IQWiG Reports – Commission No. A21-47

Cabotegravir (HIV infection) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Cabotegravir (HIV-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 July 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ABC/DTG/3TC	abacavir/dolutegravir/lamivudine
ACT	appropriate comparator therapy
ART	antiretroviral therapy
AE	adverse event
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
INI	integrase inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
Q1M	monthly
Q2M	every 2 months
RCT	randomized controlled trial
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 cabotegravir in combination with rilpivirine. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 3 May 2021.

Research question

The aim of this report is to assess the added benefit of cabotegravir in combination with rilpivirine (hereinafter cabotegravir + rilpivirine) in comparison with individualized antiretroviral therapy (ART) as the appropriate comparator therapy (ACT) in adult patients infected with human immunodeficiency virus type 1 (HIV-1) who are virologically suppressed (HIV-1 ribonucleic acid [RNA] < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to or prior virological failure with drugs of the nonnucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) class.

Treatment concept of the cabotegravir + rilpivirine combination therapy

Underthe treatment concept of the cabotegravir + rilpivirine combination therapy, cabotegravir + rilpivirine is administered for an initial 4-week oral lead-in phase. After that, both drugs are administered by intramuscular injection using 1 of 2 approved treatment regimens, either monthly (Q1M) or every 2 months (Q2M). The added benefit of cabotegravir + rilpivirine is assessed for the entire treatment concept including both the oral lead-in phase and intramuscular injection.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research questions of the benefit assessment of cabotegravir + rilpivirine

Indication	**ACT**[a]
Adults with HIV-1 infection who are on stable virological suppression (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to, and no prior virological failure with agents of the NNRTI or INI class	Individualized antiretroviral therapy, selecting from approved drugs and taking into account any prior therapies and any side effects[b]
a. Presented is the respective ACT specified by the G-BA. b. For patients not indicated for a treatment switch, continuation of the previous therapy represents the appropriate implementation of the ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1; human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 48 weeks were used for the derivation of the added benefit.

As described above, the therapeutic indication of cabotegravir + rilpivirine comprises the 2 approved treatment regimens, Q1M and Q2M. In its dossier, the company presents an adjusted indirect comparison only for the Q2M treatment regimen, reasoning that only the Q2M regimen would be marketed.

The data submitted by the company on the Q2M treatment regimen are assessed below.

Results

Study pool and study characteristics

In line with the company's findings, the check for completeness of the study pool identified no studies for the direct comparison of cabotegravir + rilpivirine Q2M with the ACT in this therapeutic indication.

For the assessment of cabotegravir + rilpivirine Q2M in comparison with individualized ART, the company presented an adjusted indirect comparison using the common comparator of cabotegravir + rilpivirine Q1M.

For its indirect comparison for cabotegravir + rilpivirine Q2M, the company identified the ATLAS-2M study with the common comparator of cabotegravir + rilpivirine Q1M and, on the comparator side, the ATLAS and FLAIR studies. Results for a 48-week data cut-off are available from all 3 studies, and additionally, results after 96 weeks are available for the ATLAS-2M and FLAIR studies. Reasoning that the results after 96 weeks offer additional information, the company limited its study pool to ATLAS-2M and FLAIR. In dissent from the company, the ATLAS study is deemed relevant as well.

The company's approach is not appropriate. Chronic diseases such as human immunodeficiency virus (HIV) require a minimum study duration of 48 weeks. While this does align with the company's inclusion criteria and looking at results obtained after 96 weeks of treatment makes sense, it does not justify excluding the ATLAS study from the study pool. In Appendix 4-I of the dossier, the company presented as supplementary information an adjusted indirect comparison with the 3 studies ATLAS-2M, FLAIR, and ATLAS on the basis of their results after 48 weeks; therefore, data for this study pool are available as well.

ATLAS-2M, FLAIR, and ATLAS included only patients without indication for a treatment switch (in line with the prerequisite in the therapeutic indication [adults who are virologically suppressed on a stable antiretroviral regimen]).

ATLAS-2M study

The ATLAS-2M study is an open-label, randomized parallel-group study investigating the treatment concept of cabotegravir + rilpivirine Q2M versus Q1M. The study included treatment-experienced adult patients with HIV-1 infection who had been on an uninterrupted regimen of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a 3rd drug from the NNRTI drug class, protease inhibitors (PIs), or INI for at least 6 months and were on stable virological suppression (HIV-1 RNA < 50 copies/mL). Further, patients were allowed to switch from ATLAS to ATLAS-2M.

The company presented the results of a subpopulation of patients with prior ART consisting of 2 NRTI in combination with a 3rd drug from the NNRTI, PI, or INI drug class. The ATLAS-2M subpopulation comprises 327 patients in the intervention arm and 327 in the comparator arm. This subpopulation presented by the company is relevant for the present research question and has been included in the benefit assessment. The dosage and administration of cabotegravir + rilpivirine Q2M and Q1M are in accordance with approval.

The primary outcome of the study is virological response (HIV RNA < 50 copies/mL) at Week 48. Other patient-relevant outcomes are mortality, morbidity, health-related quality of life, and adverse events (AEs).

ATLAS study

The ATLAS study was an open-label, randomized parallel-group study investigating the treatment concept of cabotegravir + rilpivirine Q1M versus individualized ART. The study included treatment-experienced adult patients with HIV-1 infection who had received an uninterrupted therapy consisting of 2 NRTIs in combination with a 3rd drug from the NNRTI, PI, or INI drug class for at least 6 months and were on stable virological suppression (HIV-1 RNA < 50 copies/mL).

A total of 618 patients were included in the study, with 310 patients being allocated to the intervention arm and 308 to the comparator arm. Cabotegravir + rilpivirine Q1M treatment was administered in compliance with the Summary of Product Characteristics (SPC).

The primary outcome of the study was virological response (HIV RNA < 50 copies/mL) at Week 48. Other patient-relevant outcomes were mortality, morbidity, health-related quality of life, and AEs.

