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# Dolutegravir/lamivudine (HIV infection 1) –

## 2nd addendum to Commission A19-55[1]

## Addendum

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| 3TC | lamivudine |
| ACT | appropriate comparator therapy |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ART | antiretroviral therapy |
| $CD4^+$ | Cluster of differentiation 4-positive |
| CDC | Centers for Disease Control and Prevention |
| DAIDS | Division of AIDS |
| DTG | dolutegravir |
| EQ-5D | European Quality of Life-5 Dimensions |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| 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) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside/nucleotide reverse transcriptase inhibitors |
| PI | protease inhibitor |
| PT | preferred term |
| RCT | randomized controlled trial |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | Statistical analysis plan |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| TAF | Tenofovir alafenamide |
| TDF | tenofovir disoproxil |
| VAS | visual analogue scale |

## 1 Background

On 9 December 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-55 (dolutegravir/lamivudine) – Benefit assessment according to §35a Social Code Book V) [1].

In module 4 A [2] of its dossier on dolutegravir/lamivudine, the pharmaceutical company (hereinafter referred to as "the company") presented the randomized controlled trial (RCT) ASPIRE [3-6] for adults infected[2] with human immunodeficiency virus type 1 (HIV-1) (research question 2 of the dossier assessment on Commission A19-55) who had received antiretroviral pretreatment. The patient population of this study consisted of patients without indication for treatment switch, as there were obviously no indications for a treatment switch, e.g., due to side effects. The study ASPIRE was used for the benefit assessment on dolutegravir/lamivudine (DTG/3TC) (see Commission A19-55). With its written comments [7], the company for the first time presented results of the RCT TANGO [8-11] for pretreated adults.

The G-BA commissioned IQWiG with the assessment of the TANGO study. Moreover, the G-BA's commission included the instruction to check whether a meta-analysis of the studies ASPIRE and TANGO was appropriate.

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

[2] The HIV virus must not show any known or suspected resistance to the class of INIs or 3TC.

# 2 Assessment of the subsequently submitted data (research question 2: pretreated adults)

The present addendum assesses the data at week 48 subsequently submitted by the company with its written comments on the TANGO study on HIV-1 infected adults who had received antiretroviral pretreatment under consideration of the study ASPIRE [1] included in the dossier assessment on Commission A19-55.

## 2.1 Studies included

The studies listed in Table 1 were included in the present assessment.

Table 1: Study pool – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[b] (yes/no) | Third-party study (yes/no) |
| ASPIRE[c] | No | No | Yes |
| 204862 (TANGO[d]) | Yes | Yes | No |

a. Continuation of ongoing treatment.
b. Study sponsored by the company.
c. For information on this study see dossier assessment on Commission A19-55.
d. In the following tables, the study is referred to with this abbreviated designation.
3TC: lamivudine; DTG: dolutegravir; RCT: randomized controlled trial; vs.: versus

In principle, both studies are relevant for the research question of pre-treated HIV-1-infected adults. For the reason given in Section 2.2.3, the TANGO study is used to derive the added benefit of DTG/3TC in comparison with the G-BA's ACT.

The detailed presentation and assessment of the ASPIRE study can be found in the dossier assessment on Commission A19-55.

### Study characteristics

Table 2 and Table 3 describe the TANGO study for the benefit assessment.

Table 2: Characteristics of the study included – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[b] |
|---|---|---|---|---|---|---|
| TANGO | RCT, open label, parallel | HIV-1 infected adults (≥ 18 years) with an HIV-1 RNA viral load of < 50 copies/mL before[d] and at screening who had received antiretroviral pretreatment[c] | DTG/3TC (N = 371[e])<br>Continuation of ongoing treatment: TAF-based ART[f] (N = 372) | Screening: up to 28 days<br>Treatment: 148 weeks[g]<br>Observation period: 4 weeks | 134 centres in: Australia, Belgium, Canada, France, Germany, Japan, Netherlands, Spain, United Kingdom, USA<br>01/2018–ongoing<br>Data cut-off at week 48: 19 June 2019 | Primary: virologic failure at week 48<br>Secondary: mortality, morbidity, AEs |

a. Continuation of ongoing treatment.
b. Primary outcomes include data without consideration of their relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c. ≥ 6 months before screening continuously pretreated with a TAF-based ART or pretreated with a TAF-based ART over ≥ 3 months before screening only after a switch from TDF to TAF (for tolerability/safety reasons, due to access to drugs, simplification of treatment, not because of suspected or actual treatment failure).
d. Recorded on at least 2 time points during the 12 months before screening: one within the 6 to 12-month period before screening, the other within the last 6 months prior to screening.
e. 2 patients discontinued the study after randomization on day 1 and received no medication. The data in the following tables refer to all patients who received at least 1 study medication (N = 369).
f. In Japan, only patients who had received treatment with DTG + FTC/TAF before screening were included in the study. From Japan, 5 patients were randomly assigned to the DTG/3TC arm and 6 patients to the comparator arm.
g. Subsequently, patients of the intervention arm and patients of the comparator arm can continue treatment with or switch to treatment with DTG/3TC until week 200 if the HIV-1 RNA viral load is < 50 copies/mL.

