Hence an added benefit of dolutegravir compared with raltegravir for health-related quality of life is not proven.

This concurs with the company's assessment.

Adverse events

The adverse events, SAEs, discontinuations due to adverse events and grade 3-4 severe adverse events (DAIDS) that most commonly occurred in the SAILING study are presented in Appendix C of the full dossier assessment.

Serious adverse events

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "SAEs". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

This concurs with the company's assessment.

Discontinuation due to adverse events

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "discontinuation due to adverse events". Greater/lesser harm from dolutegravir in comparison with raltegravir is therefore not proven for this outcome.

This concurs with the company's assessment.

Grade 3-4 severe adverse events (DAIDS)

In the SAILING study there was a statistically significant effect in favour of dolutegravir for the outcome "grade 3-4 severe adverse events (DAIDS)". This led to an indication of lesser harm from dolutegravir versus raltegravir.

The company did not present this outcome in its dossier.

Nervous system disorders (SOC)

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "nervous system disorders (SOC)". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

This concurs with the company's assessment, which however derived an indication of added benefit based on the subgroup analyses. The assessment of the subgroups can be found in Section 2.5.2.2.

Skin rash (PT)

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "skin rash". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

This concurs with the company's assessment.

Psychiatric disorders (SOC)

In the SAILING study there was no statistically significant difference between the treatment groups for the outcome "psychiatric disorders (SOC)". Greater/lesser harm from dolutegravir than from raltegravir is therefore not proven for this outcome.

This concurs with the company's assessment.

Musculoskeletal and connective tissue disorders (SOC)

There was a statistically significant effect in favour of dolutegravir for the outcome "musculoskeletal and connective tissue disorders (SOC)". However, this was of only marginal effect size (the upper confidence interval is above the threshold of 0.9; outcome category "non-severe/non-serious adverse events [1]) so that greater/lesser harm from dolutegravir is not proven.

This contradicts the company's assessment, which derived an indication of added benefit for this outcome (with an effect size of the same magnitude).

2.5.2.2 Subgroup analyses

Selected subgroups were investigated for the presence of heterogeneous treatment effects in order to identify possible effect modifications. The company presented the corresponding analyses for the outcomes it rated as relevant. Hence there were no subgroup analyses for the outcomes "AIDS-defining events (CDC class C events)" and "grade 3-4 severe adverse events (according to DAIDS)", which were additionally rated as relevant, and on the surrogate outcome "CD4 cells" presented as additional information, and they could also not be subsequently calculated from the available documents. The subgroup results on virologic response are also not presented because this additional surrogate outcome cannot be interpreted in isolation.

Subgroup analyses for the following characteristics were considered:

- age (</≥ 50 years)
- sex
- ethnicity (whites/non-whites)
- baseline viral load (≤ 50 000/> 50 000 HIV-1 RNA copies/mL)

The subgroup characteristics presented by the company and the cut-off values were specified a priori in the study. Only the results on subgroups and outcomes with at least indications of an interaction between treatment effect and subgroup characteristic and with statistically significant results in at least one subgroup are presented. The prerequisite for proof of different subgroup effects is a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification.

Table 27 shows the results of the subgroup analyses.

Table 27: Subgroups with at least indications of interaction – RCT, direct comparison: dolutegravir vs. raltegravir (week 48), pretreated adults

Study outcome characteristic subgroup	Dolutegravir N	Dolutegravir Patients with events n (%)	Raltegravir N	Raltegravir Patients with events n (%)	Dolutegravir vs. raltegravir RR [95% CI][a]	Dolutegravir vs. raltegravir p-value[a]
SAILING						
Nervous system disorders (SOC)						
age					interaction:	0.048
< 50 years	272	47 (17)	278	49 (18)	0.98 [0.68; 1.41]	0.915
≥ 50 years	85	10 (12)	84	22 (26)	0.45 [0.23; 0.89]	0.022
ethnicity					interaction:	0.044
white	181	33 (18)	176	28 (16)	1.15 [0.72; 1.81]	0.560
non-white	175	24 (14)	185	43 (23)	0.59 [0.37; 0.93]	0.023

a: Institute's calculation.

CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; SOC: MedDRA System Organ Class; vs.: versus

Nervous system disorders (SOC)

There was proof of an effect modification by the characteristics "age" and "ethnicity" for the outcome "nervous system disorders (SOC)".