FLAIR study

The FLAIR study is an open-label, randomized parallel-group study investigating cabotegravir + rilpivirine Q1M in comparison with abacavir/dolutegravir/lamivudine (ABC/DTG/3TC). The study included treatment-naive patients with HIV-1 infection (HIV-1 RNA ≥ 1000 copies/mL) who received ABC/DTG/3TC therapy for 20 weeks before randomization. Following 16 weeks of ABC/DTG/3TC treatment, patients had to be virologically suppressed (HIV-1 RNA < 50 copies/mL) to be randomized, after a further 4 weeks, to 1 of the 2 treatment arms

(cabotegravir + rilpivirine Q1M or ABC/DTG/3TC). In total, 566 patients were randomized to the intervention arm (N = 283) or the comparator arm (N = 283). Cabotegravir + rilpivirine Q1M treatment and ABC/DTG/3TC treatment were administered in compliance with the SPC.

The primary outcome of the study was virological response (HIV RNA < 50 copies/mL) at Week 48. Other patient-relevant outcomes were mortality, morbidity, health-related quality of life, and AEs.

Lack of similarity check for included studies

A central prerequisite for the inclusion of studies in an adjusted indirect comparison is a similarity check. The company failed to examine the similarity of the studies it included in Module 4 A. Similarity was not checked in any way for the ATLAS-2M study versus the FLAIR and ATLAS studies.

For the ATLAS-2M study, Module 4 A provided very little information on disease-specific patient characteristics (severity and duration of disease; duration and type of prior therapy). This means that not even the prerequisite for a sufficient check of similarity of the studies has been met. In addition, the ATLAS and FLAIR studies on the ART side of the indirect comparison differ markedly in duration (53 months versus 20 weeks) and in the patients' prior treatment type (NNRTI + 2 NRTI versus ABC/DTG/3TC).

Overall, the adjusted indirect comparison of cabotegravir + rilpivirine Q2M versus the ACT, as submitted by the company, is rendered unusable by both the missing data on disease-specific patient characteristics in the ATLAS-2M study and the missing similarity check. Hence, no suitable data which would allow deriving an added benefit of cabotegravir + rilpivirine Q2M in comparison with the ACT are available for the benefit assessment.

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

On the basis of the presented results, the probability and extent of added benefit of the drug cabotegravir + rilpivirine Q2M in comparison with the ACT have been assessed as follows:

In its dossier, the company only partially covered the therapeutic indication of cabotegravir + rilpivirine for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to, and no prior virological failure with agents of the NNRTI and INI

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

class and who have no indication for a treatment switch. The company did not cover the Q1M treatment regimen despite the availability of 2 RCTs comparing with the ACT. For the Q2M treatment regimen, the company presented an indirect comparison which is unsuitable for the benefit assessment due to methodological deficiencies. The company did not present any data for patients with indication for a treatment switch. Overall, there is therefore no hint of added benefit of cabotegravir + rilpivirine in comparison with the ACT; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of added benefit of cabotegravir + rilpivirine.

Table 3: Cabotegravir + rilpivirine – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with HIV-1 infection who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to, and no prior virological failure with agents of the NNRTI or INI class	Individualized antiretroviral therapy, selecting from approved drugs and taking into account any prior therapies and any side effects[b]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. For patients without indication for a treatment switch, continuation of the previous therapy represents the appropriate implementation of the ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of cabotegravir in combination with rilpivirine (hereinafter cabotegravir + rilpivirine) in comparison with individualized ART as the ACT in adult patients infected with HIV-1 who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to or prior virological failure with drugs of the NNRTI or INI class.

Treatment concept of the cabotegravir + rilpivirine combination therapy

Under the treatment concept of the cabotegravir + rilpivirine combination therapy, cabotegravir + rilpivirine is administered for an initial 4-week oral lead-in phase. After that, both drugs are administered by intramuscular injection following 1 of 2 approved treatment regimens, either monthly (Q1M) or every 2 months (Q2M) [3,4]. The added benefit of cabotegravir + rilpivirine is assessed for the entire treatment concept including both the oral lead-in phase and intramuscular injection.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research questions of the benefit assessment of cabotegravir + rilpivirine

Indication	ACT[a]
Adults with HIV-1 infection who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to, and no prior virological failure with agents of the NNRTI or INI class	Individualized antiretroviral therapy, selecting from approved drugs and taking into account any prior therapies and any side effects[b]

a. Presented is the respective ACT specified by the G-BA.
b. For patients without indication for a treatment switch, continuation of the previous therapy represents the appropriate implementation of the ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 48 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

The company's dossier only partially covers the therapeutic indication of cabotegravir + rilpivirine

As described above, the therapeutic indication of cabotegravir + rilpivirine comprises the 2 approved treatment regimens Q1M and Q2M. The company's dossier covers only the Q2M treatment regimen, for which it presents an adjusted indirect comparison. The company used available evidence on the Q1M treatment regimen only within the framework of this adjusted indirect comparison regarding the Q2M treatment regimen (see Section 2.3).

It justified this approach by stating that only the Q2M application is marketed. This approach is inadequate. The research question of the benefit assessment comprises the assessment of the complete therapeutic indication of cabotegravir + rilpivirine.

The data submitted by the company on the Q2M treatment regimen are assessed below.

2.3 Information retrieval and study pool for the Q2M treatment regimen

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on cabotegravir + rilpivirine (as of 1 March 2021)
- Bibliographic literature search on cabotegravir + rilpivirine (most recent search on 1 March 2021)
- Search in trial registries / study results databases on cabotegravir + rilpivirine (most recent search on 1 March 2021)
- Search on the G-BA website on cabotegravir + rilpivirine (most recent search on 1 March 2021)
- Bibliographic literature search on the ACT (most recent search on 1 March 2021)
- Search in trial registries or results databases on the ACT (most recent search on 1 March 2021)
- Search on the G-BA website on the ACT (most recent search on 1 March 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on cabotegravir + rilpivirine (most recent search on 6 May 2021); see Appendix A of the full dossier assessment for search strategies

In agreement with the company's findings, the check for completeness of the study pool did not identify any study for the direct comparison of cabotegravir + rilpivirine Q2M with the ACT in this therapeutic indication. Results of the currently ongoing RCT SOLAR [5], which compares cabotegravir + rilpivirine Q2M with bictegrvir/emtricitabine/ tenofoviralafenamide, are expected in June 2023.