3TC: lamivudine; AE: adverse event; ART: antiretroviral therapy; DTG: dolutegravir; FTC: emtricitabine; HIV-1: human immunodeficiency virus type 1; N: number of randomized (included) patients; RCT: randomized controlled trial; RNA: ribonucleic acid; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

Table 3: Characteristics of the intervention – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study | Intervention | Comparison |
|---|---|---|
| TANGO | DTG 50 mg/3TC 300 mg (fixed combination), once daily, orally | Continuation of ongoing TAF-based ART |
| | **Pretreatment**<br>▪ According to inclusion criteria at screening: treatment with the following ART-regimen:<br>▫ TAF-based ART for the last ≥ 6 months or<br>▫ when changing from TDF to TAF[b]: TAF-based ART for ≥ the last 3 months; switch from a protease inhibitor (PI) boosted with ritonavir to the same PI boosted with cobicistat and vice versa is allowed<br>**Concomitant treatment**<br>Chemoprophylaxis for HIV-associated diseases at the investigator's discretion<br>**Prohibited prior/concomitant treatment**<br>▪ HIV vaccines ≤ 90 days before screening and during the study<br>▪ Systemic immunomodulators/immunosuppressants, radiotherapy, cytotoxic chemotherapy ≤ 28 days before screening and during the study<br>▪ Other ART regimens (including monotherapy or dual combination)<br>▪ During the study: hepatitis C treatment based on interferon or other substances with an adverse potential of interaction with the study medication<br>▪ Paracetamol in patients with acute viral hepatitis during the study<br>▪ For patients in the intervention arm:<br>▫ Carbamazepine, oxcarbamazepine, phenobarbital, phenytoin, rifampicin, rifapentine, St. John's Wort<br>▫ < 2 before or < 6 hours after administration of the study medication: antacids or laxatives containing polyvalent cations<br>▪ For treatment with DTG: dofetilide, pilsicainide | |

a. Continuation of ongoing treatment.
b. Change from TDF to TAF not due to an expected or existing therapy failure, but solely for reasons of tolerability/safety, access to drugs or to simplify therapy.
3TC: lamivudine; ART: antiretroviral therapy; DTG: dolutegravir; HIV: human immunodeficiency virus; PI: protease inhibitor; RCT: randomized controlled trial; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil; vs.: versus

The TANGO study is an ongoing, open-label, randomized parallel group study on antiretrovirally pretreated and virologically suppressed HIV-1 infected adults. The HIV-1 ribonucleic acid (RNA) viral load of the patients had to be < 50 copies/mL on at least 2 time points within the previous 12 months before screening and at screening.

According to the company, screening for resistances of the HI virus is based on the recommendations of the International Antiviral Society-USA Panel [12]. According to this, patients showing signs of resistances listed there at or prior to the time of screening were excluded from the study. The TANGO study compared the fixed combination of DTC/3TC with a continuation of the previous tenofovir alafenamide (TAF)-based antiretroviral therapy (ART). Patients in the intervention arm received treatment with DTC/3TC in accordance with the Summary of Product Characteristics (SPC) [13]. According to the information provided by

the company, the study medication for the continuation of the ongoing treatment in the comparator arm was administered in accordance with the respective approvals.

In the study, a total of 743 patients were randomly assigned to treatment with DTG/3TC (N = 371) or continuation of their ongoing ART (N = 372) in a 1:1 ratio. Stratification was performed after the 3rd treatment component at the start of the study (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]). For patients in the comparator arm, ART consisted in a continuation of a TAF-based treatment that had been ongoing for at least 6 months. However, the study could also include patients who had switched from TDF-based treatment to TAF-based treatment and had received this therapy for at least 3 months prior to screening. When switching from TDF to TAF, this switch was not allowed to be due to suspected or confirmed treatment failure, but solely for tolerability/safety reasons, access to drugs or to simplify treatment. Further components of the ART included drugs of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), NNRTIS, PIs or INIs.

Primary outcome of the study was the virologic failure (HIV-1 RNA viral load ≥ 50 copies/mL) at week 48. Patient-relevant outcomes are mortality, morbidity and adverse events (AEs). Treatment duration was 148 weeks in both study arms. Subsequently, patients of the intervention arm and patients of the comparator arm could continue treatment with or switch to treatment with DTG/3TC until week 200 if the HIV-1 RNA viral load was < 50 copies/mL at this time point.

It can be inferred from the available study documents that the majority of the patient population consisted of patients without indication for a treatment switch. For the majority of the patient population, there are obviously no indications for a treatment switch, for instance, due to side effects. At the start of the study, only 2 patients in the DTG/3TC arm and 5 patients in the comparator arm (a total of < 1%) stated that they did not tolerate the current treatment regimen and have thus possibly had an indication for a treatment switch. In these patients, continuation of the ongoing treatment would thus not have made sense and would therefore not have corresponded to the ACT.

Table 4 shows the patient characteristics of the TANGO study included.

Table 4:Characteristics of the study population – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| **Study**<br>**Characteristics**<br>**Category** | **DTG/3TC** | **Comparator therapy[a]** |
|---|---|---|
| **TANGO** | N[b] = 369 | N[b] = 372 |
| Age [years], mean (SD) | 41 (11) | 41 (12) |
| Sex [F/M], % | 7/93 | 9/91 |
| Family origin, n (%) | | |
| White | 296 (80) | 289 (78) |
| Black/African American | 51 (14) | 58 (16) |
| Asian | 13 (4) | 13 (3) |
| Other | 9 (2) | 12 (3) |
| HIV-1 RNA viral load at baseline, n (%) | | |
| < 50 copies/mL | 362 (98) | 363 (98) |
| ≥ 50 copies/mL | 7 (2) | 9 (2) |
| $CD4^+$ cell count/$mm^3$ at baseline, n (%) | | |
| < 350 | 35 (9[c]) | 30 (8[c]) |
| ≥ 350 | 334 (91) | 342 (92) |
| $CD4^+$ cell count/$mm^3$ at baseline, median [min; max] | 682.0 [133; 1904] | 720.0 [119; 1810] |
| HIV disease state (CDC stage[d]) at baseline, n (%) | | |
| 1 | 255 (69) | 259 (70) |
| 2 | 94 (25) | 94 (25) |
| 3 (AIDS) | 20 (5) | 19 (5) |
| Components of the prior ART therapy, n (%) | | |
| INI | 289 (78) | 296 (80) |
| NRTI | 369 (100) | 372 (100) |
| NNRTI | 51 (14) | 48 (13) |
| PI | 29 (8) | 28 (8) |
| Treatment duration with the current ART before the start of the study [months], median [min; max] | 17.7 [3.6; 73.7] | 18.2 [3.9; 71.2] |
| Treatment discontinuation, n (%) | 27 (7)[e] | 29 (8)[e] |
| Study discontinuation, n (%) | 27 (7)[e] | 29 (8)[e] |