There was a statistically significant result in favour of dolutegravir for people over 50 years of age, but not for people under 50 years of age. Hence there was an indication of lesser harm from dolutegravir in people over 50 years of age.

The result was not statistically significant in the group of whites. In non-whites, there was a statistically significant result in favour of dolutegravir, which was of only marginal effect size (the upper confidence interval is above the threshold of 0.9; outcome category "non-severe/non-serious adverse events [1]) so that greater/lesser harm from dolutegravir is not proven.

Only the effect modification by age is considered further for the benefit assessment, because only for this characteristic different conclusions on added benefit arise.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.8.2.4.2 and 2.8.2.4.3 of the full dossier assessment.

2.5.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of the Institute [1].

2.5.3.1 Evaluation of added benefit at outcome level

The available data presented in Section 2.5.2 results in indications of lesser harm from dolutegravir in comparison with raltegravir in pretreated adults for the outcomes “grade 3-4 severe adverse events (DAIDS)” and “nervous system disorders (SOC)”.

There is an effect modification by the subgroup characteristic “age”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 28). In the overall assessment, it was then investigated whether different conclusions on the extent of added benefit arise for individual patient groups.

Table 28: Extent of added benefit at outcome level: dolutegravir vs. raltegravir (week 48), pretreated adults

Outcome category outcome	**Dolutegravir vs. raltegravir effect estimate [95% CI] p-value probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0.8% RR: 0.15 [0.01; 2.80] p = 0.088[c]	Added benefit not proven
Morbidity		
AIDS-defining events (CDC class C events) *Additional information: surrogate outcome "virologic response"* *Additional information: surrogate outcome "CD4 cell count"*	2.8% vs. 1.7% RR: 1.70 [0.62; 4.63] p = 0.303[c] 70.9% vs. 63.7% RR: 1.14 [1.04; 1.24]; p = 0.003 162 vs. 153 MD: 9.0 [-15.2; 33.2]; p = 0.470[c]	Added benefit not proven
Health-related quality of life		
No evaluable data		
Adverse events		
SAEs	9.2% vs. 11.6% RR: 0.80 [0.52; 1.23] p = 0.302	Greater/lesser harm not proven
Discontinuation due to AEs	2.0% vs. 3.6% RR: 0.55 [0.22; 1.35] p = 0.191	Greater/lesser harm not proven
Grade 3-4 AEs (DAIDS)	9.8% vs. 14.6% RR: 0.67 [0.45; 1.00] p = 0.049[c] probability: "indication"	Outcome category: serious/severe adverse events CI_u = 1.00 lesser harm extent: "minor"

(continued)

Table 28: Extent of added benefit at outcome level: dolutegravir vs. raltegravir (week 48), pretreated adults (continued)

Outcome category outcome	**Dolutegravir vs. raltegravir effect estimate [95% CI] p-value probability[a]**	**Derivation of extent[b]**
Nervous system disorders (SOC)	16.0% vs. 19.6% RR: 0.81 [0.59; 1.12] p = 0.203	
Age (years) < 50	17.3% vs. 17.6% RR: 0.98 [0.68; 1.41] p = 0.915	Greater/lesser harm not proven
≥ 50	11.8% vs. 26.2% RR: 0.45 [0.23; 0.89] p = 0.022 probability: "indication"	Outcome category: non-serious/non-severe AEs CI_u < 0.90 lesser harm extent: "minor"
Skin rash (PT)	5.3% vs. 5.0% RR: 1.07 [0.57; 2.01] p = 0.879[c]	Greater/lesser harm not proven
Psychiatric disorders (SOC)	11.2% vs. 8.8% RR: 1.27 [0.82; 1.97] p = 0.292	Greater/lesser harm not proven
Musculoskeletal and connective tissue disorders (SOC)	14.3% vs. 19.9% RR: 0.72 [0.52; 1.00] p = 0.048	Outcome category: non-serious/non-severe AEs CI_u > 0.90 greater/lesser harm not proven

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Institute's calculation.

AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CD4: cluster of differentiation 4; CI: confidence interval; CI_u: upper limit of CI; DAIDS: Division of AIDS; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RR: relative risk; SOC: MedDRA System Organ Class; vs.: versus

2.5.3.2 Overall conclusion on added benefit

Table 29 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 29: Positive and negative effects from the assessment of dolutegravir vs. raltegravir, pretreated adults

Positive effects	**Negative effects**
Serious/severe adverse events ▪ grade 3-4 adverse events (DAIDS): indication of lesser harm – extent: “minor”	–
Non-serious/non-severe adverse events ▪ nervous system disorders (SOC) ▫ age ≥ 50 years: indication of lesser harm – extent: “minor”	
AIDS: acquired immunodeficiency syndrome; DAIDS: Division of AIDS; MedDRA: Medical Dictionary for Regulatory Activities; SOC: MedDRA System Organ Class; vs.: versus	

Overall, only positive effects remain in the outcome categories “serious/severe adverse events” (extent: “minor”) and “non-serious/non-severe adverse events” (extent: “minor”). The effect modification by the subgroup characteristic “age” did not influence the overall conclusion on added benefit.

It is to be noted that positive effects only occur in the area of adverse events. However, from the results on all-cause mortality and AIDS-defining events of CDC class C in combination with the results on the surrogate outcomes “virologic response” and “CD4 cell count” additionally presented, there is no indication that dolutegravir achieves worse results than raltegravir with regard to these outcomes.

Overall, there is therefore an indication of an added benefit of dolutegravir in comparison with raltegravir with the extent “minor” for pretreated adult patients for whom an INI is a component of the optimized treatment.

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

2.5.4 List of included studies

SAILING

Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013; 382(9893): 700-708.

ViiV Healthcare. A phase III randomized, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults [online]. In: EU Clinical Trials Register. 13 August 2010 [accessed: 27 November 2013]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-018001-51/ES.

ViiV Healthcare. A phase III randomized, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigatorselected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral therapy-experienced adults: week 48 results; study no ING111762; clinical study report [unpublished]. 2013.

ViiV Healthcare. A randomized, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, integrase inhibitor-naïve, antiretroviral-experienced adults: result summary [online]. In: GlaxoSmithKline Clinical Study Register. 5 September 2013 [accessed: 27 November 2013]. URL: http://www.gsk-clinicalstudyregister.com/files2/cede77cb-45b6-49c0-ba5e-10df053f7e19.

ViiV Healthcare. A study of GSK1349572 versus raltegravir (RAL) with investigator selected background regimen in antiretroviral-experienced, integrase inhibitor-naive adults (SAILING): full text view [online]. In: ClinicalTrials.gov. 25 July 2013 [accessed: 27 November 2013]. URL: http://ClinicalTrials.gov/show/NCT01231516.

ViiV Healthcare. ING111762 (SAILING study): post-hoc subgroup analyses [unpublished]. 2013.

2.6 Research question 4: pretreated adolescents above 12 years of age

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 lists on dolutegravir (studies completed up to 4 December 2013)
- bibliographical literature search on dolutegravir (last search on 4 December 2013)
- search in trial registries for studies on dolutegravir (last search on 27 November 2013)

The Institute's own search to check the completeness of the study pool:

- search in trial registries for studies on dolutegravir (last search on 26 February 2014)

This check produced no deviations from the study pool presented in the dossier. No relevant study was identified.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.8.2.1 and 2.8.2.3 of the full dossier assessment.

2.6.2 Results on added benefit

No data were available for pretreated adolescents. An added benefit of dolutegravir versus the ACT is therefore not proven for this subpopulation.

2.6.3 Extent and probability of added benefit

As the company presented no data for pretreated adolescents, an added benefit of dolutegravir is not proven for this subpopulation.

References for English extract

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 7 February 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. ViiV Healthcare. Tivicay 50 mg Filmtabletten: Fachinformation [online]. January 2014 [accessed: 25 February 2014]. URL: http://www.fachinfo.de.

4. Bristol-Myers Squibb, Gilead. Atripla 600 mg/200 mg/245 mg Filmtabletten: Fachinformation [online]. March 2014 [accessed: 15 April 2014]. URL: http://www.fachinfo.de.

5. Teva. Efavirenz Teva 600 mg Filmtabletten: Fachinformation [online]. July 2013 [accessed: 11 March 2014]. URL: http://www.fachinfo.de.

6. Gilead. Emtriva 200 mg Hartkapseln: Fachinformation [online]. May 2013 [accessed: 11 March 2014]. URL: http://www.fachinfo.de.

7. Gilead. Viread 245 mg Filmtabletten: Fachinformation [online]. October 2013 [accessed: 11 March 2014]. URL: http://www.fachinfo.de.

8. 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/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a14_08_dolutegravir_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.6011.html.