Since no RCT with the ACT is available, the company made an adjusted indirect comparison according to Bucher [6]. For this purpose, it initially identified 3 studies: the ATLAS-2M study for the intervention and the ATLAS and FLAIR studies for the ACT. In its indirect comparison, the company used only ATLAS-2M and FLAIR. In disagreement with the company, the 3rd study, ATLAS, is deemed relevant as well. The ATLAS and FLAIR studies would be relevant for assessing the added benefit of the Q1M treatment regimen. As discussed in Section 2.2, this part of the therapeutic indication was not analysed by the company.

2.3.1 Studies included for the Q2M treatment regimen

For the assessment of added benefit of cabotegravir + rilpivirine Q2M, the company presented an adjusted indirect comparison using the common comparator of cabotegravir + rilpivirine Q1M. Concurring with the company, only cabotegravir + rilpivirine Q1M is a suitable common comparator for an adjusted indirect comparison since only 1 RCT with cabotegravir + rilpivirine Q2M is available in the therapeutic indication and this RCT used cabotegravir + rilpivirine Q1M as a comparator. The comparison is with individualized ART.

The studies included in the benefit assessment are listed in Table 5.

Table 5: Study pool – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication (yes/no [reference])
Cabotegravir + rilpivirine Q2M vs. cabotegravir + rilpivirine Q1M						
207966 (ATLAS-2M[c])	Yes	Yes	No	No[d]	Yes [7,8]	Yes [9]
Continuation of the previous ART vs. cabotegravir + rilpivirine Q1M						
201585 (ATLAS[c])	Yes	Yes	No	No[d]	Yes [10,11]	Yes [12]
201584 (FLAIR[c])	Yes	Yes	No	No[d]	Yes [13,14]	Yes [15,16]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this short name.
d. Due to working conditions during the coronavirus pandemic, the present assessment was conducted without access to the study report in Module 5 of the dossier.

ART: antiretroviral therapy; Q1M: monthly; Q2M: once every 2 months; RCT: randomized controlled trial

The study pool departs from the one presented by the company in Module 4 A of its dossier, which includes only the ATLAS-2M and FLAIR studies for assessing added benefit.

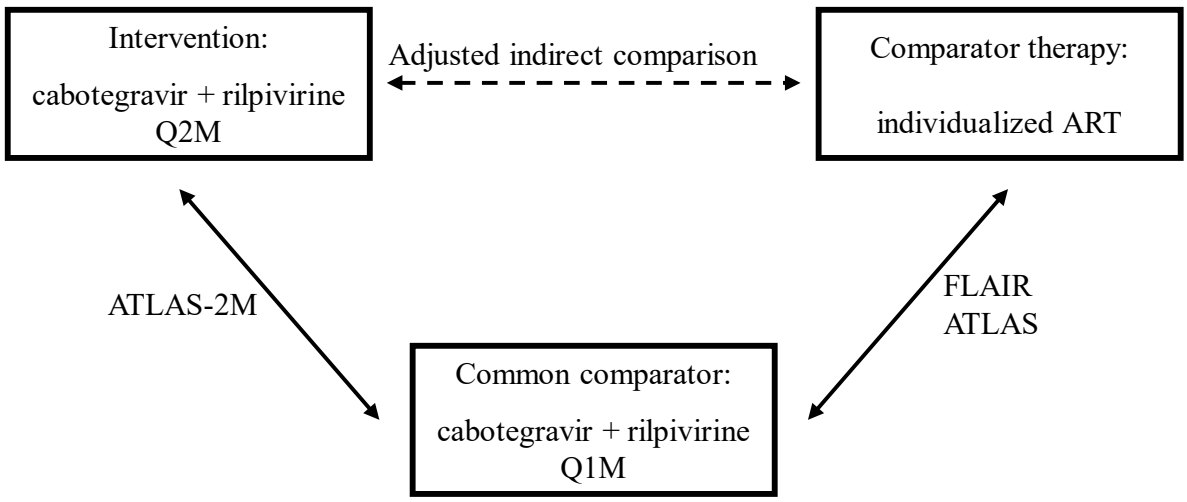
For its adjusted indirect comparison for cabotegravir + rilpivirine Q2M, the company identified the ATLAS-2M study with the common comparator of cabotegravir + rilpivirine Q1M and, on the comparator side, the FLAIR and ATLAS studies. Results for a 48-week data cut-off are available from all 3 studies, and additionally, results after 96 weeks are available for the ATLAS-2M and FLAIR studies. Reasoning that the results after 96 weeks offer additional information, the company limited its study pool to ATLAS-2M and FLAIR.

The company's approach is not appropriate. Chronic diseases such as HIV require a minimum study duration of 48 weeks. While this does align with the company's inclusion criteria and

looking at results obtained after 96 weeks of treatment makes sense, it does not justify excluding the ATLAS study from the study pool.

In Appendix 4-I of the dossier, the company presented as supplementary information an adjusted indirect comparison with the 3 studies ATLAS-2M, FLAIR, and ATLAS on the basis of their results after 48 weeks; therefore, data for this study pool are available as well.

Figure 1 schematically represents the indirect comparison.



ART: antiretroviral therapy; Q1M: monthly; Q2M: every 2 months

Figure 1: Study pool for the indirect comparison between cabotegravir + rilpivirine Q2M and individualized ART

ATLAS-2M, FLAIR, and ATLAS included only patients without indication for a treatment switch (in line with the prerequisite in the therapeutic indication [adults who are virologically suppressed on a stable antiretroviral regimen]). For adults without indication for a treatment switch, continuation of the previous individualized therapy in the comparator arm is therefore considered the adequate implementation of the ACT specified by the G-BA. Consistent with the company's findings, no study is available for adults with indication for a treatment switch.

2.3.2 Study characteristics

Table 6 and Table 7 present the studies used in the benefit assessment.