a. Continuation of ongoing treatment.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation.
d. CDC classification for HIV-1 infection (2014) [14].
e. It is unclear whether treatment or study were discontinued.

3TC: lamivudine; AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CDC: Centers of Disease Control and Prevention; $CD4^+$: Cluster of differentiation 4-positive; DTG: dolutegravir; F: female; HIV: human immunodeficiency virus; INI: integrase inhibitor; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; PI: protease inhibitor; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; vs.: versus

The demographic and clinical characteristics are essentially balanced. The mean age of the parents was 41 years, most of them were male (approx. 92%) and white (approx. 79%). 5% of the patients had acquired immunodeficiency syndrome (AIDS). A total of 2% of the patients included in the study had an HIV-1 RNA viral load of ≥ 50 copies/mL at baseline, which deviated from the criteria for study inclusion. Until week 48, less than 8% of the patients in the TANGO study had discontinued treatment with the study medication.

**Risk of bias across outcomes (study level)**

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

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

a. Continuation of ongoing treatment.
3TC: lamivudine; DTG: dolutegravir; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was assessed to be low. Limitations resulting from the open-label study design are described in Section 2.2.2 with the outcome-specific risk of bias.

## 2.2 Results on added benefit

### 2.2.1 Outcomes included

The following patient-relevant outcomes should be considered in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - AIDS-defining events (Centers of Disease Control and Prevention [CDC] stage 3)
  - Presented as supplementary information: virologic response, virologic failure and number of Cluster of differentiation 4-positive ($CD4^+$) cells as surrogate outcomes for the patient-relevant outcome “AIDS-defining illnesses”/”death”
  - Health status measured with the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analog scale (VAS)
- Health-related quality of life

- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Division of AIDS [DAIDS] grade 3–4)
  - Discontinuation due to AEs
  - Gastrointestinal disorders (System Organ Class [SOC])
  - Skin and subcutaneous tissue disorders (SOC)
  - Nervous system disorders (SOC)
  - Psychiatric disorders (SOC)
  - if applicable, further specific AEs

Table 6 shows for which outcomes data were available in the included TANGO study.

Table 6: Matrix of the outcomes – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study | Outcomes | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **All-cause mortality** | **AIDS-defining events (CDC stage 3)** | **Virologic response[b]** | **Virologic failure[b]** | **CD4⁺ cell count[b]** | **Health status (EQ-5D VAS)** | **Health-related quality of life** | **SAEs** | **Discontinuation due to AEs** | **Severe AEs (DAIDS grade 3–4)** | **Specific AEs[c]** |
| TANGO | Yes | Yes | Yes | Yes | Yes | Yes | No[d] | Yes | Yes | Yes | Yes |

a. Continuation of ongoing treatment.
b. Virologic response, virologic failure and CD4⁺ cell count are presented as supplementary surrogate outcomes for the combined outcome „AIDS-defining events/death“.
c. The following events (MedDRA coding) are considered: gastrointestinal disorders (SOC), skin and subcutaneous tissue disorders (SOC), nervous system disorders (SOC), psychiatric disorders (SOC), fatigue (PT, AE), seasonal allergy (PT, AE)
d. Outcome not recorded.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CD4⁺: cluster of differentiation 4-positive; DAIDS: Division of AIDS; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

### 2.2.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes of the TANGO study.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study | Outcomes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study level | All-cause mortality | AIDS-defining events (CDC stage 3) | Virologic response[b] | Virologic failure[b] | $CD4^+$ cell count[b] | Health status (EQ-5D VAS) | Health-related quality of life | SAEs | Discontinuation due to AEs | Severe AEs (DAIDS grade 3–4) | Specific AEs[c] |
| TANGO | L | L | L | L | L | L | H[d] | –[e] | L | H[d] | L | H[d] |

a. Continuation of ongoing treatment.
b. Virologic response, virologic failure and $CD4^+$ cell count are presented as supplementary surrogate outcomes for the combined outcome "AIDS-defining events/death".
c. The following events (MedDRA coding) are considered: gastrointestinal disorders (SOC), skin and subcutaneous tissue disorders (SOC), nervous system disorders (SOC), psychiatric disorders (SOC), fatigue (PT, AE), seasonal allergy (PT, AE).
d. Lack of blinding at subjective recording of outcomes.
e. Outcome not recorded.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; $CD4^+$: cluster of differentiation 4-positive; DAIDS: Division of AIDS; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias of the results of the considered outcomes is rated as low except for the outcomes "health status (EQ-5DVAS)", "discontinuation due to AEs" and "specific AEs". The high risk of bias for the results of the outcomes "health status (EQ-5D VAS)", "discontinuation due to AEs" and "specific AEs" result from the lack of blinding at subjective recording of outcomes.

