REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

JULUCA

50 mg/25 mg film coated tablet x 30

dolutegravir/rilpivirine

Therapeutic indications	For the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.
Start/end date of procedure	14.05.2019 - 31.10.2019
Final decision	Inclusion in the Positive Drug List (PDL): - Annex 2 for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act; - Annex 3 for the treatment of diseases paid for from the budget of the Ministry of Health.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Juluca

Health problem

Human immunodeficiency virus (HIV) is an RNA virus belonging to the family of retroviruses (Retroviridae). HIV enters the host cells (specifically CD4 T-helper lymphocytes and macrophages), where several important enzymes are involved in its replication cycle: reverse transcriptase, protease and integrase. The viral double-stranded DNA molecule thus formed is incorporated into the DNA of the host with the help of the enzyme integrase. The virus is transmitted by direct contact of mucosa or bloodstream with body fluid (blood, semen, vaginal fluid and breast milk) containing virus particles. The virus is classified into two types - HIV-1, which is the predominant genotype, and HIV-2, which is prevalent mainly in West Africa. The diagnosis of the disease is based on epidemiological, clinical and laboratory data.

HIV is characterized by a prolonged latent course of infection and the formation of viral depots in the CNS, lymphatic structures and gastrointestinal tract. HIV generally infects CD4 + T cells, leading to immune suppression and, in the absence of therapy, to a fatal outcome due to an increased risk of infection with other viruses, bacteria, parasites and fungi, as well as neoplastic processes (AIDS-defining diseases). Patients with a CD4 + T cell count below 200 cells/mm³ or with concomitant AIDS-defining disease are defined as AIDS patients. Nowadays, HIV infection has become a chronic disease with a significant life expectancy of patients, provided they adhere to appropriate antiretroviral therapy (ART), which is lifelong. According to current European and American guidelines, all HIV-infected patients should be treated with combination antiretroviral therapy (cART), regardless of immune status. Thus far, the registered HIV-positive patients in Bulgaria (including the deceased) are about 3150. Of these, about 1600 patients are on ART, and about 100 patients are to start ART, based on the new treatment recommendations.

Antiretroviral drugs for the treatment of HIV patients are listed in Table 1, and those currently included in combination tablets are listed in Table 2.

Table 1: Antiretroviral drugs

Nucleoside reverse transcriptase inhibitors	Protease inhibitors (PIs)	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Fusion inhibitors (FIs)	Entry inhibitors (EIs)	Integrase inhibitors (INSTIs)
Zidovudin	Saquinavir	Nevirapine	Enfuvirtid	Maraviroc	Raltegravir
Didanosin	Ritonavir	Delavirdine		Vicriviroc	Dolutegravi
Stavudine	Indinavir	Efavirenz		Cenicrivir	Elvitegravir
Lamivudin	Nelfinavir	Etravirine			Cabotegravi
Abacavir	Lopinavir/rit	Rilpivirine			Bictegravir
Tenofovir	Atazanavir	Doravirine			
Emtricitabi	Fosamprenav	Dapivirine			
	Tipranavir				
	Darunavir				

Table 2: Combined antiretroviral drugs

Drug product	Type
AZT+3TC (Combivir)	2 NRTIs
AZT+3TC+ABC (Trizivir)	3 NRTIs
3TC+ABC (Kivexa, Epzicom)	2 NRTIs
TDF+FTC (Truvada)	2 NRTIs
TAF+FTC (Descovy)	2 NRTIs
LPV+RTV (Kaletra)	boosted PI
DRV+COBI (Resolsta)	boosted PI
EFV+TDF+FTC (Atripla)	one NNRTI + 2 NRTIs
TDF+FTC+RPV (Copmplera, Eviplera)	one NNRTIs + 2 NRTIs
TAF+FTC+RPV (Odefsey)	one NNRTI + 2 NRTIs
TDF+FTC+ELV/c (Stribild)	one boosted INSTI+ 2 NRTIs
TAF+FTC+ ELV/c (Genvoya)	one boosted INSTI+ 2 NRTIs
3TC+AVC+DTV (Triumeq)	one INSTI+ 2 NRTIs
TAF+FTC+DRV/c (Simtuza)	one boosted PI+ 2 NRTIs
TAF+FTC+BIC/c (Bictarvy)	one boosted INSTI+ 2 NRTIs
DTG+RPV (Juluca)	one INSTI+ one NNRTI
DTG+3TC (Dovato)	one NRTI + one INSTI