Table 6: Characterization of the included studies – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
Cabotegravir + rilpivirine Q2M vs. cabotegravir + rilpivirine Q1M						
ATLAS-2M	RCT, open-label, parallel-group	HIV-1 infected adults who have been on stable virological suppression (HIV-1 RNA < 50 copies/mL) for ≥ 6 months on their current antiretroviral therapy (2 NRTIs + INI or NNRTI or PI [typically boosted]).	Cabotegravir + rilpivirine Q2M (N = 524) Cabotegravir + rilpivirine Q1M (N = 525) Relevant subpopulation[b] Cabotegravir + rilpivirine Q2M (N = 327) Cabotegravir + rilpivirine Q1M (N = 327)	Screening: up to 35 days Treatment: 100 weeks Follow-up observation: at least 52 weeks[c]	119 centres in: Argentina, Australia, Canada, France, Germany, Italy, Korea, Mexico, Russia, South Africa, Spain, Sweden, United States 10/2017 – ongoing Analysis for 48-week cut-off: 06/2019 Analysis for 96-week cut-off: 06/2020	Primary: percentage of patients with viral load ≥ 50 copies/mL at Week 48 Secondary: mortality, morbidity, health-related quality of life, AEs
Continuation of the previous ART vs. cabotegravir + rilpivirine Q1M						
ATLAS	RCT, open-label, parallel-group	HIV-1 infected adults who have been on stable virological suppression (HIV-1-RNA < 50 copies/mL) for ≥ 6 months on their current antiretroviral therapy (2 NRTIs + INI [except for ABC/DTG/3TC] or NNRTI or PI [typically boosted]).	Cabotegravir + rilpivirine Q1M (N = 310) Continuation of the previous ART (N = 308): ▪ PI + NRTI (N = 54) ▪ NNRTI + NRTI (N = 155) ▪ INI + NRTI (N = 99)	Screening: up to 35 days Treatment: 52 weeks Follow-up observation: at least 52 weeks[c]	115 centres in: Argentina, Australia, Canada, France, Germany, Italy, Korea, Mexico, Russia, South Africa, Spain, Sweden, United States 10/2016–ongoing Analysis for 48-week cut-off: 05/2018	Primary: percentage of patients with viral load ≥ 50 copies/mL at Week 48 Secondary: mortality, morbidity, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
FLAIR	RCT, open-label, parallel-group	Adult HIV-1 infected patients who did not receive any antiretroviral treatment prior to the start of the induction phase, with a viral load of ▪ ≥ 1000 copies/mL at the start of the induction phase and ▪ < 50 copies/mL 4 weeks before the start of the randomized treatment	Cabotegravir + rilpivirine Q1M (N = 283) Continuation of the previous ART (N = 283): ▪ ABC/DTG/3TC (N = 269) ▪ FTC/TDF/DTG (N = 9) ▪ FTC/TAF/DTG (N = 3) ▪ 3TC/TDF/DTG (N = 2)	Screening: up to 35 days Treatment: ▪ Induction phase: 20 weeks ▪ Randomized treatment: 100 weeks Follow-up observation: 52 weeks[c]	108 centres in: Canada, France, Germany, Italy, Japan, Netherlands, Russia, South Africa, Spain, United Kingdom, United States 10/2016–ongoing Analysis for 48-week cut-off: 08/2018 Analysis for 96-week cut-off: 09/2019	Primary: percentage of patients with viral load ≥ 50 copies/mL at Week 48 Secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise only relevant available outcomes from the information provided in Module 4 A of the company's dossier.
b. Patients who received no prior ART or cabotegravir + rilpivirine.
c. Follow-up observation of all patients who received at least 1 dose of long-acting cabotegravir + rilpivirine and discontinued treatment early and switched to HAART for at least 52 weeks. Patients treated with cabotegravir + rilpivirine who had a viral load (HIV-RNA) < 50 copies/mL at the time point of 4 weeks before the end of the treatment phase were eligible for continuing their treatment in an optional extension phase until local drug approval and drug availability or for as long as they benefited from it. Patients in the comparator arm of the ATLAS and FLAIR studies who had a viral load < 50 copies/mL at 4 weeks before the end of the treatment phase were eligible for switching to cabotegravir + rilpivirine in the extension phase.

3TC: lamivudine; ABC: abacavir; AE: adverse event; ART: antiretroviral therapy; DTG: dolutegravir; FTC: emtricitabine; HAART: highly active antiretroviral therapy; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; n: relevant subpopulation; N: number of randomized patients; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; Q1M: monthly; Q2M: every 2 months; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil

Table 7: Characteristics of the interventions – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART (multipage table)

Study	Intervention / comparator therapy	Common comparator
Cabotegravir + rilpivirine Q2M vs. cabotegravir + rilpivirine Q1M		
ATLAS-2M	Oral lead-in phase (4 weeks): cabotegravir 30 mg, once daily, orally + rilpivirine 25 mg, once daily, orally Maintenance phase[a]: cabotegravir 600 mg long acting at Months 2 and 3, then Q2M, i. m. + rilpivirine 900 mg long acting at Months 2 and 3, then Q2M, i.m.	Oral lead-in phase (4 weeks): cabotegravir 30 mg, once daily, orally + rilpivirine 25 mg, once daily, orally Maintenance phase[a]: cabotegravir 600 mg long acting at Month 2, then 400 mg Q1M, i. m. + rilpivirine 900 mg long acting at Month 2, then 600 mg Q1M, i.m.
	Required prior treatment ▪ ART uninterrupted for at least the past 6 months[b] (either initial or 2nd ART), consisting of 2 NRTI plus ▫ INI ▫ NNRTI or ▫ PI boosted or atazanavir nonboosted (one switch within this class due to safety concerns was allowed) ▪ Patients from the ATLAS study: individualized ART for 52 weeks until the day of randomization in ATLAS-2M **Nonpermitted prior treatment** ▪ Antiretroviral monotherapy or dual therapy ▪ Radiotherapy or chemotherapy, immunomodulators ≤ 28 days before study start ▪ HIV vaccine ≤ 90 days before study start and during the study ▪ ART for HIV other than the necessary ≤ 28 days before randomization and during the study (aciclovir/valaciclovir was permitted) ▪ Medications associated with Torsade de Pointes ▪ Etravirine ▪ Tipranavir/ritonavir or fosamprenavir/ritonavir **Permitted concomitant treatment** ▪ Chemoprophylaxis for HIV-associated diseases **Nonpermitted concomitant treatment** ▪ Treatment of HCV infection up to Week 48 (interferon-based HCV therapy disallowed throughout the study) ▪ Drugs affecting the cabotegravir and/or rilpivirine concentration	

Table 7: Characteristics of the interventions – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART (multipage table)