### 2.2.3 Results

A meta-analysis of the two studies ASPIRE and TANGO is basically possible. However, in the present benefit assessment on research question 2 (pretreated adults), the results of the TANGO and ASPIRE studies are not considered jointly, but the results of the TANGO study are used instead. The reason for this is as follows: 90 patients were included in the ASPIRE study, 89 of whom were included in the analyses. This corresponds to approx. 12% of the combined population of the studies TANGO and ASPIRE. If the studies had been considered jointly, the

results would thus have been chiefly determined by the TANGO study due to the significantly larger sample size and the higher precision of the TANGO study.

The company also conducted no joint consideration of the two studies in the documents subsequently submitted with its statement, nor does it carry out a meta-analysis of both studies. It did no justify its approach.

Table 8 and Table 9 summarize the results of the TANGO study on the comparison of DTG/3TC with the continuation of ongoing treatment in pretreated HIV-1 infected adults without indication for a treatment switch. Where necessary, the data provided by the company were supplemented with the Institute's calculations. Tables on common AEs and discontinuations are presented in Appendix A. Appendix A presents no tables for SAEs and severe AEs (DAIDS grade 3–4), because events with a frequency of > 5% did not occur in a study arm.

The results of the outcomes from the ASPIRE study for which (usable) data were available (see dossier assessment on Commission A19-55) do not contradict those of the TANGO study.

Table 8: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study<br>Outcome category<br>Outcome | DTG/3TC<br>N | DTG/3TC<br>Patients with event n (%[b]) | Continuation of ongoing treatment<br>N | Continuation of ongoing treatment<br>Patients with event n (%[b]) | DTG/3TC vs. continuation of ongoing treatment<br>RR [95% CI]; p-value |
|---|---|---|---|---|---|
| **TANGO** | | | | | |
| **Mortality** | | | | | |
| All-cause mortality | 369 | 1 (0.3) | 371 | 0 (0.0) | 3.02 [0.12; 73.80]; 0.499 |
| **Morbidity** | | | | | |
| AIDS-defining events (CDC stage 3) | 369 | 1 (0.3) | 372 | 0 (0.0) | 5.03 [0.24; 104.35]; 0.160[c] |
| Supplementary information: surrogate outcome "virologic response" (HIV-1 RNA < 50 copies/mL)[d] | 369 | 344 (93.0) | 372 | 346 (93.0) | 0.99 [0.95; 1.04]; 0.790 |
| Supplementary information: surrogate outcome "virologic failure" (HIV-1 RNA ≥ 50 copies/mL)[d] | 369 | 1 (0.3) | 372 | 2 (0.5) | 0.51 [0.05; 5.62]; 0.584 |
| **Health-related quality of life** | | | | | |
| Outcome not recorded | | | | | |
| **Side effects** | | | | | |
| AEs (supplementary information) | 369 | 295 (79.9) | 371 | 292 (78.7) | – |
| SAEs | 369 | 20 (5.4) | 371 | 16 (4.3) | 1.26 [0.66; 2.39]; 0.480 |
| Severe AEs (DAIDS grade 3–4) | 369 | 22 (6.0) | 371 | 21 (5.7) | 1.05 [0.59; 1.88]; 0.860 |
| Discontinuation due to AEs | 369 | 13 (3.5) | 371 | 2 (0.5) | 6.54 [1.49; 28.80]; 0.013 |
| gastrointestinal disorders (SOC, AEs) | 369 | 92 (24.9) | 371 | 80 (21.6) | 1.15 [0.89; 1.50]; 0.289 |
| Skin and subcutaneous tissue disorders (SOC, AEs) | 369 | 40 (10.8) | 371 | 41 (11.1) | 0.98 [0.65; 1.48]; 0.936 |
| Nervous system disorders (SOC, AEs) | 369 | 49 (13.3) | 371 | 43 (11.6) | 1.15 [0.78; 1.68]; 0.485 |
| Psychiatric disorders (SOC, AEs) | 369 | 50 (13.6) | 371 | 37 (10.0) | 1.35 [0.90; 2.01]; 0.144 |
| Fatigue (PT, AEs) | 369 | 20 (5.4) | 371 | 3 (0.8) | 6.70 [2.01; 22.36]; < 0.001[c] |
| Seasonal allergy (PT, AEs) | 369 | 12 (3.3) | 371 | 3 (0.8) | 4.02 [1.14; 14.13]; 0.019[c] |

a. Continuation of ongoing treatment.
b. Institute's calculation.
c. Institute's calculation: 95% CI asymptotic; unconditional exact test, (CSZ method according to [15]).
d. Analysis according to FDA snapshot algorithm.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; CI: confidence interval; CSZ: convexity, symmetry, z score; DAIDS: Division of AIDS; DTG: dolutegravir; FDA: Food and Drug Administration; HIV: human immunodeficiency virus; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RNA: ribonucleic acid; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 9: Results (morbidity, continuous) – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study<br>Outcome category<br>Outcome | DTG/3TC | | | Continuation of ongoing treatment | | | DTG/3TC vs. continuation of ongoing treatment |
|---|---|---|---|---|---|---|---|
| | N[b] | Values at baseline mean (SD) | Change at week 48 mean (SE) | N[b] | Values at baseline mean (SD) | Change at week 48 mean (SE) | MD [95% CI]; p-value |
| **TANGO** | | | | | | | |
| **Morbidity** | | | | | | | |
| Health status (EQ-5D VAS)[c] | ND | 87.5 (11.32) | 1.1 (0.52)[d] | ND | 87.5 (12.21) | 1.7 (0.43)[d] | −0.5 [−1.9; 0.8]; 0.414[d] |
| Supplementary information: $CD4^+$ cell count/$mm^3$ | 369 | 702.0 (289.2) | 23.96 (9.09)[e] | 372 | 726.0 (273.5) | 0.27 (9.08)[e] | 23.68 [−1.57; 48.94]; > 0.066[e] |

a. Continuation of ongoing treatment.
b. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
c. Higher values reflect a better health status; a positive group difference corresponds to an advantage of DTG/3TC.
d. MMRM-LOCF analysis of the ITT population.
e. MMRM analysis of the ITT population.