The usual combinations for starting ART are:

1. Two nucleoside reverse transcriptase inhibitors + one integrase inhibitor (2 NRTIs + 1 INSTI)
2. Two nucleoside reverse transcriptase inhibitors + one protease inhibitor (2 NRTIs + 1 PI)

3. Two nucleoside reverse transcriptase inhibitors + one non-nucleoside reverse transcriptase inhibitor (2 NRTIs + 1 NNRTIs) for treatment.

When optimal viral suppression is achieved, combinations of two drugs (including Juluca) are also used to reduce long-term toxicity.

The recommended antiretroviral regimens for the treatment naive and previously treated HIV patients are set out in the Guidelines for Antiretroviral Treatment and Monitoring of Adults with HIV in Bulgaria, based on the guidance of the European Commission on HIV/AIDS (EACS) version 9.0., last updated Oct., 2018. Recently, in the Draft Pharmacotherapeutic Guide for Infectious Diseases, the Expert Council on Infectious Diseases unanimously adopted a section, concerning treatment of HIV/AIDS. The medicinal product Juluca is listed as a treatment option in patients with optimal viral suppression aimed at reducing long-term toxicity. The new Juluca health technology (DTG/RPV) is also listed in the updated treatment guidelines published in AIDSinfo, 2019.

Efficacy data

To evaluate the therapeutic efficacy and safety of Juluca (DTG/RPV) for the treatment of HIV-1 infected adults with current viral suppression in a two-nucleoside reverse transcriptase inhibitor (NRTI) regimen plus a third agent, subsequently switching to a two-drug regimen, the results of three clinical trials and four real world studies were compared and analyzed:

- Clinical trial SWORD-1.
- SWORD-2 clinical trial.
- DEXA clinical trial.
- Study with data from real clinical practice Capetti et al, 2016.
- Study with data from real clinical practice Diaz et al, 2016.
- Study with data from real clinical practice Palacios et al, 2016.
- Study with data from real clinical practice Saling et al, 2016.

Clinical trials SWORD-1 and SWORD-2

Primary endpoint: HIV 1 RNA <50 copies / mL at week 48.

Summarizing the results of SWORD-1 and SWORD-2, it became clear that 95% of patients (ITT-E population) in both treatment groups had a response to therapy.

Similar results were observed in the separate analyses of SWORD 1 and SWORD 2. 96% of patients in the SWORD-1 study and 94% in the SWORD-2 study responded to treatment. A very small proportion of patients did not achieve a virologic response; for the remaining patients, no virologic data were available until week 48.

The analysis shows that the combination DTG + RPV was non-inferior to CAR at week 48, as the lower limit of 95% CI for the corrected treatment difference (-3.0; 2.5) was greater than -8%. Similar pattern is seen in the analysis of individual data from studies. The SWORD-1 analysis showed that the combination of DTG + RPV was non-inferior to the combined ART (cART) at week 48, as the lower limit of 95% CI for the adjusted treatment difference (-4.3; 3,0) is greater than -10%. Analysis of SWORD-2 data revealed that DTG + RPV was non-inferior to cART at week 48, as the lower limit of 95% CI for the adjusted treatment difference (-3.9; 4.2) is greater than -10%. No mutations associated with INSTI resistance were identified and one patient in the DTG + RPV group eligible for study withdrawal criteria due to virologic failure or rebound was identified with NNRTI resistance-associated mutation (K101K/E).