Study	Intervention / comparator therapy	Common comparator
Continuation of the previous ART vs. cabotegravir + rilpivirine Q1M		
ATLAS	Continuation of the current ART consisting of 2 NRTI + 1 INI, NNRTI, or PI	Oral lead-in phase (4 weeks): Cabotegravir 30 mg, once daily, orally + Rilpivirine 25 mg, once daily, orally Maintenance phase[a]: Cabotegravir 600 mg long acting at Month 2, then 400 mg Q1M, i.m. + Rilpivirine 900 mg long acting at Month 2, then 600 mg Q1M, i.m.
	Pretreatment and concomitant treatment ▪ ART uninterrupted for at least the past 6 months[b] (either initial or 2nd ART), consisting of 2 NRTI plus ▫ INI ▫ NNRTI or ▫ PI boosted or atazanavir nonboosted (a switch within this class due to safety concerns was allowed) **Nonpermitted prior treatment** ▪ ABC/DTG/3TC at study start ▪ Any NNRTI monotherapy in prior history or exclusive administration of 1 or 2 NRTI before the start of the current ART ▪ Radiotherapy or chemotherapy, immunomodulators ≤ 28 days before study start ▪ HIV vaccine ≤ 90 days before the study start or during the study ▪ ART for HIV other than the necessary ≤ 28 days before randomization and during the study ▪ Medications associated with Torsade de Pointes ▪ Etravirine ▪ Tipranavir/ritonavir or fosamprenavir/ritonavir **Permitted concomitant treatment** ▪ Chemoprophylaxis for HIV-associated diseases **Nonpermitted concomitant treatment** ▪ See data on ATLAS-2M study	

Table 7: Characteristics of the interventions – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART (multipage table)

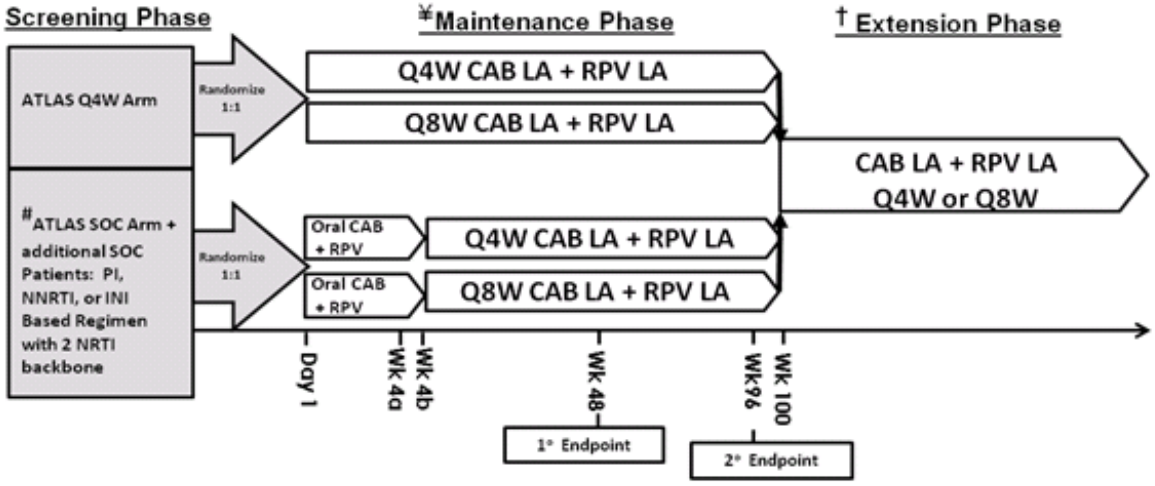
Study	Intervention / comparator therapy	Common comparator
FLAIR	Induction phase (Week –20 until Day 1) ABC/DTG/3TC: 600/50/300 mg once daily, orally Patients with positive HLAB*5701 test: DTG 50 mg once daily, orally + 2 NRTI (upon the investigator's discretion, but excluding ABC)	
	Continuation of therapy given in induction phase	Oral lead-in phase (4 weeks): Cabotegravir 30 mg, once daily, orally + Rilpivirine 25 mg, once daily, orally Maintenance phase[a]: Cabotegravir 600 mg long acting at Month 2, then 400 mg Q1M, i.m. + Rilpivirine 900 mg long acting at Month 2, then 600 mg Q1M, i.m.
	Nonpermitted prior treatment ▪ INI and NNRTI ▪ Further ART for a duration of ≥ 10 days and ≤ 28 days before study start ▪ Radiotherapy or chemotherapy, immunomodulators ≤ 28 days before study start ▪ HIV vaccine ≤ 90 days before study start and during the study ▪ Medications associated with Torsade de Pointes **Nonpermitted concomitant treatment** ▪ Treatment for HCV infection up to Week 48 (interferon-based HCV therapy disallowed throughout the study) ▪ Drugs influencing the concentration of cabotegravir and/or rilpivirine or ART	

a. In patients who will miss planned injections, oral bridging with cabotegravir + rilpivirine (identical to the lead-in phase) is available until the next possible injections.
b. In case of intolerance, pausing individual drugs for < 1 month was allowed. Treatment switch (of 1 or more drugs) due to virological failure was disallowed.

3TC: lamivudine; ABC: abacavir; ART: antiretroviral therapy; DTG: dolutegravir; HCV: hepatitis C virus; HIV: human immunodeficiency virus; i.m.: intramuscular; INI: integrase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; Q1M: monthly; Q2M: every 2 months; RCT: randomized controlled trial

ATLAS-2M study

The ATLAS-2M study is an open-label, randomized parallel-group study investigating the treatment concept of cabotegravir + rilpivirine Q2M versus Q1M. Figure 2 below shows the design of the ATLAS-2M study:



CAB: cabotegravir; INI: integrase inhibitor; LA: long acting; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; Q4W: every 4 weeks (monthly); Q8W: every 8 weeks (every 2 months); RPV: rilpivirine; SOC: standard of care

Figure 2: Design of the ATLAS-2M study

The study included treatment-experienced adult patients with HIV-1 infection who had been on an uninterrupted regimen of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a 3rd drug from the NNRTI drug class, protease inhibitors (PIs), or INI for at least 6 months and were on stable virological suppression (HIV-1 RNA < 50 copies/mL). Further, patients were allowed to switch from the ATLAS study (see below) to the ATLAS-2M study. Two groups were distinguished: Patients who had already been on cabotegravir + rilpivirine Q1M treatment before study start in the context of the ATLAS study versus patients who were on ART consisting of 2 NRTIs in combination with an NNRTI, PI, or INI. A total of 1049 patients were included and randomized at a 1:1 ratio to 1 of 2 treatment arms (Q2M or Q1M), stratified by the duration of prior cabotegravir + rilpivirine exposure (0, 1–24, or > 24 weeks).