3TC: lamivudine; CD4+: cluster of differentiation 4-positive; CI: confidence interval; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; LOCF: last observation carried forward; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Based on the available data, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

## Mortality

### *All-cause mortality*

There was no statistically significant difference between the treatment groups for the outcome "overall mortality" at week 48.

This resulted in no hint of an added benefit of DTG/3TC versus continuation of ongoing treatment for the outcome “overall mortality”; an added benefit is therefore not proven.

## Morbidity

### *AIDS-defining events (CDC stage 3), supplementary consideration of the surrogate outcomes “virologic response” and “$CD4^+$ cell count”*

A statistically significant difference between the treatment groups is neither shown for the outcome “AIDS-defining events (CDC stage 3)” nor for the outcomes “virologic response” and “$CD4^+$cell count” presented as supplementary information.

This resulted in no hint of an added benefit of DTG/3TC in comparison with continuation of ongoing treatment for the outcome “AIDS-defining events”; an added benefit is therefore not proven.

***Health status (EQ-5D VAS)***

There was no statistically significant difference between the treatment groups for the outcome "health status" (EQ-5D VAS).

For the outcome “health status”, this resulted in no hint of an added benefit of DTG/3TC in comparison with continuation of ongoing treatment; an added benefit is therefore not proven.

**Health-related quality of life**

Health-related quality of life was not investigated in the TANGO study.

This resulted in no hint of an added benefit of DTG/3TC in comparison with continuation of ongoing treatment for the outcome “health-related quality of life”; an added benefit is therefore not proven.

**Side effects**

***SAEs and severe AEs (DAIDS grade 3–4)***

No statistically significant difference between the treatment groups was shown for the outcomes "SAEs” and "severe AEs (DAIDS grade 3–4)".

This resulted in no hint of greater or lesser harm from DTG/3TC in comparison with continuation of ongoing treatment for each of these outcomes; greater or lesser harm is therefore not proven for these outcomes.

***Discontinuation due to AEs***

A statistically significant difference to the disadvantage of DTG/3TC in comparison with continuation of ongoing treatment was shown for the outcome "discontinuation due to AEs".

This resulted in a hint of greater harm from DTG/3TC in comparison with continuation of ongoing treatment for the outcome “discontinuation due to AEs".

***Specific adverse events***

The methods for choosing specific AEs are described in Section 2.8.4.3.2 of dossier assessment A19-55.

*Gastrointestinal disorders, skin and subcutaneous tissue disorders, nervous system disorders and psychiatric disorders*

No statistically significant difference between the treatment groups is shown for each of the outcomes “gastrointestinal disorders”, "skin and subcutaneous tissue disorders”, “nervous system disorders” and “psychiatric disorders”. This resulted in no hint of greater or lesser harm

from DTG/3TC in comparison with continuation of ongoing treatment for each of the mentioned outcomes; greater or lesser harm is therefore not proven.

*Fatigue and seasonal allergy*

A statistically significant difference to the disadvantage of DTG/3TC in comparison with continuation of ongoing treatment was shown for the outcomes "fatigue" and "seasonal allergy". This resulted in a hint of greater harm from DTG/3TC in comparison with continuation of ongoing treatment for the outcomes "fatigue" and "seasonal allergy".

### 2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were basically relevant for the present benefit assessment:

- Sex (female/male)
- Age (< 35 years/35 to < 50 years/≥ 50 years)
- Family origin (white/non-white)
- CD4+ cell count at baseline (< 200/> 200)

The documents submitted subsequently comprised analyses on the mentioned subgroup characteristics. However, since the statistical analysis plan (SAP) for the TANGO study is not available, it is unclear whether the respective cut-off values of the mentioned subgroup characteristics were prespecified. Therefore, the available subgroup results were not considered in the present assessment.

## 2.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [16].

The approach for deriving an overall conclusion on the 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.

### 2.3.1 Assessment of the added benefit at outcome level

Based on the results presented in Section 2.2.3, the extent of the respective added benefit was estimated at outcome level on the basis of the TANGO study (see Table 10).

**Determination of the outcome category on side effects**

Not for all outcomes considered in the present benefit assessment did the dossier indicate whether they were non-severe/non-serious or severe/serious. The classification of these outcomes is justified below.

***Discontinuation due to AEs as well as specific AEs (fatigue and seasonal allergy)***

The events that occurred on the outcome "discontinuation due to AEs" were mostly non-serious/non-severe. All events that occurred within the specific AEs "fatigue" and "seasonal allergy" were non-severe/non-serious. Therefore, the cited outcomes were assigned to the category non-serious/non-severe side effects.