Secondary endpoints

The pooled analysis shows that the mean change from baseline in CD4 + cell count was 28.0 cells/mm³ in the DTG + RPV group and 22.0 cells/mm³ in the group remaining on combined ART. Differences in the mean change from baseline in CD4 + cell count between SWORD-1 and SWORD-2 were observed. In SWORD-1, the mean change from baseline was 25.0 cells/mm³ in the DTG + RPV group and 35.0 cells/mm³ in the cART group. In SWORD-2, the mean change from baseline was 29.0 cells/mm³ in the DTG + RPV group and 13.0 cells/mm³ in the cART group.

The differences between baseline and week 48 in the various lipid parameters are small. DTG + RPV is most commonly associated with a slight increase in total cholesterol, HDL and LDL cholesterol. The total cholesterol/HDL ratio, which is often used to assess long-term cardiovascular risk, is similar between groups at week 48. Overall, the DTG + RPV group showed a slight improvement in the triglyceride profile and various changes in cholesterol (general data analysis and separate analyses).

Secondary endpoints for biomarkers

Biomarker analyses were performed to determine any changes associated with renal, bone, and cardiovascular disease in adults with HIV-1 infection. No change in mean cystatin C from baseline through week 48 was observed in patients in both groups, regardless of whether they received baseline TDF. Changes in bone biomarkers are associated with an increased risk of bone loss. Lower levels of biomarkers suggest weaker bone metabolism. In the DTG + RPV group, all bone metabolism biomarkers levels (BSAP, P1NP and osteocalcin) diminished from baseline level through week 48. The reduction in bone biomarkers levels observed in the DTG + RPV group was statistically significantly greater than the changes observed in the cART group. For BSAP and osteocalcin, a significant interaction was found between the treated group and the third-agent class. The significant reduction in the DTG + RPV group compared to the cART group was maintained within each third-agent class.

For cardiovascular biomarkers included in the SWORD studies, no clear trend was observed in terms of changes from baseline level through week 48.

Combined analysis of SWORD-1 and SWORD-2 at week 100, which includes data from patients who switched to DTG + RPV at week 52

Of 1,024 patients randomized and treated with DTG + RPV or cART, 892 (87%) completed the 100-week follow-up period. During the period, the efficacy of DTG + RPV was maintained in the group with early transition to DTG + RPV, similar to efficacy data in the group with late phase transition to DTG + RPV. Through week 100, a small number of withdrawals was reported due to virologic failure or rebound in the populations studied (1%; 10/990). Withdrawals were associated with treatment-related resistance mutations, being low in both groups and detected in 3 participants, all of them receiving DTG + RPV (0.3%; 3/990). At least 1 mutation associated with NNRTI resistance was detected in all 3 participants.

Biomarker analyses - There is no noticeable trend in changes from baseline in mean serum lipid concentration (total cholesterol, LDL, HDL or triglycerides) in the groups with early or late transition to DTG + RPV.

A reduction in all bone marrow biomarkers from baseline through week 100 was observed, with the exception of procollagen 1 N-terminal propeptide, in the early phase transition group to DTG + RPV. DTG + RPV treatment had a neutral effect on atherogenesis and biomarkers of inflammation, with no additional changes at week 100 compared to week 48. Improvement in renal tubular function, as measured by a change from baseline in retinol-binding protein/ creatinine ratio and urinary beta-2 microglobulin/creatinine was retained at week 100 in the group of early transition to DTG + RPV.

DEXA clinical trial

Primary endpoint

A significant difference between the groups with DTG + RPV and cART was reported for the femur and the lumbar spine. In patients in the DTG + RPV group, a greater positive change from baseline was observed in both indicators; the changes in the cART group are small.

Secondary endpoints

Analysis of the change from baseline in the total bone mineral density of the femur and the lumbar region of the spine was performed using T-scores and Z-scores. A statistically significant difference was reported for both measurements, with better results in the DTG + RPV group.

Score from FRAX

The FRAX tool was employed for assessing the 10-year risk of femoral fractures and osteoporotic fracture on day 1, week 48, 100, 148 and at study withdrawal. There was no significant difference in the change from baseline over a 10-year period between DTG + RPV

and cART for either femoral fracture (p = 0.697) or osteoporotic fractures (p = 0.732) at α = 10%.