The company presented the results of a subpopulation of patients who had prior ART consisting of 2 NRTI in combination with a 3rd drug from the NNRTI, PI, or INI drug class and completed, in the intervention arm, the entire therapy concept of cabotegravir + rilpivirine, including the oral lead-in phase in the intervention arm. The ATLAS-2M subpopulation comprises 327 patients in the intervention arm and 327 in the comparator arm. This subpopulation presented by the company is relevant for the present research question and is used for the benefit assessment.

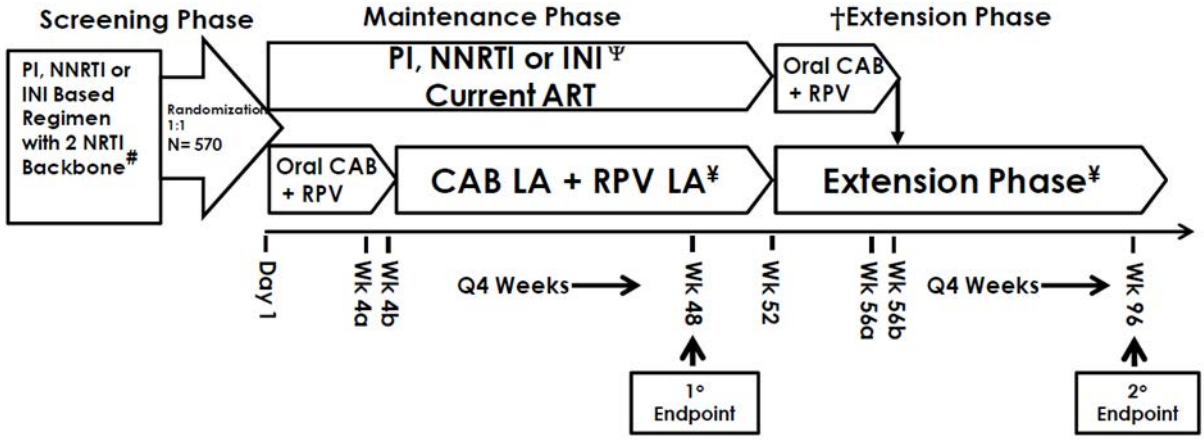
The dosage and administration of cabotegravir + rilpivirine Q2M and Q1M are in accordance with approval [3,4,17,18].

The primary outcome of the study is virological response (HIV RNA < 50 copies/mL) at Week 48. Other patient-relevant outcomes are mortality, morbidity, health-related quality of

life, and AEs. The study started in 2017 and is still ongoing. The 1st data cut-off was after 24 weeks on 20 December 2018, the 2nd data cut-off was after 48 weeks on 6 June 2019, and the 3rd data cut-off was after 96 weeks on 5 June 2020.

ATLAS study

The ATLAS study is an open-label, randomized parallel-group study investigating the treatment concept of cabotegravir + rilpivirine Q1M versus individualized ART. The study included treatment-experienced adult patients with HIV-1 infection who had received an uninterrupted therapy consisting of 2 NRTIs in combination with a 3rd drug from the NNRTI, PI, or INI drug class for at least 6 months and were on stable virological suppression (HIV-1 RNA < 50 copies/mL). Figure 3 below shows the design of the ATLAS study:



ART: antiretroviral therapy; CAB: cabotegravir; LA: long acting; INI: integrase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; Q4W: every 4 weeks (monthly); RPV: rilpivirine

Figure 3: Design of the ATLAS study

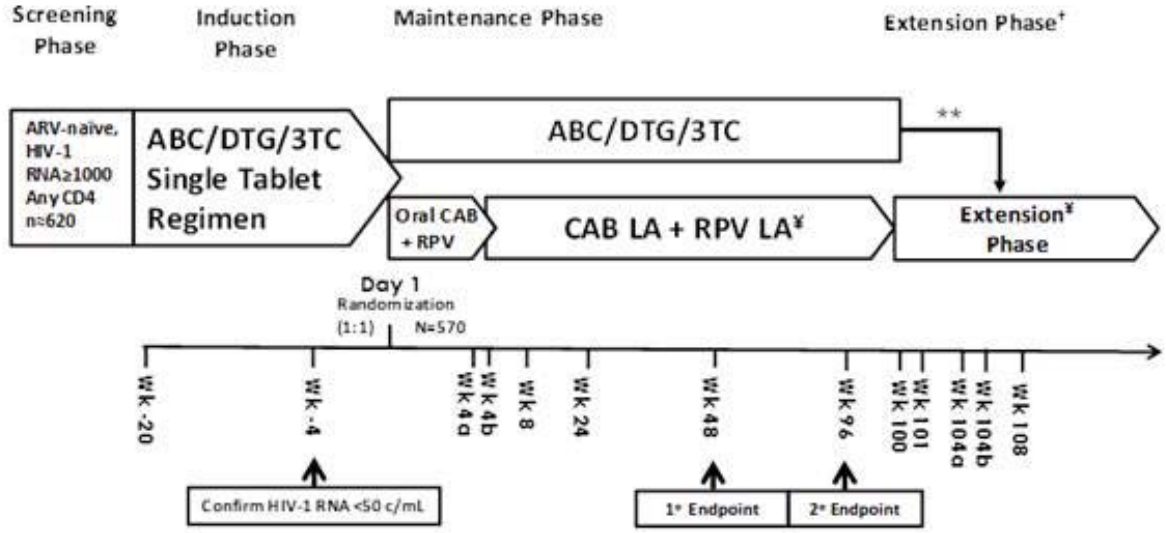
A total of 618 patients were included in the study and randomized at a 1:1 ratio to 1 of the 2 treatment arms (cabotegravir + rilpivirine Q1M or individualized ART), stratified by sex and 3rd combination partner (NNRTI, PI, INI) of the existing ART. In the ATLAS study, 310 patients were allocated to the intervention arm and 308 to the comparator arm.

The treatment with cabotegravir + rilpivirine Q1M is in accordance with approval [3,4,17,18].

The primary outcome of the study is virological response (HIV RNA <50 copies/mL) at Week 48. Other patient-relevant outcomes are mortality, morbidity, health-related quality of life, and AEs. The study started in 2016 and is still ongoing. The 48-week data cut-off was on 29 May 2018. After the 52-week randomized treatment duration, patients were eligible for continuing the treatment in an optional extension phase and/or switch to the ATLAS-2M study.

FLAIR study

The FLAIR study is an open-label, randomized parallel-group study investigating cabotegravir + rilpivirine Q1M in comparison with ABC/DTG/3TC. Figure 4 below shows the design of the FLAIR study:



3TC: lamivudine; ABC: abacavir; CAB: cabotegravir; CD4: cluster of differentiation 4; DTG: dolutegravir; HIV-1: human immunodeficiency virus type 1; LA: long acting; RNA: ribonucleic acid; RPV: rilpivirine

Figure 4: Design of the FLAIR study

The study included treatment-naive patients with HIV-1 infection (HIV-1 RNA ≥ 1000 copies/mL) who received ABC/DTG/3TC therapy for 20 weeks before randomization. Patients who tested positive for the HLA-B*5701 allele were allowed to switch to DTG + 2 NRTI upon the investigator's discretion, excluding ABC, in accordance with the respective SPC. This applied to a total of 28 patients (5%), of which 14 were randomized to the comparator arm. Following 16 weeks of ABC/DTG/3TC treatment, patients had to be virologically suppressed (HIV-1 RNA < 50 copies/mL) to be randomized, after a further 4 weeks, to 1 of the 2 treatment arms (cabotegravir + rilpivirine Q1M or ABC/DTG/3TC). In total, 566 patients were randomized to the intervention arm (N = 283) or the comparator arm (N = 283), stratified by sex and baseline viral load (< 100 000 copies/mL and ≥ 100 000 copies/mL).

The treatment with cabotegravir + rilpivirine Q1M and ABC/DTG/3TC is in accordance with the SPC specifications [3,4,17-19].

The primary outcome of the study is virological response (HIV RNA <50 copies/mL) at Week 48. Other patient-relevant outcomes are mortality, morbidity, health-related quality of life, and AEs. The study started in 2016 and is still ongoing. The 1st data cut-off was after 48 weeks on 30 August 2018, and the 2nd data cut-off was after 96 weeks on 12 September 2019.

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

Table 8: Characterization of the study populations – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART (multipage table)

Study	ATLAS-2M		ATLAS		FLAIR	
Characteristic Category	Cabotegravir + rilpivirine Q2M	Cabotegravir + rilpivirine Q1M	Cabotegravir + rilpivirine Q1M	Continuation of the previous therapy[a]	Cabotegravir + rilpivirine Q1M	Continuation of the previous therapy[b]
	N[c] = 327	N[c] = 327	N[c] = 310	N[c] = 308	N[c] = 283	N[c] = 283
Age [years], mean (SD)	ND	ND	42 (10)	43 (11)	36 (10)	36 (10)
< 35 years, n (%)	84 (26)	98 (30)	80 (26)	80 (26)	143 (51)	145 (51)
35 to < 50 years, n (%)	154 (47)	143 (44)	162 (53)	132 (43)	107 (38)	109 (39)
≥ 50 years, n (%)	89 (27)	86 (26)	66 (21)	96 (31)	33 (12)	29 (10)
Sex [f/m], %	22/78	23/77	32/68	34/66	22/78	23/77
Family origin, n (%)						
White	238 (73)	256 (78)	214 (69)	207 (67)	216 (76)	201 (71)
Non-white	89 (27)	71 (22)	94 (31)	101 (33)	67 (24)	80 (28)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)
Region, n (%)						
North America	118 (36)	135 (41)	93 (30)	107 (35)	47 (17)	62 (22)
Europe	165 (50)	155 (47)	145 (47)	146 (47)	213 (75)	192 (68)
Other	44 (13)	37 (11)	70 (23)	55 (18)	23 (8)	29 (10)
Baseline $CD4^+$ cell count [per mm^3], mean (SD)	689 (266)	741 (289)	679 (257)	693 (289)	666 (272)	646 (253)
Baseline $CD4^+$ cell count [per mm^3], n (%)						
< 350	ND	ND	23 (7)	27 (9)	19 (7)	27 (10)
350 to < 500	ND	ND	56 (18)	57 (19)	64 (23)	60 (21)
≥ 500	ND	ND	229 (74)	224 (73)	200 (71)	196 (69)
CDC category at baseline, n (%)						
Class 1	ND	ND	229 (74)	224 (73)	200 (71)	196 (69)
Class 2	ND	ND	78 (25)	83 (27)	78 (28)	82 (29)

Table 8: Characterization of the study populations – RCT, indirect comparison: cabotegravir + rilpivirine Q2M vs. continuation of the previous ART (multipage table)

Study	ATLAS-2M		ATLAS		FLAIR	
Characteristic Category	Cabotegravir + rilpivirine Q2M	Cabotegravir + rilpivirine Q1M	Cabotegravir + rilpivirine Q1M	Continuation of the previous therapy[a]	Cabotegravir + rilpivirine Q1M	Continuation of the previous therapy[b]
	N[c] = 327	N[c] = 327	N[c] = 310	N[c] = 308	N[c] = 283	N[c] = 283
Class 3	ND	ND	1 (< 1)	1 (< 1)	5 (2)	5 (2)
Prior ART, n (%)						
PI + NRTI	ND	ND	51 (17)	54 (18)	0 (0)	0 (0)
NNRTI + NRTI	ND	ND	155 (50)	155 (50)	0 (0)	0 (0)
INI + NRTI	ND	ND	102 (33)	99 (32)	283 (100)	283 (100)
Duration of prior ART [months], median [min; max]	ND	ND	52 [7; 222]	52 [7; 257]	–[d]	–[d]
Treatment discontinuation[e], n (%)	ND[f]	ND[f]	26 (8[g])	18 (6[g])	25 (9[g])	22 (8[g])
Study discontinuation, n (%)	ND	ND	ND	ND	ND	ND

a. Individualized ART
b. Previous therapy: ABC/DTG/3TC or DTG + 2 NRTI
c. Number of randomized patients. For the ATLAS-2M study, exclusively patients who received prior ART, but not yet cabotegravir + rilpivirine. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
d. Treatment-naive patients who were treated with an initial ART regimen during a 20-week induction phase were included.
e. By Week 48; unclear whether this represents study or treatment discontinuation.
f. Number of treatment discontinuations for the total population 36 (7) vs. 42 (8); no data on the relevant subpopulation.
g. IQWiG calculations.

3TC: lamivudine; ABC: abacavir; ART: antiretroviral therapy; $CD4^+$: cluster of differentiation 4-positive; CDC: Center for Disease Control and Prevention; DTG: dolutegravir; f: female; INI: integrase inhibitor; m: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; Q1M: monthly; Q2M: every 2 months; RCT: randomized controlled trial; SD: standard deviation; SOC: standard of care

In Module 4 A of the dossier, the company submitted incomplete data on the patient characteristics of the ATLAS-2M study. The data are limited to demographic characteristics such as sex, age, family origin, and region. Information on the severity and duration of disease or on the type and duration of prior therapies is largely lacking.

Patients' demographic characteristics are sufficiently balanced in the individual arms of each of the studies. The patients in the 3 studies were predominantly male (about 75%) and white (about 70%). Patient age differs slightly between the studies. Nearly half of patients in the ATLAS-2M and ATLAS study populations are between 35 and < 50 years old. In the FLAIR study, in contrast, half of the study population is under 35 years of age.

FLAIR and ATLAS exhibit marked differences in the duration of prior therapy. The median treatment duration was 52 months in the ATLAS study. The FLAIR study, in contrast, included treatment-naive patients who were treated with an ART in a 20-week induction phase. The studies also differ in the type of prior treatment. Half of the ATLAS study population received prior ART based on NNRTI + 2 NRTI. In the FLAIR study, all patients received prior treatment with an INI + 2 NRTI (predominantly ABC/DTG/3TC) before randomization.

No relevant differences between the FLAIR and ATLAS studies were found regarding severity of disease. Most patients were categorized as Centers for Disease Control and Prevention (CDC) class 1 and exhibited a cluster of differentiation 4-positive ($CD4^+$) cell count of ≥ 500 cells/mm^3.

Lack of similarity check for included studies

A central prerequisite for the inclusion of studies in an adjusted indirect comparison is a similarity check [1,20,21]. The similarity assumption states that all investigated studies are comparable in terms of potential effect modifiers across all interventions. In addition to potential effect modifiers (e.g. patient characteristics, study characteristics, intervention characteristics), methodological factors (e.g. outcome characteristics) must be taken into account [22].

The company failed to examine the similarity of the studies it included in Module 4 A. Module 4 A Section 4.3.2.1, "Indirect comparisons on the basis of RCTs", presents only the FLAIR study, and Appendix 4-I presents the FLAIR and ATLAS studies. Similarity was not checked in any way for the ATLAS-2M study versus the FLAIR and ATLAS studies. The company merely commented that 3 RCTs were conducted by the company itself and that the planning was homogeneous in terms of design and study population, thus deeming the prerequisites for applying the Bucher method to have been readily satisifed.

The company's approach is not appropriate. For the ATLAS-2M study, Module 4 A provides very little information on disease-specific patient characteristics (see Table 8). This means that not even the prerequisite for a sufficient check of similarity of the studies is met. In addition, even the ATLAS and FLAIR studies on the ART side of the indirect comparison differ

markedly in duration and type of prior treatment received by patients. The company mentioned that it conducted all 3 RCTs. Consequently, it is safe to assume that the company has access to the disease-specific patient characteristics missing from Module 4 A and that a comprehensive check of similarity would have been possible. It therefore remains unclear why they were not presented in Module 4 A.

Overall, the adjusted indirect comparison of cabotegravir + rilpivirine Q2M versus the ACT, as submitted by the company, is rendered unusable by both the missing data on disease-specific patient characteristics in the ATLAS-2M study and the missing similarity check.

In addition to the described shortcomings regarding the similarity check, the presentation of results of the indirect comparison fails to meet the requirements of the dossier templates. In Module 4 A Section 4.3.2.1, "Indirect comparisons on the basis of RCTs", the company presented only the FLAIR study, and in Appendix 4-I, only the ATLAS and FLAIR studies. No comparative presentation of the outcome operationalizations and results of the ATLAS-2M study versus the FLAIR study or the ATLAS and FLAIR studies is provided at all. For each of the outcomes it used, the company presented only effect estimators, the 95% confidence interval (CI), and the p-value of the indirect comparison.

Hence, no suitable data which would allow deriving an added benefit of cabotegravir + rilpivirine Q2M in comparison with the ACT are available for the benefit assessment. Neither the 48-week analyses of ATLAS-2M, FLAIR, and ATLAS nor the 96-week analyses of ATLAS-2M and FLAIR showed any favourable effects of cabotegravir + rilpivirine Q2M in comparison with the ACT.

2.4 Results on added benefit

In its dossier, the company only partially covered the therapeutic indication of cabotegravir + rilpivirine for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to, and no prior virological failure with agents of the NNRTI and INI class and who have no indication for a treatment switch. The company did not cover the Q1M treatment regimen despite the availability of 2 RCTs comparing with the ACT. For the Q2M treatment regimen, the company presented an indirect comparison which is unsuitable for the benefit assessment due to methodological deficiencies. The company did not present any data for patients with indication for a treatment switch. Overall, there is therefore no hint of added benefit of cabotegravir + rilpivirine in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 9 presents a summary of the results of the benefit assessment of cabotegravir + rilpivirine in comparison with the ACT.

Table 9: Cabotegravir + rilpivirine – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with HIV-1 infection who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of resistance to, and no prior virological failure with agents of the NNRTI or INI class	Individualized antiretroviral therapy, selecting from approved drugs and taking into account any prior therapies and any side effects[b]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. For patients without indication for a treatment switch, continuation of the previous therapy represents the appropriate implementation of the ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid		

The assessment described above deviates from that by the company, which derived a hint of non-quantifiable added benefit.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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