Table 10: Extent of added benefit at outcome level: DTG/3TC vs. comparator therapy[a]

| **Outcome category**<br>**Outcome** | **DTG/3TC vs. comparator therapy[a] proportion of events (%) or change at week 48 (mean)**<br>**Effect estimation [95% CI]; p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| **Mortality** | | |
| All-cause mortality | 0.3% vs. 0%<br>RR: 3.02 [0.12; 73.80]; p = 0.499 | Lesser benefit/added benefit not proven |
| **Morbidity** | | |
| AIDS-defining events (CDC stage 3) | 0.5% vs. 0%<br>RR: 5.03 [0.24; 104.35]; p = 0.160 | Lesser benefit/added benefit not proven |
| Presented as supplementary information: | | |
| Virologic response[b] | 93.0 % vs. 93.0 %<br>RR: 0.99 [0.95; 1.04]; p = 0.790 | |
| Virologic failure[d] | 0.3% vs. 0.5%<br>RR: 0.51 [0.05; 5.62]; p = 0.584 | |
| $CD4^+$ cell count/$mm^3$ | Change: 23.96 vs. 0.27<br>MD: 23.68 [-1.57; 48.94]; p = 0.066 | |
| Health status (EQ-5D VAS) | Change: 1.1 vs. 1.7<br>MD: -0.5 [-1.9; 0.8]; p = 0.414 | Lesser benefit/added benefit not proven |

(continued)

Table 10: Extent of added benefit at outcome level: DTG/3TC vs. comparator therapy[a] (continued)

| **Outcome category**<br>**Outcome** | **DTG/3TC vs. comparator therapy[a] proportion of events (%) or change at week 48 (mean)**<br>**Effect estimation [95% CI]; p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| **Health-related quality of life** | Outcomes of this outcome category were not recorded. | |
| **Side effects** | | |
| SAEs | 5.4% vs. 4.3%<br>RR: 1.26 [0.66; 2.39]; p = 0.480 | Greater/lesser harm not proven |
| Severe AEs (DAIDS grade 3–4) | 6.0% vs. 5.7%<br>RR: 1.05 [0.59; 1.88]; p = 0.860 | Greater/lesser harm not proven |
| Discontinuation due to AEs | 3.5% vs. 0.5%<br>RR: 6.54 [1.49; 28.80];<br>RR: 0.15 [0.03; 0.67][e]; p = 0.013<br>probability: "hint" | Outcome category: "non-serious/non-severe side effects"<br>$CI_u < 0.80$<br>Greater harm, extent: "considerable" |
| Gastrointestinal disorders (SOC, AEs) | 24.9% vs. 21.6%<br>RR: 1.15 [0.89; 1.50]; p = 0.289 | Greater/lesser harm not proven |
| Skin and subcutaneous tissue disorders (SOC, AE) | 10.8% vs. 11.1%<br>RR: 0.98 [0.65; 1.48]; p = 0.936 | Greater/lesser harm not proven |
| Nervous system disorders (SOC, AE) | 13.3% vs. 11.6%<br>RR: 1.15 [0.78; 1.68]; p = 0.485 | Greater/lesser harm not proven |
| Psychiatric disorders (SOC, AE) | 13.6% vs. 10.0%<br>RR: 1.35 [0.90; 2.01]; p = 0.144 | Greater/lesser harm not proven |
| **Side effects** | | |
| Fatigue (PT, AE) | 5.4% vs. 0.8%<br>RR: 6.70 [2.01; 22.36];<br>RR: 0.15 [0.04; 0.50][e]; p = 0.001<br>probability: "hint" | Outcome category: "non-serious/non-severe side effects"<br>$CI_u < 0.80$<br>Greater harm, extent: "considerable" |
| Seasonal allergy (PT, AE) | 3.3% vs. 0.8%<br>RR: 4.02 [1.14; 14.13];<br>RR: 0.25 [0.07; 0.88][e]; p = 0.019<br>probability: "hint" | Outcome category: "non-serious/non-severe side effects"<br>$0.80 \leq CI_u < 0.90$<br>Greater harm, extent: "minor" |

a. Continuation of ongoing treatment.
b. Probability given if statistically significant differences are present.
c. Estimations of effect size are made depending on the outcome category with different limits based on the $CI_u$.
d. According to FDA snapshot algorithm.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

3TC: lamivudine; AE: adverse event; AIDS: acquired immunodeficiency syndrome; CDC: Centers for Disease Control and Prevention; $CD4^+$: cluster of differentiation 4-positive; CI: confidence interval; $CI_u$: upper limit of confidence interval; DAIDS: Division of AIDS; DTG: dolutegravir; EQ-5D: European Quality of Life-5 Dimensions; FDA: Food and Drug Administration; MD: mean difference; RR: relative risk; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale; vs.: versus

### 2.3.2 Overall conclusion on added benefit

Table 11: Positive and negative effects from the assessment of DTG/3TC vs. comparator therapy[a]

| Positive effects | Negative effects |
|---|---|
| – | Non-serious/non-severe side effects<br>▪ Discontinuation due to AEs; hint of greater harm - extent: “considerable”<br>▪ Fatigue: hint of greater harm – extent: "considerable"<br>▪ Seasonal allergy: hint of greater harm - extent: “minor” |
| a. Continuation of ongoing treatment.<br>3TC: lamivudine; DTG: dolutegravir; vs.: versus | |
| | |

Overall, there were exclusively negative effects for DTG/3TC in comparison with continuation of ongoing treatment in the outcome category “non-serious/non-severe adverse events”, including hints of greater harm for the outcomes “discontinuation due to AEs” and “fatigue”, each with the extent considerable.

In summary, this resulted in a hint of lesser benefit of DTC/3TC in comparison with continuation of ongoing treatment for pretreated HIV-1 infected[3] adults without indication for a treatment switch.