Clinical study	Country (s)	Participants	Type of study, duration	Intervention	Comparative alternatives	Results
SWORD-1 (NCT02429791)	Argentina Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Russian Federation, Spain, Taiwan, Great Britain, USA	510 HIV-1 infected adult patients with current viral suppression on a 2 NRTI plus third agent regimen and HIV-1 infected adult patients with current viral suppression on a 2 NRTI plus third agent regimen switching to a DTG + RPV regimen. Age, median (limits): DTG + RPV: 43.0 (23-79) CAR: 43.0 (22-76) - Gender, n (%): Women: median (IQR): DTG + RPV: 58 (23) DTG + RPV: 2.970 (-11.111; 16.197) CAR: 51 (20) CAR: 2.872 (-6.667; 11.888) - Race, n (%): Race, not white: DTG +	Phase III, multicenter, randomized, open-label clinical trial to evaluate non-inferior efficacy Randomization 1: 1 Stratification by third agent class age ≥50 Duration: April 2015 - September 2016	DTG + RPV, current antiretroviral therapy with 2 NRTIs plus a third agent	DTG + RPV against ongoing antiretroviral therapy with 2 NRTIs plus a third agent	Proportion of patients with HIV-1 RNA <50 copies /mL at week 48: DTG + RPV: 95% CAR: 96% Proportion of patients with HIV-1 RNA <50 copies /mL at week 24: DTG + RPV: 98% CAR: 96% Change in CD4 + cell count from baseline at week 48, median (IQR): DTG + RPV: 25.0 (-68.0 - 119.0) CAR: 35.0 (-37.0,104.0) Change in total cholesterol (mmol / L) from baseline at week 48, median (IQR): DTG + RPV:

		RPV: 54 (21) CAR: 68 (27) - Number of CD4 + cells, cells/ mm3, ≤500, n (%): DTG + RPV: 85 (34) CAR: 74 (29) - Number of CD4 + cells, cells /mm3, > 500, n (%): DTG + RPV: 167 (66) CAR: 182 (71)				1.211 (-9.434; 15.703) CAR: 0.324 (-7.018; 13.023) Change in HDL cholesterol (mmol)/L from baseline at week 48, median (IQR): DTG + RPV: 2.970 (-11.111; 16.197) CAR: 2,872 (-6,667; 11,888) Change in LDL cholesterol from baseline (mmol / L) at week 48, median (IQR): DTG + RPV: 2.839 (-11.035; 22.134) CAR: 0.385 (-10.159; 15.649) Change in triglycerides (mmol/L) from baseline at week 48, median (IQR): DTG + RPV: -8,046

						(-31,544; 19,697) CAR: 0,000 (-25,424; 30,952)
SWORD-2 (NCT02422797)	Argentina Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Russian Federation, Spain, Taiwan, UK, US	518 HIV-1 infected adult patients with current viral suppression on a 2 NRTI plus third agent regimen and HIV-1 infected adult patients with current viral suppression on a 2 NRTI plus third agent regimen switching to DTG + RPV regimen. Age, median (limits): DTG + RPV: 43.0 (21-79) CAR: 43.0 (22-69) - Gender, n (%): Women: DTG + RPV: 62 (24) CAR: 57 (22) - Race, n (%): Race, not white: DTG + RPV: 38 (15) CAR: 45 (18) - Number of CD4 + cells, cells / mm3, ≤500,n (%): DTG + RPV: 80 (31)	Phase III, multicenter, randomized, open-label clinical trial to evaluate non-inferior efficacy Randomization 1: 1 Stratification by third agent class age ≥50 duration: april 2015 – september 2016	DTG + RPV, current antiretroviral therapy with 2 NRTIs plus a third agent	DTG + RPV against ongoing antiretroviral therapy with 2 NRTIs plus a third agent	(-47.0, 108.0) CAR: 13.0 (-59.0,108.0) Change in total cholesterol (mmol / L) from baseline at week 48, median (IQR): DTG + RPV: -0.232 (-10.799; 9.223) CAR: -0,616 (-8,778; 8,133) Change in HDL cholesterol (mmol) / L from baseline at week 48, median (IQR): DTG + RPV: 5.590 (-5.579; 16.049) CAR: 3,266 (-5,988; 14,285) Change in LDL cholesterol from baseline (mmol / L) at week 48,

		CAR:75 (29) - Number of CD4 + cells, cells /mm3,> 500, n (%): DTG + RPV: 181 (69) CAR: 180 (71)				median (IQR): DTG + RPV: -0.843 (-13.520; 15.224) CAR: -2,185 (-13,676; 8,830) Change in triglycerides (mmol/ L) from baseline at week 48, median (IQR): DTG + RPV: -9,890 (-32,558; 20,833) CAR: 1,015 (-22,549; 25,714)
DEXA 202094 (NCT02478632)	USA, Argentina, Belgium, Canada, Spain, Great Britain	102 Patients with SWORD-1 and SWORD-2 - Age, mean: DTG + RPV: 42.6 CAR: 44.8 - Gender, n (%): Women: DTG + RPV:27 (51) CAR: 26 (53) - Race, n (%): Race, not white: DTG + RPV: 9 (17) CAR: 9 (18) - BMI, median (kg / m2): DTG + RPV: 24.4	Open parallel sub-study of SWORD-1 and SWORD-2 Duration: June 2015 - September 2016	Patients do not receive additional intervention The group of participants was transferred from the main SWORD-1 and SWORD-2	From SWORD-1 and SWORD-2: DTG + RPV versus current antiretroviral therapy	Biomarker for bone-specific alkaline phosphatase DTG + RPV: 0.753 KING: 1,145 Biomarker for osteocalcin INSTI: DTG + RPV: 0.635 CAR: 1,059 NNRTI: DTG+ RPV: 0.787 CAR: 0.932 PI: DTG + RPV: 0.682 CAR: 1,011 Biomarker for

		CAR: 24.7				procollagen 1N-terminal propeptide DTG + RPV: 0.660 CAR: 0.891 Biomarker for vitamin D. DTG+ RPV: 0.784 CAR: 0.813 Change from baseline to the probability of a fracture of femur in a 10-year period DTG+ RPV: 0.85 CAR: 0.81 Change from baseline to likelihood of osteoporotic fracture over a 10-year period DTG+ RPV: 0.98 CAR: 0.96

* HIV-1 - human immunodeficiency virus type-1; RNA - ribonucleic acid; DTG - dolutegravir; RPV - rilpivirine; CAR - current antiretroviral treatment; ART - antiretroviral therapy; TDF - tenofovir disoproxil fumarate; DEXA - dual energy X-ray absorptiometry; NRTI - nucleoside reverse transcriptase inhibitor; INSTI - integrase inhibitor; PI - protease inhibitors; BMI - body mass index; IQR - interquartile range; HDL - high density lipoproteins; LDL - low density lipoproteins

Real world clinical data studies

Four studies with DTG + RPV have been identified in patients receiving ART. Most of them are prospective, only one is a retrospective database analysis. The group size in these studies ranged from 38 to 1232 HIV patients. In the shortest study, patients were followed for 24 weeks, and in the longest one for an average of 24 months. The studied populations are similar; patients are mostly men (50-70.5%), with an average age of 51.8 to 53.4 years. Four studies included a large proportion of patients with baseline resistance mutations. The most common class of mutations are NRTI resistance mutations ranging from 34.8% to

64.7%, followed by PIs resistance mutations (21.4–44.7%). Patients in these studies had previously been treated with different ART regimens. Exposure to ART has been reported in 2 studies and ranged from 37 months to 19.4 years. The most common reasons for switching to a 2-drug regimen were toxicity/intolerance/adverse reactions (29-57%), followed by regimen simplification (25-53%). The majority of patients had an undetectable viral load (60-67.4%) or viral suppression (78.1–100%) when enrolled in the studies and a baseline CD4 + T cell count between 510 and 721.5 cells/mm³.

The results of the majority of studies show a moderate increase in CD4 + T cell counts and a large proportion of patients having viral suppression. The results for the actual efficacy of DTG + RPV in ART-treated patients are generally similar to those observed in the randomized controlled trials SWORD-1 and SWORD-2. In most studies, the proportion of patients with viral suppression at the end of treatment was high (range: 96.5-100%). The results of the studies by Diaz et al. (2016) and Palacios et al. (2016) are similar: HIV-1 RNA <37 copies/ mL in 97% of patients with prior treatment (HTE) at week 24 (Diaz 2016); the proportion of patients with prior ART treatment in Palacios et al. 2016, who are with viral suppression was 78.1% at baseline and 96.5% at the end of follow-up. In addition, a retrospective analysis of the database of HIV patients switching to DTG + RPV due to virologic failure and ADRs showed an increase in the proportion of patients with viral suppression from 57% at baseline to 100% at the end of follow-up. However, no statistical analysis of the results of viral suppression in these studies was performed (Saling et al, 2016). A Spanish study reported a significant increase in the number of CD4 + T cells from 552 cells/mm³ at baseline to 622 cells/mm³ at the end of follow-up with DTG + RPV treatment (p = 0.008) (Diaz et al, 2016). Two other studies reported a numerical increase in the number of CD4 + T cells, with no statistically significant results (Saling et al, 2016; Capetti et al, 2016a; Capeti et al, 2016b).

An observational cohort study of 132 subjects, with a median follow-up duration of 24 months (mean duration 33 months), reported resistance to DTG + RPV. Six patients that were followed for 48 weeks were resistant to RPV, none of them had treatment failure (Capetti et al, 2016a; Capeti et al, 2016b).

Clinical study	Country(s)	Participants	Type of study, duration	Intervention	Comparative alternatives	Results			
						Viral load	**Number of CD4 cells**	**Treatment failure**	**Resistance**
Capetti et al, 2016a	Italy	132 Patients starting DTG + RPV treatment between October 2014 and September 2015.	Prospective observational, cohort study Duration: Average: 33 months Median: 24 months	DTG + RPV	N/A	Week 4: Median: (scope) HIV-1 RNA 1.71 (1.69-1.75) log10 copies / mL -No virus detected: 114 -HIV-1 RNA 1–49 copies / mL: 15 -HIV-1 RNA > 50 copies / mL: 3 Week 24: -Median HIV-1 RNA: 4.17 log10 copies / mL -No virus detected: 112 -HIV-1 RNA 1–49 copies / mL: 19	Week 24: Median: (range): 750.5 (100–2338)	At week 24, only one patient had viral rebound without mutations due to missed medication (11,030 copies/ mL).	One case of low level of resistance to RPV, one case of medium level of resistance and four cases of high level of resistance; none of these patients' treatment failed
Capetti et al, 2016b	Italy	50 patients 48-week follow-up	Prospective observational, cohort study Duration: Average: 33 months Median: 24 months	DTG + RPV	N/A	Week 4: Median: (scope) HIV-1RNA 1.71 (1.69–1.75) log10 copies / mL -No virus detected:	Week 24: Median: (scope): 697 (1000-1635) Week 48: Median: (coverage	No cases of virologic failure observed	All patients with RPV resistance reach 48 weeks of follow-up

						34 -HIV-1 RNA 1–49 copies / mL: 13 -HIV-1 RNA > 50 copies / mL: 3 Week 24: -Median HIV-1 RNA: 4.04 log10 copies / mL -virus not detected: 38 -HIV-1 RNA 1–49 c / ml: 1-HIV-1 RNA -HIV-1 RNA> 50 copies / mL: 1 Week 48: -Median HIV-1 RNA: 4.17 log10 copies / mL -virus not detected: 45 -HIV-1 RNA 1–49 copies / mL: 4 -HIV-1 RNA > 50 copies / mL: 1	): 718.5 (670–1745)		
Diaz et al, 2016	Spain	38 HIV-treated patients with multiple virologic	Prospective cohort study Duration: 36 weeks	Transition to DTG (50	N/A	HIV-1 RNA <37 copies / mL, Week 4:	Median, week 24: 633 Median, week 48:	Not reported	Not reported

		failures and resistance mutations who are on an ongoing suppressive regimen		mg QD) +RPV (25 mg QD)		38/38 (100%) HIV-1 RNA <37 copies / mL, Week 24: 33/34 (97%)	707.7 (95% CI: 591.7 to 823.6); p = 0.99		
Palacios et al, 2016	Spain	105 HIV patients switched to DTG + RPV who reached week 24 of the study	Prospective open, multicenter, uncontrolled study Duration: 24 weeks	DTG (50 mg QD) +RPV (25 mg QD)	N/A	Undetectable: 82/85 (96.5%)	average 622, p=0,008	None of the patients discontinued treatment due to side effects	Not reported
Saling et al, 2016	USA	1232 treated patients with HIV	Database analysis (EMR) Duration not reported	Switching to DTG (50 mg QD) + RPV (25 mg QD) for reasons other than regimen simplification	N/A	< 20 copies/mL: 14 (100%)	Median: 547b	Not reported	Not reported

Safety data

Adverse reactions, considered at least possibly related to DTG + RPV treatment from clinical trials (SWORD 1 and 2) and post-marketing experience are listed in the table by system-organ class and frequency. Frequencies are defined as very common (≥1 / 10), common (≥1 / 100 to

<1/10), uncommon (≥1 / 1,000 to <1/100), rare (≥1 / 10,000 to <1). / 1,000), very rare (<1 / 10,000), not known (cannot be estimated from the available data).

Table: Adverse drug reactions

System Organ Class (SOC)	**Frequency category***	**Adverse drug reactions**
Blood and lymphatic systems disorders:	common	decreased white blood cell count decreased haemoglobin decreased platelet count
Immune system disorders	uncommon	hypersensitivity (see section 4.4)
	not known	immune reconstitution syndrome
Metabolism and nutrition disorders	very common	increased total cholesterol (fasted) increased LDL cholesterol (fasted)
	common	decreased appetite increased triglycerides (fasted)
Psychiatric disorders	very common	insomnia
	common	abnormal dreams depression sleep disorders depressed mood anxiety
	uncommon	suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)
Nervous system disorders	very common	headache dizziness
	common	somnolence

Gastrointestinal disorders	very common	nausea increased pancreatic amylase diarrhoea
	common	abdominal pain vomiting flatulence increased lipase abdominal discomfort upper abdominal pain dry mouth
Hepatobiliary disorders	very common	increased transaminases (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations)
	common	increased bilirubin
	uncommon	hepatitis
	rare	acute hepatic failure**
Skin and subcutaneous tissue disorders	common	rash pruritus
Musculoskeletal and connective tissue disorders	uncommon	arthralgia myalgia
General disorders and administration site conditions	common	fatigue
Investigations	common	creatine phosphokinase (CPK) elevations

The most frequently reported adverse reactions considered to be possibly or likely related to the combined use of DTG + RPV in 513 HIV-1 infected participants in phase 3 studies were diarrhea (2%) and headache 2%).
The DEXA study did not provide safety profile data.

Real world data studies
Three of the studies found that DTG + RPV treatment reduced eGFR compared to baseline. In general, treatment with DTG + RPV is well tolerated (Saling et al, 2016; Palacios et al, 2016; Diaz et al, 2016; Capetti et al. 2016; Capetti et al, 2016).

Data on comparators

Antiretroviral drugs from different classes, currently available in Bulgaria and included in the Positive Drug List (PDL) as of April 2019 have been selected as alternatives for comparison:

- darunavir/cobicistat + emtricitabine/tenofovir disoproxil
- darunavir/cobicistat + abacavir/lamivudine
- raltegravir + abacavir/lamivudine
- raltegravir + emtricitabine/tenofovir disoproxil
- dolutegravir + emtricitabine/tenofovir disoproxil
- dolutegravir/abacavir/lamivudine

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions intended for the health care systems of other countries

There are 4 publicly available positive health technology assessments for the medicinal product, performed by government institutions for the purposes of other national health care systems: CADTH - Canadian Agency for Drugs and Technologies in (Health, Canada 2018), HAS, France (2018), IQWIG, Germany (2018) and the Scottish Medicines Consortium, Scotland (2018).

Applied analysis

The presented analysis includes comparative alternatives in line with the recommendations for treatment of HIV/AIDS, the perspective is on the paying institution, Ministry of Health, the time horizon is lifelong, the level of discounting of costs and outcomes is 3.5%. The measure of therapeutic outcome is QALY and LYG. To model the development of the disease, a combination of Markov model and a tree of therapeutic solutions has been applied.

As comparative alternative, the main groups of antiretroviral medicinal products available in Bulgaria and included in Annex 3 of the PDL were selected: DRV/c + TDF/FTC; DRV/c + ABC/3TC (two protease inhibitors and a nucleoside reverse transcriptase inhibitor PIs + PIs + NRTI); RAL + TDF/FTC; RAL + ABC/3TC (integrase inhibitor and nucleoside reverse transcriptase inhibitor IIs + NRTI) and DTG/ABC/3TC (fixed combination); DTG + TDF/ FTC (integrase inhibitor and nucleoside reverse transcriptase inhibitor IIs + NRTI). The selection complies with the guidelines of the European AIDS Clinical Society Guidelines.

The selected method for comparative evaluation of Juluca health technology is cost-benefit analysis and minimum cost analysis.

Given the similar therapeutic efficacy between the alternatives, a minimum cost analysis has been applied, and the selection of this method is based on studies SWORD-1, SWORD-2, DEXA, demonstrating non-inferior efficacy compared to current ARTs, including 2 NRTIs and third agent and based on QALY values.

As regards the secondary results, the pooled analysis shows that the mean change from baseline in CD4 + cell count was 28.0 cells/m³ in the DTG + RPV group and 22.0 cells/m³ in the CAR group. In SWORD-1, the mean change from baseline was 25.0 cells/m³ in the DTG + RPV group and 35.0 cells/m³ in the CAR group. In SWORD-2, the mean change from baseline was 29.0 cells/m³ in the DTG + RPV group and 13.0 cells/m³ in the CAR group. Cost-benefit analysis has been applied to the secondary results.

The measure of the outcome is a quality-adjusted life year (QALY). Outcomes of a published study in 2008 on the health benefits of different health conditions depending on the number of CD4 cells were borrowed.
A deterministic hybrid Markov model with a transition in health conditions has been applied. The choice of time horizon and duration of the cycle has been justified, as well as the health conditions included in the model. Input data are based on therapeutic outcomes from multicenter randomized clinical trials and from literature sources.
The outcomes show that the applied health technology is cost-effective compared to the alternatives RAL + TDF/FTC and DTG + TDF/FTC, leads to savings for a patient with HIV-1 infection compared to DTG/ABC/3TC and has a higher cost per patient with similar therapeutic efficacy compared to DRV/c + ABC/3TC, RAL + ABC/3TC.

Costs for the assessed health technology
Only direct medical costs for drug therapy with the applied health technology and comparative alternatives have been included in the analysis.

Analyses of subgroups
A group of patients with HIV infection who were on stable antiretroviral therapy for at least 6 months without a history of virologic failure and without resistance to a non-nucleoside reverse transcriptase inhibitor or integrase inhibitor has been analyzed.

Budget impact
The estimated number of patients for a five-year period is 25 for the first year, increasing to 75 in the fifth year, and the inclusion of the medicinal product is accompanied by an increase in the paying institution's budget, without taking into account framework risk-sharing agreements and patient access schemes.

Conclusion

1. **DTG/RPV treatment leads to savings for a given patient with HIV-1 infection compared to DTG/ ABC/3TC** within a one year period and for the entire time horizon.

2. Given the expected increase in the number of patients, the use of the medicinal product Juluca will **generate additional costs for the paying institution**.