There are no data for the assessment of the added benefit of DTC/3TC versus continuation of ongoing treatment for pretreated HIV-1 infected[3] adults with indication for a treatment switch. This resulted in no hint of an added benefit for this population; an added benefit is therefore not proven.

## 2.4 Summary

The data subsequently submitted by the company in the commenting procedure have changed the conclusion on the added benefit of DTG/3TC from dossier assessment A19-55 for research question 2: For pretreated HIV-1-infected[3] adults without indication for a treatment switch, there is a hint of lesser benefit of DTG/3TC in comparison with continuation of the ongoing treatment.

The G-BA decides on the added benefit.

[3] The HI virus was not to have any known or suspected resistances to the INI class or 3TC.

## 3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dolutegravir/Lamivudin (HIV-Infektion): Nutzenbewertung gemäß § 35a SGB V [online]. 30.10.2019 [Accessed: 04.11.2019]. (IQWiG-Berichte; Volume 831). URL: https://www.iqwig.de/download/A19-55_Dolutegravir-Lamivudin_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. ViiV Healthcare. Dolutegravir/Lamivudin (Dovato): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 03.07.2019 [Accessed: 13.11.2019]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/477/.

3. Taiwo B. Dolutegravir antiretroviral strategy to promote improvement and reduce drug exposure (ASPIRE): study results [online]. In: ClinicalTrials.gov. 19.03.2019 [Accessed: 23.07.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02263326.

4. Taiwo B. Dolutegravir antiretroviral strategy to promote improvement and reduce drug exposure (ASPIRE): study details [online]. In: ClinicalTrials.gov. 19.03.2019 [Accessed: 23.07.2019]. URL: https://ClinicalTrials.gov/show/NCT02263326.

5. Taiwo B. Dolutegravir Antiretroviral Strategy to Promote Improvement and Reduce drug Exposure (ASPIRE) study: study protocol, statistical analysis plan, and informed consent form [online]. 25.06.2015 [Accessed: 01.08.2019]. URL: https://clinicaltrials.gov/ProvidedDocs/26/NCT02263326/Prot_SAP_ICF_000.pdf.

6. Taiwo BO, Marconi VC, Berzins B, Moser CB, Nyaku AN, Fichtenbaum CJ et al. Dolutegravir plus lamivudine maintains human immunodeficiency virus-1 suppression through week 48 in a pilot randomized trial. Clin Infect Dis 2018; 66(11): 1794-1797.

7. ViiV Healthcare. Stellungnahme zum IQWiG-Bericht Nr. 831: Dolutegravir/Lamivudin (HIV Infektion); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A19-55. [soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/477/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

8. ViiV Healthcare. A phase III, randomized, multicenter, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus lamivudine in HIV 1 infected adults who are virologically suppressed: study 204862; clinical study protocol amendment [unpublished]. 2018.

9. ViiV Healthcare. A phase III, randomized, multicenter, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus lamivudine in HIV 1 infected adults who are virologically suppressed: week 48; study 204862; clinical study report [unpublished]. 2019.

10. ViiV Healthcare. A phase III, randomized, multicenter, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus lamivudine in HIV 1 infected adults who are virologically suppressed: week 48; study 204862; Zusatzanalysen [unpublished]. 2019.

11. ViiV Healthcare. Dolutegravir/Lamivudin: Anhang zur Stellungnahme; nachgereichte Ergebnisse der 48-Wochen Daten der TANGO-Studie [unpublished]. 2019.

12. Wensing AM, Calvez V, Gunthard HF, Johnson VA, Paredes R, Pillay D et al. 2017 update of the drug resistance mutations in HIV-1. Top Antivir Med 2016; 24(4): 132-133.

13. ViiV Healthcare. Dovato 50 mg/300 mg Filmtabletten: Fachinformation [online]. 07.2019 [Accessed: 17.07.2019]. URL: http://www.fachinfo.de.

14. Center of Disease, Control and Prevention. Revised surveillance case definition for HIV infection [online]. 2014 [Accessed: 05.02.2019]. URL: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm?s_cid=rr6303a1_e#Tab.

15. 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.

16. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

## Appendix A – Results on side effects (TANGO)

The following tables present events for (System Organ Class) SOCs and (preferred terms) PTs according to Medical Dictionary for Regulatory Activities (MedDRA) for the overall rates of "AEs", "SAEs" and "severe AEs (DAIDS grade 3–4), each on the basis of the following criteria:

- Overall rate AEs (irrespective of the severity grade): events that occurred in at least 10% of the patients in one study arm
- Overall rates severe AEs (DAIDS grade 3–4) and SAEs: events that occurred in at least 5% of the patients in one study arm
- in addition for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

For the outcome "discontinuation due to adverse events", all events (SOCs/PTs) that resulted in discontinuation were presented".

SAEs and severe AEs (DAIDS grade 3–4) are not presented hereinafter, because events with a frequency of > 5% did not occur in a study arm.

Table 12: Common AEs – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **DTG/3TC N = 369** | **Continuation of ongoing treatment N = 371** |
| **TANGO** | | |
| **Overall rate AEs** | 295 (80) | 292 (79) |
| Infections and infestations | 196 (53) | 187 (50) |
| Nasopharyngitis | 43 (12) | 41 (11) |
| Upper respiratory tract infection | 31 (8) | 32 (9) |
| Syphilis | 24 (7) | 13 (4) |
| Gastroenteritis | 13 (4) | 16 (4) |
| Bronchitis | 8 (2) | 20 (5) |
| Pharyngitis | 14 (4) | 11 (3) |
| Anal chlamydia infection | 8 (2) | 12 (3) |
| Gastrointestinal disorders | 92 (25) | 80 (22) |
| Diarrhoea | 30 (8) | 26 (7) |
| Nausea | 15 (4) | 7 (2) |
| Musculoskeletal and connective tissue disorders | 68 (18) | 65 (18) |
| Back pain | 21 (6) | 28 (8) |
| Arthralgia | 12 (3) | 13 (4) |
| Nervous system disorders | 49 (13) | 43 (12) |
| Headache | 24 (7) | 17 (5) |
| Psychiatric disorders | 50 (14) | 37 (10) |
| Anxiety | 17 (5) | 9 (2) |
| Insomnia | 10 (3) | 7 (2) |
| Skin and subcutaneous tissue disorders | 40 (11) | 41 (11) |
| General disorders and administration site conditions | 48 (13) | 28 (8) |
| Fatigue | 20 (5) | 3 (0.8[c]) |
| Injury, poisoning and procedural complications | 32 (9) | 42 (11) |
| Respiratory, thoracic and mediastinal disorders | 36 (10) | 34 (9) |
| Metabolism and nutrition disorders | 29 (8) | 15 (4) |
| Vitamin D deficiency | 12 (3) | 11 (3) |
| Reproductive system and breast disorders | 23 (6) | 19 (5) |
| Investigations | 17 (5) | 16 (4) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 17 (5) | 8 (2) |

(continued)

Table 12: Common AEs – RCT, direct comparison: DTG/3TC vs. comparator therapy[a] (continued)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **DTG/3TC N = 369** | **Continuation of ongoing treatment N = 371** |
| Vascular disorders | 13 (4) | 12 (3) |
| Ear and labyrinth disorders | 10 (3) | 11 (3) |
| Immune system disorders | 16 (4) | 5 (1) |
| Seasonal allergy | 12 (3) | 3 (0.8[c]) |
| Renal and urinary disorders | 9 (2) | 10 (3) |
| Eye disorders | 7 (2) | 11 (3) |
| Cardiac disorders | 5 (1) | 11 (3) |

a. Continuation of ongoing treatment.
b. MedDRA version 22.0.
c. Institute's calculation.

AE: adverse event; 3TC: lamivudine; DTG: dolutegravir; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 13: Discontinuation due to AEs – RCT, direct comparison: DTG/3TC vs. comparator therapy[a]

| Study | Patients with event n (%) | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **DTG/3TC N = 369** | **Continuation of ongoing treatment N = 371** |
| **TANGO** | | |
| **Overall rate discontinuation due to AEs** | 13 (4) | 2 (0.5[c]) |
| Psychiatric disorders | 7 (2) | 2 (0.5[c]) |
| Anxiety | 3 (0.8[c]) | 0 (0) |
| Insomnia | 3 (0.8[c]) | 0 (0) |
| Depression | 0 (0) | 1 (0.3[c]) |
| Irritability | 1 (0.3[c]) | 0 (0) |
| Suicidal ideation | 1 (0.3[c]) | 0 (0) |
| Suicide attempt | 0 (0) | 1 (0.3[c]) |
| Investigations | 2 (0.5[c]) | 1 (0.3[c]) |
| Increased weight | 2 (0.5[c]) | 1 (0.3[c]) |
| Gastrointestinal disorders | 2 (0.5[c]) | 2 (0.5[c]) |
| Abdominal discomfort | 1 (0.3[c]) | 0 (0) |
| Gastrooesophageal reflux disease | 1 (0.3[c]) | 0 (0) |
| Hypoaesthesia, oral | 1 (0.3[c]) | 0 (0) |
| Nausea | 1 (0.3[c]) | 0 (0) |
| Paraesthesia, oral | 1 (0.3[c]) | 0 (0) |
| General disorders and administration site conditions | 2 (0.5[c]) | 0 (0) |
| Fatigue | 2 (0.5[c]) | 0 (0) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 2 (0.5[c]) | 0 (0) |
| Diffuse large cell B-cell lymphoma | 1 (0.3[c]) | 0 (0) |
| Adenocarcinoma in the lungs | 1 (0.3[c]) | 0 (0) |
| Nervous system disorders | 2 (0.5[c]) | 0 (0) |
| Disturbance in attention | 1 (0.3[c]) | 0 (0) |
| Hypoaesthesia | 1 (0.3[c]) | 0 (0) |
| Paraesthesia | 1 (0.3[c]) | 0 (0) |
| Immune system disorders | 1 (0.3[c]) | 0 (0) |
| Drug hypersensitivity | 1 (0.3[c]) | 0 (0) |
| Injury, poisoning and procedural complications | 1 (0.3[c]) | 0 (0) |
| Gunshot wound | 1 (0.3[c]) | 0 (0) |

(continued)

Table 13: Discontinuation due to AEs – RCT, direct comparison: DTG/3TC vs. comparator therapy[a] (continued)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | DTG/3TC N = 369 | Continuation of ongoing treatment N = 371 |
| Reproductive system and breast disorders | 1 (0.3[c]) | 0 (0) |
| Hypaesthesia in the genital area | 1 (0.3[c]) | 0 (0) |
| Genital paraesthesia | 1 (0.3[c]) | 0 (0) |
| Skin and subcutaneous tissue disorders | 1 (0.3[c]) | 0 (0) |
| Pruritus | 1 (0.3[c]) | 0 (0) |

a. Continuation of ongoing treatment.
b. MedDRA version 22.0.
c. Institute's calculation.

AE: adverse event; 3TC: lamivudine; DTG: dolutegravir; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus