A prospective, multicenter, randomized, open-label trial to assess the safety, tolerability and efficacy of dual therapy with boosted Darunavir + Dolutegravir when switching from standard of care ART in HIV-patients with sustained virological suppression: The DUALIS study

Phase IIIb Study

Test products: Darunavir® (DRV), Ritonavir® (RTV), Dolutegravir® (DTG), Kivexa®, Truvada®, Descovy®

Protocol Code Number: DUA-1463-SPI-0320-I

Eudra-CT Number: 2015-000360-34

First Patient First Visit: 31.07.2015 – Last Patient Last Visit: 01.06.2018

Sponsor
Technische Universität München (TUM), Fakultät für Medizin
Ismaninger Strasse 22
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1 Synopsis

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Name of Finished Product: Prezista® (DRV), Norvir ®(RTV), Tivicay®(DTG), Kivexa®, Truvada®, Descovy® **Name of Active Ingredient:** Darunavir monoethanolat, Ritonavir, Dolutegravir, Abacavir sulfate/Lamivudine, Tenofovirdisoproxil/Emtricitabin, Tenofovir alafenamide/Emtricitabin
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Eudra-CT Number: 2015-000360-34
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Poster presentation: MOPEB269, 10th IAS Conference on HIV Science (IAS 2019), Mexiko City, Mexiko. Oral presentation: 9. German-Austrian HIV-Congress, Hamburg, Germany. Full publication is pending and has not been submitted yet.

Study period:
Planned study period**:**
First patient first visit (FPFV): II. Quarter 2015; Last patient last visit (LPLV): II. Quarter 2017
Due to slower than anticipated recruitment, the **actual** study period was**:**
FPFV: 31.07.2015
Last patient in: 27.06.2017
LPLV: 01.06.2018
Premature termination: 15.06.2018 due to lack of recruitment

Phase: IIIb

Approvals:
After simultaneous submission to EC and Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) on 27.03.2015 and subsequent approval by EC (05.06.2015), the first amendment has been submitted (17.06.2015) before FPI due to sample size calculation and change in DSMB members (EC approval: 22.06.2015). BfArM approved first submission and first amendment on 26.06.2015. The study was thus started with the Study protocol version 1.2 from 16.06.2015. A second amendment was submitted on 15.04.2016 to both EC and BfArM (reduction of number of visits, reduction of laboratory parameters, change of inclusion and exclusion criteria: additional IMP Descovy (Emtricitabine/Tenefovir AF) accepted and reduction of required pre-ART period, extension of study period): approval EC (06.05.2016); approval BfArM (19.05.2016). In the meantime further study sites have been submitted and approved.

Study Design:

Prospective, national, multicenter, randomized, open label parallel-group, non-inferiority design. A switch strategy to investigate whether a dual therapy with Ritonavir-boosted (RTV) Darunavir (DRV) + Dolutegravir (DTG) over 48 weeks is non-inferior to a continuous standard of care therapy with RTV-boosted DRV in combination with 2 Nucleosidic Reverse Transcriptase Inhibitors (NRTIs) in HIV patients, who are at least 24 weeks prior to randomization on a stable and fully suppressive antiretroviral therapy (ART) with RTV-boosted DRV in combination with 2 NRTIs for at least 28 days prior to randomization.

Objectives:

Primary objective:

The clinical trial investigates whether a switch strategy of dual therapy with DRV/r + DTG is non-inferior with respect to HIV RNA < 50 cps/ml (ITTe analysis, FDA snapshot analysis (missing, switch or discontinuation of investigational study drugs for any reason = failure; change of NRTI backbone combination will not be classified as failure for primary endpoint analysis)) to a continuous standard of care therapy with DRV/r in combination with 2 NRTIs (ABC/3TC, F/TDF or F/TAF) over 48 weeks in HIV patients, who are on at least 24 weeks prior to randomisation of a stable and fully suppressive ART, consisting of 2 NRTI (ABC/3TC, F/TDF or F/TAF) in combination with DRV/r for a period of at least 28 days prior to randomisation (HIV RNA < 50 cps/ml and within a period of 24 weeks prior to randomisation with one accepted blip of HIV- RNA < 200 cps/ml).

Secondary objectives:

- Time to confirmed plasma viremia rebound (>50 copies/ml, confirmed by next measurement; Kaplan-Meier analysis)

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- Number (%) of patients with unconfirmed plasma viremia >50 copies/ml (“blips”)
- Number (%) of patients with HIV RNA < 50 cps/ml at week 24
- Number (%) of patients with HIV RNA < 200 cps/ml at weeks 24, 48
- Immunological response (change in CD4 cell count) at week 24 and 48
- Safety and tolerability
    - Changes in renal function (inclunding serum creatinine, CKD-EPI-, MDRD eGFR, Cystatin-C-GFR, albumin/creatinine-ratio, proteinuria and beta-2-microglobulin in serum)
    - Changes in lipids, insulin (HOMA-IR, QUICKI) resistance and glucose metabolism
    - Incidence of Grade 3-4 adverse events (AEs) and AR (CTC AE catalogue)
    - Psychological and psychosocial Assessment
- Pharmacokinetic Substudy I (PK I, 10/160 subjects in interventional arm at estimated 5 centers)
    - DTG and DRV serum levels 0, 1, 2, 4, 8, 12 hours after intake of medication; week 4
- Pharmacokinetic Substudy II (PK II, 50/160 subjects in interventional arm)
    - DTG and DRV serum levels at single time point; week 4, 12 and 24
- Self reported adherence

Number of patients (planned/analysed):
Planned: 320 patients (160 patients in interventional (dual) arm and 160 patients in control arm)
Analysed: In toal N=269 patients were enrolled in the study. The analyses involved 3 analysis sets, i.e. the safety analysis (SA) set, and the ITTe (Intention-to-treat, exposed) set and the PP (per protocol) set.
The SA set consisted of 266 patients; 3 patients had been excluded (1 patient withdraw consent before exposure to study drug and 2 screening failures, with no IMP exposure).
The ITTe set included 263 patients, namely 131 patients in the interventional arm and 132 in the control arm. Six patients (3 interventional arm, 3 control arm) had been excluded, as 1 patient withdraw consent before exposure to study drug and 2 screening failures, with no IMP exposure (these 3 patients had been also excluded from safety analyses (SA) set).
2 patients (1 interventional, 1 control) were screening failures with potential IMP exposure, but did not show up at the study center after randomization, with no further information on duration of IMP exposure could be given. One further patient was excluded from the ITTe set after randomization (he turned out to be a screening failure).
The PP set consisted of 241 patients: 28 patients had to be excluded from the PP set, including 10 patients withdrawing consent (including 1 patient with AEs), 6 patients who discontinued due to adverse events, 6 patients lost to follow-up, 5 protocol violations concerning in-/exclusion criteria and 1 discontinuation due to drug-drug interaction.

Diagnosis and criteria for inclusion:
Indication: Infectious Diseases: HIV
Inclusion criteria

1. Age ≥ 18 years
2. HIV- infection with HIV- RNA < 50 cps/ml within a period of at least 24 weeks suppressive ART prior to randomization, with one accepted blip of HIV- RNA < 200 cps/ml and well-tolerated antiretroviral therapy: consisting of 2 NRTI (ABC/3TC, F/TDF or F/TAF) in combination with DRV/r for a period of at least 28 days prior to randomization.
3. No known genotypic DRV- or integrase inhibitor-related HIV resistance
4. Signed written informed consent

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5. Documented negative HLA B*57:01 (only in case of Abacavir-containing ART)
6. A female subject may be eligible to enter and participate in the study if she:
   - is of non-child-bearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥ 45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy or
   - is of child-bearing potential with a negative pregnancy test at both screening and Day 1 and agrees to use one of the following methods of contraception to avoid pregnancy:
7. Complete abstinence from penile-vaginal intercourse from 2 weeks prior to administration of IMP, throughout the study, and for at least 2 weeks after discontinuation of all study medications
8. Double barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide)
9. Male partner sterilization confirmed prior to the female subject's entry into the study, and this male is the sole partner for that subject
10. Approved hormonal contraception without DRV/r interactions and a barrier method
11. Any other method with published data showing that the expected failure rate is <1% per year. Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of IMP.

Diagnosis and criteria for exclusion:
Exclusion Criteria:

1. Pregnant women and nursing mothers
2. Chronic HBV infection (HBsAg positive); known anti-HBsAb > 10 IU/ml within the last 36 months or a history of infection with known anti-HBcAb positive AND anti-HBsAb > 10 IU/ml AND HBsAg-loss are not exclusionary)
3. Any evidence of a Center for Disease Control and Prevention (CDC) Category C disease at screening, except cutaneous Kaposi's sarcoma not requiring systemic therapy. Historical or current CD4 cell counts < 200 cells/mm3 or historic CDC C diseases are not exclusionary
4. History or presence of allergy to the study drugs or their components
5. Subject has creatinine clearance of <50 mL/min by MDRD eGFR calculation
6. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN), OR ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin)
7. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
8. Subjects with severe hepatic impairment (Class B or greater) as determined by Child-Pugh classification
9. Anticipated need for interferon-based Hepatitis C virus (HCV) therapy during the study
10. Participation in other interventional clinical trials at the same time
11. Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
12. Persons held in an institution by legal or official order
13. Imprisoned people, people requiring in-house treatment for psychiatric disorders or people who are unable to give informed consent

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Study treatment:
Interventional arm:
DRV 800 mg tablets (Prezista®), oral, once daily and
RTV 100 mg tablets (Norvir®), oral, once daily and
DTG 50 mg tablets (Tivicay®), oral, once daily
Control arm:
DRV 800 mg tablets (Prezista®), oral, once daily and
RTV 100 mg tablets (Norvir®), oral, once daily
in combination with
Tenofovir disoproxil / emtricitabine 245/200 mg (Truvada®), oral, once daily
or
DRV 800 mg tablets (Prezista®), oral, once daily and
RTV 100 mg tablets (Norvir®), oral, once daily
in combination with
Abacavir / Lamivudine 600/300 mg (Kivexa®), oral, once daily
or in combination with
Tenofovir alafenamid / emtricitabine 10/200 mg (Descovy®); oral; once daily

Batch No.:
DRV: DUALIS/201529; DUALIS/201536; DUALIS/201539; DUALIS/ 201541; DUALIS/ 201549; DUALIS/ 201635; DUALIS/ 201707
RTV: DUALIS/201530; DUALIS/ 201537; DUALIS/ 201551; DUALIS/ 201637; DUALIS/ 201709; DUALIS/ 201710;
DTG: DUALIS/ 201530; DUALIS/ 201550; DUALIS/ 201636; DUALIS/ 201708; DUALIS/ 201711;
IMPs have been first released and distributed by pharmacy of Heidelberg.

Duration of treatment:
Duration of treatment per patient in both groups: 48 weeks

Blinding:
Not applicable

Safety assessments
Adverse event (AE); Serious AE (SAE); Suspected Unexpected Serious Adverse Reactions (SUSAR);

Interim analyses
An interim analysis of number (%) of patients with HIV RNA < 50 cps/ml at week 24 will be performed when patient 160 completed week 24. The interim analysis has been provided to the DSMB and has been used in addition to safety data for overall risk benefit assessment. The recommendation was given to continue with the study.

Statistical methods:
Sample size calculation
The sample size calculation is based on the primary objective of the trial i.e. assessment of non-inferiority of a dual therapy with boosted DRV + DTG compared with boosted DRV + 2 NRTIs over 48-weeks with respect to HIV RNA < 50 cps/ml.
The following assumptions were made:

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(1) Virological efficacy rate of 90% in the standard combination arm (boosted DRV + 2 NRTIs) based on published data. Assumption of virological efficacy of 90% for boosted DRV + DTG, based on DTG-based ART in therapy naïve patients.
(2) Non-inferiority margin of 10%; this threshold deemed clinically appropriate by a panel of clinicians experienced in the management of HIV infection and is used in clinical trials evaluating non-inferiority of investigational regimens in comparison to standard-of-care regimens.
(3) Overall two-sided 95% confidence interval
(4) At least 80% power to detect non-inferiority.
(5) The O'Brien-Fleming adjustment with alpha1=0.01 and alpha2=0.04519 (overall alpha of 5%) is used for accounting for the interim analysis. This changes the confidence interval for the interim analysis to 99% and for the final analysis to 95.481%.

Under these assumptions 292 analyzable patients are required in the study (146 per treatment group). Allowing for approximately 9% loss to follow-up, a total of 320 patients will be enrolled (160 per treatment group).

Randomisation: All patients have been be randomized 1:1 after study inclusion

Analysis sets
The intention-to-treat (ITT) population consists of all trial subjects enrolled into the trial and randomized with at least a baseline visit and at least one dose of study drug.
The per-protocol (PP) population consists of all all trial subjects who were treated according to protocol. Patients with major protocol violations have been excluded from the PP analysis due to decision at data review meeting.
The safety population consists of all trial subjects who received at least one dose of IMP.
All efficacy analyses were performed "as randomized" on the ITT population and "as treated" on the PP populations. The ITT population was the primary analysis population. All safety analyses were based on the safety population. Safety analysis was performed "as treated."

Efficacy Analyses
The primary efficacy analysis was performed on the ITTe set. Secondary efficacy analysis involved the analysis of the PP set in a non-confirmative manner.

Safety Analyses
Adverse Events and Serious Adverse Events were classified according to CTCAE V. 4.0 and coded according to MedDRA V. 18.0 English. Frequencies of observed AE and SAE are presented by System Organ Class and Prefered Term in both study groups. Distributions of AE intensity and expected relation to study medication are presented.

Summary Results, Conclusions:

Patient demographics and patient disposition
In total 269 patients were included in the study (FPFV: 31.07.2015 – LPI: 27.06.2017).
The age range in this clinical trial was between 21 and 73 (median 48) years; 26 (9.9 %) females and 237 (90.1 %) males were included into the study. 119 of the interventonal group (reason for premature discontinuation: 6 adverse events, 2 lost to FU, 4 withdraw of consent) and 122 of the control group (reason for premature discontinuation: 1 adverse events, 5 lost to FU, 4 withdraw of consent) completed week 48.

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Compliance
Protocol Violation:
572 protocol violations (PV) were reported in 183 patients. 563 of them were classified as minor (mainly change in visit timeframe: 158 PV or missing laborytory values). 9 PV (in 8 patients) were classified as major: 5 of the 8 patients belong to the interventional arm, 3 patients belong to the control arm. Five patients with major PV were excluded from the PP and ITT set.

Primary Endpoint
Number (%) of patients with HIV RNA < 50 cps/ml at week 48 (ITTe set):

Number (%) of patients with HIV RNA <50 copies/ml at week 48-ITT	2DR		3DR		Total	
	N	%	N	%	N	%
HIV RNA <50 copies/ml	113	86.3	116	87.9	229	87.1

Mean difference (proportion (2DR) - proportion (3DR)): -0.0162
95.48% CI (based on the adjusted alpha-level accounting for the interim analysis at week 24): -0.0991 - 0.0667
Non-inferiority has been demonstrated.

Secondary Endpoints
Number (%) of patients with HIV RNA < 50 cps/ml at week 48 (PP set):

Number (%) of patients with HIV RNA <50 copies/ml at week 48 - PP set	2DR		3DR		Total	
	N	%	N	%	N	%
HIV RNA <50 copies/ml	113	95.8	116	95.1	229	95.4

Mean difference (proportion (2DR) - proportion (3DR)): 0.0068
95% CI: -0.0460 - 0.0597

Time to confirmed plasma viremia rebound ≥50 copies/ml (ITTe set):

Study arm	Until week	Number of patients with confirmed HIV RNA ≥50 copies/ml	Kaplan-Meier estimates of confirmed HIV RNA ≥50 copies/ml [%]
2DR	24	1	0.8
2DR	48	2	1.6
3DR	24	2	1.5
3DR	48	4	3.1

Log-rank test P=0.4227

Number (%) of patients with unconfirmed plasma viremia ≥50 copies/ml ('blips') - ITTe set:

Number (%) of patients with unconfirmed plasma viremia ≥50 copies/ml ('blips') -	2DR	3DR	Total

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ITTe set

	N	%	N	%	N	%
At least one plasma viremia ≥50 copies/ml	19	15.0	20	15.5	39	15.2
No blips	108	85.0	109	84.5	217	84.8
Total	**127**	**100.0**	**129**	**100.0**	**256**	**100.0**

Fisher's exact test P=1.0000
Annotation (SAP section 8.3): Each subject will only be counted once and any repetitions of HIV RNA ≥50 copies/ml will be ignored.

Number (%) of patients with HIV RNA < 50 cps/ml at week 24
ITTe set: 117 patients in the 2 DR arm (89.3%) and 116 patients in the 3DR arm (87.9%).Mean difference (proportion (2DR) - proportion (3DR)): 0.0220
95% CI: -0.0537 - 0.0976
PP set: 115 patients in the 2 DR arm (96.6%) and 112 patients in the 3DR arm (93.3%). Mean difference (proportion (2DR) - proportion (3DR)): 0.0331
95% CI: -0.0221 - 0.0882

Number (%) of patients with HIV RNA < 200 cps/ml at weeks 24, 48
ITTe set-week 24: 121 patients in the 2 DR arm (92.4%) and 122 patients in the 3DR arm (92.4%).Mean difference (proportion (2DR) - proportion (3DR)): 0.0071
95% CI: -0.0555 - 0.0696
ITTe set-week 48: 118 patients in the 2 DR arm (90.1%) and 121 patients in the 3DR arm (91.7%). Mean difference (proportion (2DR) - proportion (3DR)): 0.0071
95% CI: -0.0555 - 0.0696
PP set-week 24: 118 patients in the 2 DR arm (99.2%) and 118 patients in the 3DR arm (98.3%). Mean difference (proportion (2DR) - proportion (3DR)): 0.0083
95% confidence interval: -0.0199 - 0.0364
PP set-week 48: 118 patients in the 2 DR arm (100%) and 121 patients in the 3DR arm (99.2%)

Immunological response (change in CD4 cell count) at week 24 and 48

Change in absolute CD4 cell count from baseline [cells/µl]-ITT	Visit	N	Mean	SD
2DR	Week 24	122	25.2	172.8
2DR	Week 48	124	31.3	165.1
3DR	Week 24	125	-9.8	137.9
3DR	Week 48	121	23.9	138.6

Change in absolute CD4 cell count from baseline [cells/µl]-PP	Visit	N	Mean	SD
2DR	Week 24	119	22.3	173.8
2DR	Week 48	118	30.8	168.0
3DR	Week 24	121	-7.7	137.6
3DR	Week 48	119	23.2	139.6

Changes in renal function
Change in serum creatinine:

Change in serum creatinine from baseline [mg/dl]	Visit	N	Mean	SD
2DR	Week 24	122	0.1	0.2
2DR	Week 48	125	0.1	0.1

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3DR	Week 24	127	0.0	0.1
3DR	Week 48	125	0.0	0.1

Cange in CKD-EPI- eGFR

Change in Creatinine-CKD-EPI-eGFR from baseline [ml/min/1.73 m²]; Equation 2009	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	122	-6.7	13.3
2DR	Week 48	125	-7.9	13.5
3DR	Week 24	127	-1.2	11.5
3DR	Week 48	125	-1.2	11.6

Change in MDRD eGFR

Change in MDRD-eGFR from baseline [ml/min/1.73 m²]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	122	-7.1	15.0
2DR	Week 48	125	-7.8	15.5
3DR	Week 24	127	-1.2	14.7
3DR	Week 48	125	-0.8	14.6

Change in Cystatin-C-GFR

Change in cystatin C [mg/l] from baseline	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	79	-0.0	0.1
2DR	Week 48	77	-0.0	0.1
3DR	Week 24	75	-0.0	0.1
3DR	Week 48	77	0.0	0.1

Change in urine albumin/creatinine-ratio (proteinurea)

Change in albumin/creatinine-ratio from baseline [mg/g]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	79	5.4	123.8
2DR	Week 48	77	-4.0	30.1
3DR	Week 24	87	-8.2	207.7
3DR	Week 48	85	-5.5	98.0

Change in beta-2-microglobulin in serum

Change in beta-2-microglobulin in serum [mg/l]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	66	-0.1	0.6
2DR	Week 48	68	-0.2	0.6
3DR	Week 24	71	0.0	0.4
3DR	Week 48	71	0.0	0.4

Changes in lipids

Change in total cholesterol from baseline [mg/dl]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	121	21.4	29.9
2DR	Week 48	124	20.2	31.2
3DR	Week 24	124	1.4	26.8

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3DR	Week 48	122	1.7	34.0

Change in HDL cholesterol from baseline [mg/dl]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	120	5.2	10.3
2DR	Week 48	120	5.5	11.5
3DR	Week 24	120	-1.4	14.2
3DR	Week 48	120	-1.8	13.0

Change in LDL cholesterol from baseline [mg/dl]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	120	12.9	26.5
2DR	Week 48	120	14.1	25.8
3DR	Week 24	119	-0.5	33.7
3DR	Week 48	120	3.5	29.1

Change in triglycerides from baseline [mg/dl]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	121	19.7	95.7
2DR	Week 48	124	17.4	124.1
3DR	Week 24	123	20.8	108.7
3DR	Week 48	121	18.1	123.7

Change in insulin (HOMA-IR, QUICKI) resistance and glucose metabolism

Change in Homeostatic model assessment (HOMA) insulin resistance (IR) from baseline	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	50	0.2	2.1
2DR	Week 48	51	0.9	3.7
3DR	Week 24	58	-0.2	4.9
3DR	Week 48	61	0.1	4.6

Change in Quantitative insulin sensitivity check index (QUICKI) from baseline	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	50	-0.0	0.0
2DR	Week 48	51	-0.0	0.0
3DR	Week 24	58	0.0	0.0
3DR	Week 48	61	0.0	0.0

Change in fasting glucose from baseline [mg/dl]	**Visit**	**N**	**Mean**	**SD**
2DR	Week 24	84	-0.6	20.1
2DR	Week 48	89	3.4	18.8
3DR	Week 24	97	6.0	29.0
3DR	Week 48	96	4.5	27.1

Incidence of Grade 3-4 adverse events (AEs) and AR (CTC AE catalogue)
Cumulative incidence of grade 3-4 (serious) adverse events (CTCAE catalogue)
(Cumulative incidence is calculated by the number of new grade 3-4 (serious) adverse events until 48 week divided by the number of subjects at risk in the SA set.)
2DR: 11/133 (8.3%)

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3DR: 6/133 (4.5%)
Cumulative incidence of (serious) adverse reactions (AR)
(Cumulative incidence is calculated by the number of new (serious) adverse reactions until 48 week divided by the number of subjects at risk in the SA set.)
2DR: 34/133 (25.6%)
3DR: 10/133 (7.5%)

Psychological and psychosocial Assessment:
Health-related quality of life (HRQoL) were collected by using three standardized self reporting questionnaires. Hereby, 14 items which focus on general and mental health (Hospital Anxiety and Depression Scale (HADS)) and 30 items measuring HRQOL (MOS-HIV) were assessed. Sociodemographic data, the Hospital Anxiety and Depression Scale (HADS-HIV) and Medical Outcomes Study HIV Health Survey (MOS-HIV) were descriptiley assessed (Table 1).

In regards to the psychosocial assessment, the Hospital Anxiety and Depression Score was applied over all four study visits (Baseline, Week 4, 24 and 48). Furthermore HIV-related quality of life was assessed by the MOS-HIV questionnaire. The intervention group and the control group did not differ in any of the dimensions measured by the HADS or the MOS-HIV in Week 24. Nevertheless, at Baseline there was a cross-sectional highly significant difference in the dimension „Mental Health“ (p=0.002), as well as a significant difference in the dimension social functioning (p=0,019). In Week 4 the HADS score „anxiety“ differed in the two groups (p=0,020) as well as the dimension „Mental Health“ (p=0,014). In week 48, there was a cross-sectional highly significant difference in the dimension „Mental Health“ (p=0.038).

Pharmacokinetic Substudy I (PK I, 10/160 subjects in interventional arm at estimated 5 centers)

- DTG and DRV serum levels 0, 1, 2, 4, 8, 12 hours after intake of medication; week 4

Ten subjects (7 males, 3 females) with a median (IQR) age of 46 (37-50) years, body mass index (BMI) of 24.6 (23.2-25.2), HIV RNA of 39 (19-44) copies/mL, and CD4 cell count of 715 (450-860) cells/µL at the baseline visit and a CD4 nadir of 60 (18-323) cells/µL were enrolled.

Concerning pharmacokinetic analysis, 9 out of 10 patients had detectable DTG and DRV plasma levels prior to their intake (C_{trough}). One patient (a 50-year old man) had undetectable DRV C_{trough} and very low DTG C_{trough} levels. However, after direct observation of drug intake, DTG and DRV levels were within expected ranges without evidence of malabsorption.

Overall, median (IQR) C_{trough} levels were 637 (483-923) ng/mL for DTG and 1245 (575-1818) ng/mL for DRV. Maximum levels measured were 3427 (2964-4048) ng/mL for DTG and 6170 (5708-8950) ng/mL for DRV. Median levels after 1, 2, 4, 8, and 12 h were 3053 ng/mL, 3020 ng/mL, 2679 ng/mL, 1846 ng/mL, and 1359 ng/mL for DTG and 5271 ng/mL, 6125 ng/mL, 4771 ng/mL, 2699 ng/mL, and 2199 ng/mL for DRV, respectively. C_{trough} remained 4 to 17-fold above the protein-adjusted IC90 (64 ng/mL) for DTG and 1 to 22-fold above the protein-adjusted EC_{90} (200 ng/mL) for DRV (excluding the patient with undetectable DRV and low DTG C_{trough} levels). Median (IQR) AUC_{12} for DTG was 26,09 (22,441-28,459) ng·h/mL and for DRV 49,920 (36,729-56,234) ng·h/mL. DTG AUC_{24}, C_{max}, and C_{min} decreased 22%, 11%, and 38%, respectively.

Pharmacokinetic Substudy II (PK II, 50/160 subjects in interventional arm)

- DTG and DRV serum levels at single time point; week 4, 12 and 24

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Plasma concentration of DTG [ng/ml] (PK II/2DR study arm)	**N**	**Mean**	**SD**
Week 4	54	1683.3	1291.5
Week 12	55	1862.8	1359.6
Week 24	53	1648.6	1162.5

Plasma concentration of DRV [ng/ml] (PK II/2DR study arm)	**N**	**Mean**
Week 4	54	2189.9
Week 12	55	2408.4
Week 24	53	2300.1

Number (%) of patients with HIV RNA <50 copies/ml (PK II/2DR study arm)

Visit	**Categories**	**N**	**%**
Week 4	<50 copies/ml	53	98.1
Week 4	**Total**	**54**	**100.0**
Week 12	<50 copies/ml	52	96.3
Week 12	**Total**	**54**	**100.0**
Week 24	<50 copies/ml	52	96.3
Week 24	**Total**	**54**	**100.0**

Self reported adherence
In the 2 DR arm, a mean of 87.6 % of the patients who reported intake of DTG were compliant, for the intake of Darunavir a mean of 87.5 % were compliant and for Ritonavir 87.5 % were compliant. In the 3 DR arm a mean of 91.7% of the patients who reported intake of Darunavir were compliant, for the intake of Ritonavir a mean of 92.6 % were compliant and for 2NRTI 93.1 % were compliant.

Safety assessments
Development Safety Update Reports (DSUR) were provided to BfArM and EC for the following periods: DSUR 1: 31.07.2015-26.06.2016; DSUR 2: 27.06.2016-26.06.2017; DSUR 3: 27.06.2017-26.06.2018.

Data Safety Monitoring Board (DSMB):
A group of independent experts formed an independent Data Safety Monitoring Board (DSMB). The DSMB independently reviewed the data during study duration. The board was to review the data at least semiannually to assess the safety profile and an interim analysis concerning the endpoint (HIV RNA <50 cps/mL) at week 24.
No change in risk benefit ratio was assessed by the DSMB during the course of the study.

Adverse Events (AEs)
A total of **621** AE (306 in interventional arm, 315 in control arm) were reported in 263 patients, who experienced at least one AE (see Table 2). 7 AEs in the control group and 26 AEs in the interventional group were deemed related or possibly related to treatment administered (see Table 3).

Serious AEs (SAEs)

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A total of 21 SAE reports were sent - including 26 SAE diagnoses in **14/263** patients (7 in interventional, 7 in control arm) (see Table 4, 5).

Suspected Serious Adverse Reactions (SARs)
One SAE was related to the IMP of interventional arm. One patient had an episode: a febrile neutropenia with relation to DRV/RTV. Date of resulation after discontinuation of DRV/r (Prezista/Norvir) was reported 6 days later.

Suspected Unexpected Serious Adverse Reactions (SUSARs)
The assessment of expectedness was determined by referring to the respective IBs. No SUSAR were reported in the study.

Overall Conclusion
Switching to 2DR (DTG plus bDRV) was non-inferior to continuing 3DR with high rates of maintained viral suppression and comparable rates of AEs even in subgroups.

Date Clinical Study Report:

Date: **Version:** Final 1.0 11.06.2019
Amended V1.0 18.05.2020

Appendix:

Table 1: Psychological and psychosocial Assessment: Sociodemographic data, the Hospital Anxiety and Depression Scale (HADS-HIV) and Medical Outcomes Study HIV Health Survey (MOS-HIV) descriptiley assessed

Item	Visit	2DR	3DR	p-value
HADS Anxiety	Baseline	12.328	13.414	0.101
HADS Depression	Baseline	13.359	13.534	0.659
Physical function	Baseline	86.940	87.311	0.895
Role function	Baseline	86.194	86.364	0.966
Mental health	Baseline	69.248	76.409	**0.002**
Energy	Baseline	62.481	67.214	0.058
Health distress	Baseline	78.788	82.710	0.115
Cognitive function	Baseline	77.669	78.902	0.583
General Health perception	Baseline	62.127	65.720	0.148
Pain	Baseline	80.299	83.333	0.330
Social functionong	Baseline	83.433	90.000	**0.019**
Quality of Life Health	Baseline	69.737	73.674	0.079
Health transition	Baseline	38.993	39.773	0.752
HADS Anxiety	Week 4	12.405	14.107	**0.020**
HADS Depression	Week 4	13.905	13.679	0.568
Physical function	Week 4	86.450	86.873	0.890
Role function	Week 4	86.382	83.850	0.541
Mental health	Week 4	71.260	77.451	**0.014**
Energy	Week 4	65.366	67.566	0.418
Health distress	Week 4	80.854	85.619	0.051
Cognitive function	Week 4	78.943	80.885	0.395
General Health perception	Week 4	62.195	65.044	0.295
Pain	Week 4	79.512	83.717	0.219
Social functionong	Week 4	85.366	90.000	0.098
Quality of Life Health	Week 4	68.293	72.788	0.069
Health transition	Week 4	43.293	43.080	0.928
HADS Anxiety	Week 24	12.695	13.352	0.374
HADS Depression	Week 24	13.641	13.844	0.610
Physical function	Week 24	85.890	85.133	0.812
Role function	Week 24	86.229	84.677	0.708
Mental health	Week 24	71.453	73.710	0.377
Energy	Week 24	64.828	62.840	0.478
Health distress	Week 24	82.500	83.750	0.624
Cognitive function	Week 24	80.636	77.702	0.205
General Health perception	Week 24	64.195	64.600	0.892
Pain	Week 24	82.881	80.320	0.452

Social functionong	Week 24	86.496	87.258	0.788
Quality of Life Health	Week 24	70.551	71.600	0.689
Health transition	Week 24	42.161	44.758	0.318
HADS Anxiety	Week 48	12.825	14.180	0.051
HADS Depression	Week 48	13.407	13.975	0.151
Physical function	Week 48	83.604	86.295	0.412
Role function	Week 48	84.350	84.426	0.986
Mental health	Week 48	69.545	75.174	**0.038**
Energy	Week 48	63.811	65.042	0.667
Health distress	Week 48	80.574	83.583	0.247
Cognitive function	Week 48	78.667	80.702	0.393
General Health perception	Week 48	64.024	62.705	0.634
Pain	Week 48	78.374	83.607	0.112
Social functionong	Week 48	86.179	87.869	0.560
Quality of Life Health	Week 48	68.033	72.107	0.135
Health transition	Week 48	43.182	45.208	0.441

Table 2: Adverse events (per event) - MedDRA System Organ Class (SOC) and MedDRA Preferred Term (PT)

(Serious) Adverse events (per event) - MedDRA System Organ Class (SOC) and MedDRA Preferred Term (PT)		2DR		3DR		Total	
MedDRA SOC	**MedDRA PT**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders	Bicytopenia	0	0.0	1	0.3	1	0.2
Blood and lymphatic system disorders	Bone marrow failure	0	0.0	1	0.3	1	0.2
Blood and lymphatic system disorders	Febrile neutropenia	1	0.3	0	0.0	1	0.2
Blood and lymphatic system disorders	Iron deficiency anaemia	0	0.0	2	0.6	2	0.3
Blood and lymphatic system disorders	Leukocytosis	0	0.0	1	0.3	1	0.2
Blood and lymphatic system disorders	Lymphadenopathy	2	0.7	0	0.0	2	0.3
Cardiac disorders	Angina pectoris	2	0.7	1	0.3	3	0.5
Cardiac disorders	Cardiovascular disorder	1	0.3	0	0.0	1	0.2
Cardiac disorders	Myocardial infarction	0	0.0	1	0.3	1	0.2
Ear and labyrinth disorders	Deafness	1	0.3	0	0.0	1	0.2
Ear and labyrinth disorders	Tinnitus	0	0.0	1	0.3	1	0.2
Ear and labyrinth disorders	Vertigo	0	0.0	1	0.3	1	0.2
Endocrine disorders	Hypothyroidism	1	0.3	0	0.0	1	0.2
Eye disorders	Conjunctivitis allergic	0	0.0	1	0.3	1	0.2
Eye disorders	Eye movement disorder	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Abdominal distension	1	0.3	0	0.0	1	0.2
Gastrointestinal disorders	Abdominal pain	3	1.0	1	0.3	4	0.6
Gastrointestinal disorders	Abdominal pain lower	1	0.3	0	0.0	1	0.2
Gastrointestinal disorders	Abdominal pain upper	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Anal fissure	2	0.7	1	0.3	3	0.5
Gastrointestinal disorders	Anal pruritus	0	0.0	2	0.6	2	0.3
Gastrointestinal disorders	Anorectal disorder	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Anorectal swelling	0	0.0	1	0.3	1	0.2

Gastrointestinal disorders	Chronic gastritis	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Colitis	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Diarrhoea	13	4.2	14	4.4	27	4.3
Gastrointestinal disorders	Dyspepsia	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Dysphagia	1	0.3	0	0.0	1	0.2
Gastrointestinal disorders	Enteritis	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Gastritis	2	0.7	2	0.6	4	0.6
Gastrointestinal disorders	Gastrooesophageal reflux disease	1	0.3	2	0.6	3	0.5
Gastrointestinal disorders	Haemorrhoids	1	0.3	1	0.3	2	0.3
Gastrointestinal disorders	Inguinal hernia	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Nausea	3	1.0	1	0.3	4	0.6
Gastrointestinal disorders	Oral pain	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Toothache	1	0.3	1	0.3	2	0.3
Gastrointestinal disorders	Umbilical hernia	0	0.0	1	0.3	1	0.2
Gastrointestinal disorders	Vomiting	1	0.3	5	1.6	6	1.0
General disorders and administration site conditions	Asthenia	2	0.7	0	0.0	2	0.3
General disorders and administration site conditions	Chest pain	2	0.7	0	0.0	2	0.3
General disorders and administration site conditions	Chills	1	0.3	0	0.0	1	0.2
General disorders and administration site conditions	Fatigue	0	0.0	8	2.5	8	1.3
General disorders and administration site conditions	Oedema peripheral	2	0.7	0	0.0	2	0.3
General disorders and administration site conditions	Pyrexia	4	1.3	3	1.0	7	1.1
Hepatobiliary disorders	Cholelithiasis	1	0.3	0	0.0	1	0.2
Immune system disorders	Seasonal allergy	0	0.0	1	0.3	1	0.2
Infections and infestations	Abdominal abscess	1	0.3	0	0.0	1	0.2
Infections and infestations	Acarodermatitis	2	0.7	0	0.0	2	0.3
Infections and infestations	Acute hepatitis C	2	0.7	2	0.6	4	0.6
Infections and infestations	Acute sinusitis	1	0.3	0	0.0	1	0.2
Infections and infestations	Acute tonsillitis	2	0.7	0	0.0	2	0.3
Infections and infestations	Amoebiasis	0	0.0	1	0.3	1	0.2
Infections and infestations	Anal chlamydia infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Anorectal infection bacterial	0	0.0	1	0.3	1	0.2
Infections and infestations	Appendicitis	1	0.3	0	0.0	1	0.2
Infections and infestations	Balanitis candida	0	0.0	1	0.3	1	0.2
Infections and infestations	Bronchitis	11	3.6	4	1.3	15	2.4
Infections and infestations	Bronchitis viral	0	0.0	1	0.3	1	0.2
Infections and infestations	Chlamydial infection	0	0.0	2	0.6	2	0.3
Infections and infestations	Chronic hepatitis C	1	0.3	0	0.0	1	0.2
Infections and infestations	Conjunctivitis	3	1.0	4	1.3	7	1.1
Infections and infestations	Corynebacterium infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Cystitis	1	0.3	0	0.0	1	0.2
Infections and infestations	Diverticulitis	1	0.3	0	0.0	1	0.2
Infections and infestations	Epididymitis	2	0.7	0	0.0	2	0.3
Infections and infestations	Erythema migrans	0	0.0	1	0.3	1	0.2
Infections and infestations	Febrile infection	0	0.0	2	0.6	2	0.3
Infections and infestations	Folliculitis	0	0.0	1	0.3	1	0.2
Infections and infestations	Fungal infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Fungal skin infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Gastroenteritis	4	1.3	8	2.5	12	1.9
Infections and infestations	Gastroenteritis viral	1	0.3	1	0.3	2	0.3

Infections and infestations	Genital herpes	5	1.6	0	0.0	5	0.8
Infections and infestations	Genitourinary tract gonococcal infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Gonorrhoea	2	0.7	5	1.6	7	1.1
Infections and infestations	Herpes simplex	1	0.3	0	0.0	1	0.2
Infections and infestations	Herpes virus infection	1	0.3	0	0.0	1	0.2
Infections and infestations	Herpes zoster	3	1.0	1	0.3	4	0.6
Infections and infestations	Herpes zoster infection neurological	0	0.0	1	0.3	1	0.2
Infections and infestations	Hordeolum	1	0.3	0	0.0	1	0.2
Infections and infestations	Impetigo	0	0.0	1	0.3	1	0.2
Infections and infestations	Infected dermal cyst	1	0.3	0	0.0	1	0.2
Infections and infestations	Infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Influenza	1	0.3	3	1.0	4	0.6
Infections and infestations	Laryngitis	1	0.3	0	0.0	1	0.2
Infections and infestations	Mycoplasma genitalium infection	1	0.3	0	0.0	1	0.2
Infections and infestations	Nasopharyngitis	50	16.3	46	14.6	96	15.5
Infections and infestations	Onychomycosis	1	0.3	1	0.3	2	0.3
Infections and infestations	Oral herpes	0	0.0	1	0.3	1	0.2
Infections and infestations	Oropharyngeal gonococcal infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Osteomyelitis	1	0.3	0	0.0	1	0.2
Infections and infestations	Otitis media	0	0.0	1	0.3	1	0.2
Infections and infestations	Periodontitis	0	0.0	1	0.3	1	0.2
Infections and infestations	Peritoneal abscess	1	0.3	0	0.0	1	0.2
Infections and infestations	Pharyngitis	3	1.0	2	0.6	5	0.8
Infections and infestations	Pneumonia	1	0.3	1	0.3	2	0.3
Infections and infestations	Postoperative wound infection	0	0.0	1	0.3	1	0.2
Infections and infestations	Proctitis chlamydial	2	0.7	0	0.0	2	0.3
Infections and infestations	Proctitis gonococcal	0	0.0	1	0.3	1	0.2
Infections and infestations	Proctitis mycoplasmal	0	0.0	1	0.3	1	0.2
Infections and infestations	Respiratory syncytial virus infection	1	0.3	0	0.0	1	0.2
Infections and infestations	Respiratory tract infection	0	0.0	3	1.0	3	0.5
Infections and infestations	Sinobronchitis	0	0.0	1	0.3	1	0.2
Infections and infestations	Sinusitis	1	0.3	3	1.0	4	0.6
Infections and infestations	Syphilis	3	1.0	6	1.9	9	1.4
Infections and infestations	Tinea cruris	1	0.3	0	0.0	1	0.2
Infections and infestations	Tinea pedis	0	0.0	1	0.3	1	0.2
Infections and infestations	Tinea versicolour	1	0.3	0	0.0	1	0.2
Infections and infestations	Tonsillitis	3	1.0	2	0.6	5	0.8
Infections and infestations	Upper respiratory tract infection	2	0.7	6	1.9	8	1.3
Infections and infestations	Urethritis chlamydial	0	0.0	1	0.3	1	0.2
Infections and infestations	Urethritis gonococcal	1	0.3	1	0.3	2	0.3
Infections and infestations	Urethritis mycoplasmal	0	0.0	1	0.3	1	0.2
Infections and infestations	Urinary tract infection	1	0.3	1	0.3	2	0.3
Injury, poisoning and procedural complications	Animal bite	1	0.3	1	0.3	2	0.3
Injury, poisoning and procedural complications	Bone contusion	1	0.3	0	0.0	1	0.2
Injury, poisoning and procedural complications	Clavicle fracture	0	0.0	1	0.3	1	0.2

Injury, poisoning and procedural complications	Contusion	3	1.0	3	1.0	6	1.0
Injury, poisoning and procedural complications	Coronary artery restenosis	0	0.0	1	0.3	1	0.2
Injury, poisoning and procedural complications	Epicondylitis	1	0.3	0	0.0	1	0.2
Injury, poisoning and procedural complications	Fall	1	0.3	1	0.3	2	0.3
Injury, poisoning and procedural complications	Foot fracture	0	0.0	1	0.3	1	0.2
Injury, poisoning and procedural complications	Hand fracture	0	0.0	1	0.3	1	0.2
Injury, poisoning and procedural complications	Heat stroke	0	0.0	1	0.3	1	0.2
Injury, poisoning and procedural complications	Inflammation of wound	1	0.3	0	0.0	1	0.2
Injury, poisoning and procedural complications	Joint injury	0	0.0	1	0.3	1	0.2
Injury, poisoning and procedural complications	Laceration	2	0.7	0	0.0	2	0.3
Injury, poisoning and procedural complications	Ligament injury	1	0.3	0	0.0	1	0.2
Injury, poisoning and procedural complications	Ligament sprain	1	0.3	0	0.0	1	0.2
Injury, poisoning and procedural complications	Lower limb fracture	1	0.3	0	0.0	1	0.2
Investigations	Albumin urine present	0	0.0	1	0.3	1	0.2
Investigations	Blood HIV RNA	0	0.0	1	0.3	1	0.2
Investigations	Blood chloride decreased	1	0.3	0	0.0	1	0.2
Investigations	Blood cholesterol increased	1	0.3	0	0.0	1	0.2
Investigations	Blood creatine phosphokinase increased	0	0.0	1	0.3	1	0.2
Investigations	Blood glucose	0	0.0	1	0.3	1	0.2
Investigations	Blood glucose increased	1	0.3	0	0.0	1	0.2
Investigations	Blood phosphorus increased	1	0.3	0	0.0	1	0.2
Investigations	Blood pressure increased	2	0.7	1	0.3	3	0.5
Investigations	Blood thyroid stimulating hormone increased	1	0.3	0	0.0	1	0.2
Investigations	Blood triglycerides increased	0	0.0	3	1.0	3	0.5
Investigations	C-reactive protein increased	1	0.3	1	0.3	2	0.3
Investigations	Creatinine renal clearance decreased	0	0.0	1	0.3	1	0.2
Investigations	Gamma-glutamyltransferase increased	1	0.3	0	0.0	1	0.2
Investigations	Intraocular pressure increased	1	0.3	0	0.0	1	0.2
Investigations	Weight increased	1	0.3	0	0.0	1	0.2
Investigations	White blood cells urine positive	1	0.3	0	0.0	1	0.2
Metabolism and nutrition disorders	Dyslipidaemia	1	0.3	1	0.3	2	0.3
Metabolism and nutrition disorders	Hypercholesterolaemia	1	0.3	1	0.3	2	0.3
Metabolism and nutrition disorders	Vitamin D deficiency	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Arthralgia	4	1.3	3	1.0	7	1.1
Musculoskeletal and connective tissue disorders	Back pain	8	2.6	5	1.6	13	2.1

Musculoskeletal and connective tissue disorders	Bursitis	0	0.0	2	0.6	2	0.3
Musculoskeletal and connective tissue disorders	Chest wall cyst	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Fistula	1	0.3	0	0.0	1	0.2
Musculoskeletal and connective tissue disorders	Groin pain	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Haemarthrosis	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Intervertebral disc displacement	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion	1	0.3	1	0.3	2	0.3
Musculoskeletal and connective tissue disorders	Muscle haemorrhage	1	0.3	0	0.0	1	0.2
Musculoskeletal and connective tissue disorders	Muscle spasms	2	0.7	0	0.0	2	0.3
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain	1	0.3	0	0.0	1	0.2
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Myalgia	1	0.3	3	1.0	4	0.6
Musculoskeletal and connective tissue disorders	Myosclerosis	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Osteochondrosis	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Osteoporosis	1	0.3	0	0.0	1	0.2
Musculoskeletal and connective tissue disorders	Pain in extremity	2	0.7	3	1.0	5	0.8
Musculoskeletal and connective tissue disorders	Spinal osteoarthritis	0	0.0	1	0.3	1	0.2
Musculoskeletal and connective tissue disorders	Tendinous contracture	1	0.3	0	0.0	1	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acanthoma	0	0.0	1	0.3	1	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Anogenital warts	1	0.3	1	0.3	2	0.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	0	0.0	2	0.6	2	0.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Melanocytic naevus	1	0.3	0	0.0	1	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin papilloma	1	0.3	1	0.3	2	0.3
Nervous system disorders	Carotid artery stenosis	0	0.0	1	0.3	1	0.2
Nervous system disorders	Cervicobrachial syndrome	0	0.0	2	0.6	2	0.3
Nervous system disorders	Disturbance in attention	1	0.3	0	0.0	1	0.2
Nervous system disorders	Dizziness	0	0.0	1	0.3	1	0.2
Nervous system disorders	Headache	4	1.3	8	2.5	12	1.9
Nervous system disorders	Hypertonia	0	0.0	6	1.9	6	1.0
Nervous system disorders	Hypoaesthesia	0	0.0	1	0.3	1	0.2
Nervous system disorders	Intercostal neuralgia	2	0.7	0	0.0	2	0.3
Nervous system disorders	Memory impairment	1	0.3	0	0.0	1	0.2
Nervous system disorders	Migraine	1	0.3	0	0.0	1	0.2

Nervous system disorders	Paraesthesia	1	0.3	1	0.3	2	0.3
Nervous system disorders	Sciatica	1	0.3	0	0.0	1	0.2
Nervous system disorders	Syncope	0	0.0	1	0.3	1	0.2
Nervous system disorders	Tremor	1	0.3	1	0.3	2	0.3
Nervous system disorders	Vertigo CNS origin	0	0.0	1	0.3	1	0.2
Pregnancy, puerperium and perinatal conditions	Vomiting in pregnancy	0	0.0	1	0.3	1	0.2
Psychiatric disorders	Acute stress disorder	0	0.0	1	0.3	1	0.2
Psychiatric disorders	Apathy	1	0.3	0	0.0	1	0.2
Psychiatric disorders	Depression	3	1.0	4	1.3	7	1.1
Psychiatric disorders	Insomnia	2	0.7	1	0.3	3	0.5
Psychiatric disorders	Irritability	1	0.3	0	0.0	1	0.2
Psychiatric disorders	Mental disorder	0	0.0	1	0.3	1	0.2
Psychiatric disorders	Sleep disorder	2	0.7	1	0.3	3	0.5
Renal and urinary disorders	Albuminuria	1	0.3	0	0.0	1	0.2
Renal and urinary disorders	Dysuria	2	0.7	2	0.6	4	0.6
Renal and urinary disorders	Microalbuminuria	1	0.3	0	0.0	1	0.2
Renal and urinary disorders	Pollakiuria	0	0.0	1	0.3	1	0.2
Renal and urinary disorders	Proteinuria	1	0.3	1	0.3	2	0.3
Renal and urinary disorders	Renal impairment	1	0.3	0	0.0	1	0.2
Renal and urinary disorders	Urethral discharge	0	0.0	1	0.3	1	0.2
Reproductive system and breast disorders	Balanoposthitis	0	0.0	2	0.6	2	0.3
Reproductive system and breast disorders	Breast pain	1	0.3	0	0.0	1	0.2
Reproductive system and breast disorders	Calculus prostatic	1	0.3	0	0.0	1	0.2
Reproductive system and breast disorders	Genital erythema	0	0.0	1	0.3	1	0.2
Reproductive system and breast disorders	Penile swelling	0	0.0	1	0.3	1	0.2
Reproductive system and breast disorders	Prostatitis	1	0.3	0	0.0	1	0.2
Reproductive system and breast disorders	Testicular pain	1	0.3	0	0.0	1	0.2
Reproductive system and breast disorders	Varicocele	1	0.3	0	0.0	1	0.2
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	1	0.3	0	0.0	1	0.2
Respiratory, thoracic and mediastinal disorders	Cough	2	0.7	2	0.6	4	0.6
Respiratory, thoracic and mediastinal disorders	Dysphonia	1	0.3	0	0.0	1	0.2
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	0.3	0	0.0	1	0.2
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	4	1.3	3	1.0	7	1.1
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	1	0.3	0	0.0	1	0.2
Skin and subcutaneous tissue disorders	Angioedema	1	0.3	1	0.3	2	0.3
Skin and subcutaneous tissue disorders	Dermal cyst	1	0.3	0	0.0	1	0.2
Skin and subcutaneous tissue disorders	Dermatitis acneiform	1	0.3	0	0.0	1	0.2

Skin and subcutaneous tissue disorders	Dermatitis contact	0	0.0	1	0.3	1	0.2
Skin and subcutaneous tissue disorders	Dry skin	1	0.3	0	0.0	1	0.2
Skin and subcutaneous tissue disorders	Dyshidrotic eczema	0	0.0	1	0.3	1	0.2
Skin and subcutaneous tissue disorders	Eczema	4	1.3	3	1.0	7	1.1
Skin and subcutaneous tissue disorders	Erythema	1	0.3	0	0.0	1	0.2
Skin and subcutaneous tissue disorders	Granuloma skin	0	0.0	1	0.3	1	0.2
Skin and subcutaneous tissue disorders	Hyperhidrosis	1	0.3	0	0.0	1	0.2
Skin and subcutaneous tissue disorders	Hyperkeratosis	0	0.0	1	0.3	1	0.2
Skin and subcutaneous tissue disorders	Neurodermatitis	1	0.3	0	0.0	1	0.2
Skin and subcutaneous tissue disorders	Night sweats	1	0.3	1	0.3	2	0.3
Skin and subcutaneous tissue disorders	Palmar erythema	0	0.0	1	0.3	1	0.2
Skin and subcutaneous tissue disorders	Pruritus	6	2.0	0	0.0	6	1.0
Skin and subcutaneous tissue disorders	Psoriasis	0	0.0	1	0.3	1	0.2
Skin and subcutaneous tissue disorders	Rash	3	1.0	3	1.0	6	1.0
Skin and subcutaneous tissue disorders	Skin exfoliation	1	0.3	0	0.0	1	0.2
Skin and subcutaneous tissue disorders	Skin fissures	0	0.0	1	0.3	1	0.2
Surgical and medical procedures	Endodontic procedure	1	0.3	0	0.0	1	0.2
Surgical and medical procedures	Limb operation	1	0.3	0	0.0	1	0.2
Surgical and medical procedures	Lipoma excision	0	0.0	1	0.3	1	0.2
Surgical and medical procedures	Peripheral nerve decompression	0	0.0	1	0.3	1	0.2
Surgical and medical procedures	Psychotherapy	1	0.3	0	0.0	1	0.2
Vascular disorders	Aortic calcification	0	0.0	1	0.3	1	0.2
Vascular disorders	Arteriosclerosis	1	0.3	0	0.0	1	0.2
Vascular disorders	Circulatory collapse	0	0.0	1	0.3	1	0.2
Vascular disorders	Haematoma	2	0.7	0	0.0	2	0.3
Vascular disorders	Hypertension	3	1.0	2	0.6	5	0.8
Vascular disorders	Hypertensive crisis	1	0.3	0	0.0	1	0.2
Vascular disorders	Peripheral arterial occlusive disease	1	0.3	0	0.0	1	0.2
Vascular disorders	Thrombophlebitis superficial	1	0.3	1	0.3	2	0.3
Vascular disorders	Thrombosis	1	0.3	0	0.0	1	0.2
nicht kodierbar	Keine Medikamente für 4 Tage	0	0.0	1	0.3	1	0.2
nicht kodierbar	Spanngefühl	1	0.3	0	0.0	1	0.2
nicht kodierbar	keine Medikamenteneinnahme	1	0.3	0	0.0	1	0.2
nicht kodierbar	unpurified skin	1	0.3	0	0.0	1	0.2
Total		**306**	**100.0**	**315**	**100.0**	**621**	**100.0**

Table 3: Adverse reactions (per event) - MedDRA System Organ Class (SOC)

(Serious) Adverse reactions (per event) - MedDRA System Organ Class (SOC)	2DR		3DR		Total	
	N	%	N	%	N	%
Blood and lymphatic system disorders	1	2.9	0	0.0	1	2.3
Gastrointestinal disorders	7	20.6	1	10.0	8	18.2
General disorders and administration site conditions	0	0.0	2	20.0	2	4.5
Infections and infestations	1	2.9	0	0.0	1	2.3
Investigations	4	11.8	3	30.0	7	15.9
Metabolism and nutrition disorders	1	2.9	1	10.0	2	4.5
Musculoskeletal and connective tissue disorders	3	8.8	0	0.0	3	6.8
Nervous system disorders	4	11.8	1	10.0	5	11.4
Psychiatric disorders	4	11.8	1	10.0	5	11.4
Renal and urinary disorders	0	0.0	1	10.0	1	2.3
Skin and subcutaneous tissue disorders	7	20.6	0	0.0	7	15.9
Vascular disorders	1	2.9	0	0.0	1	2.3
nicht kodierbar	1	2.9	0	0.0	1	2.3
Total	**34**	**100.0**	**10**	**100.0**	**44**	**100.0**

Table 4: Cumulative Summary Tabulation of all serious adverse events

CIOMS II Summary Tabulation

Study Short Name: Dualis / EudraCT: 2015-000360-34

Cumulative Summary Tabulation of all serious Adverse Events

System Organ Class Preferred Term	Number of events Total up to 26.06.2018
Blood and lymphatic system disorders	**2**
Lymphadenopathy	2
coronary artery disorders	**1**
Myocardial infarction	1
Gastrointestinal disorders	**3**
Anorectal disorder	1
Gastritis	1
Hemorrhoids	1
General disorders and administration site conditio	**1**
in-stent arterial stenosis	1
Hepatobiliary disorders	**1**
Cholelithiasis	1
Infections and infestations	**7**
Abdominal abscess	1
Appendicitis	1
Diverticulitis	1
Neutropenic infektion	1
Osteomyelitis	1
Peritoneal abscess	1
Postoperative wound infection	1
Injury, poisoning and procedural complications	**2**
Accident	1
Lower limb fracture	1
Musculoskeletal and connective tissue disorders	**4**
Bursitis	1
Intervertebral disc displacement	1
Intervertebral disc protrusion	1
spinal osteoarthritis	1
Nervous system disorders	**4**
Headache	1
Migraine	1
Paresthesia	1
Syncope	1
Surgical and medical procedures	**1**
Papilloma excision	1

Table 5: Summary Tabluation of all serious adverse envents (per patient)

SAE Overview Dualis / EudraCT: 2015-000360-34

Onset Date	SAE_Nr	PatientNr	Rand.	Pat.Age	Sex	SAE-Type	Status	First Recieved	Expected ?	Relationship to IMP?	SUSAR
CenterNr: 11										**Number of SAEs: 1**	
20.09.2017	110017-01	0017	Arm B	44	male	initial	closed	08.11.2017		not related	
Reaction: Disc prolaps						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	
CenterNr: 12										**Number of SAEs: 2**	
25.11.2017	120009-01	0009	Arm B	58	male	initial	closed	08.12.2017		not related	
Reaction: Myocardial infarction						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	
28.04.2017	120010-01	0010	Arm A	44	female	initial + follow-up	closed	02.05.2017	not done	not related	no
Reaction: headache and paresthesia, migraine						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	
CenterNr: 14										**Number of SAEs: 1**	
05.09.2017	140001-01	0001	Arm A	59	male	initial	closed	06.10.2017	not done	not related	no
Reaction: exstirpation of 2 lymph nodes axille right						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	
CenterNr: 11										**Number of SAEs: 1**	
20.09.2017	110017-01	0017	Arm B	44	male	initial	closed	08.11.2017		not related	
Reaction: Disc prolaps						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	
CenterNr: 12										**Number of SAEs: 2**	
25.11.2017	120009-01	0009	Arm B	58	male	initial	closed	08.12.2017		not related	
Reaction: Myocardial infarction						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	
28.04.2017	120010-01	0010	Arm A	44	female	initial + follow-up	closed	02.05.2017	not done	not related	no
Reaction: headache and paresthesia, migraine						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	
CenterNr: 14										**Number of SAEs: 1**	
05.09.2017	140001-01	0001	Arm A	59	male	initial	closed	06.10.2017	not done	not related	no
Reaction: exstirpation of 2 lymph nodes axille right						SAE-Criteria: Inpatient hospitalization or prolongation				Outcome: Recovered/Resolved	

CenterNr: 19 **Number of SAEs: 2**

11.06.2017	**190014-01**	**0014**	**Arm A**	**48**	**male**	**initial**	**closed**	**08.09.2017**	**not done**	**not related**	**no**
Reaction: acute appendicitis with peritoneal abscess					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			
24.06.2017	**190014-02**	**0014**	**Arm A**	**48**	**male**	**initial**	**closed**	**08.09.2017**	**not done**	**not related**	**no**
Reaction: abdominal wall phlegmone					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			

CenterNr: 20 **Number of SAEs: 1**

24.01.2017	**200002-01**	**0002**	**Arm A**	**68**	**male**	**initial**	**closed**	**24.01.2017**	**yes**	**related**	**no**
Reaction: Neutropenic Infection					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			

CenterNr: 22 **Number of SAEs: 3**

12.05.2017	**220020-01**	**0020**	**Arm A**	**40**	**male**	**initial**	**closed**	**29.06.2017**	**not done**	**not related**	
Reaction: Lymphknotenvergrößerung, zervikal, rechts					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			
28.07.2017	**220025_01**	**0025**	**Arm B**	**41**	**male**	**initial**	**closed**	**04.08.2017**	**not done**	**not related**	**no**
Reaction: Bursitis left elbow					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			
23.08.2017	**220025-02**	**0025**	**Arm B**	**41**	**male**	**initial**	**closed**	**08.09.2017**	**not done**	**not related**	**no**
Reaction: wound infection after surgery					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			

CenterNr: 23 **Number of SAEs: 3**

20.04.2016	**230003-01**	**0003**	**Arm B**	**47**	**male**	**initial + follow-up**	**closed**	**22.04.2016**	**not done**	**not related**	**no**
Reaction: Other specified intervertebral disc displacement					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			
10.03.2017	**230006-01**	**0006**	**Arm B**	**33**	**male**	**initial**	**closed**	**13.03.2017**	**not done**	**not related**	**no**
Reaction: Excisions of condylomata					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			
06.04.2017	**230006-02**	**0006**	**Arm B**	**33**	**male**	**initial**	**closed**	**06.04.2017**	**not done**	**not related**	**no**
Reaction: Disease of anus and rectum, unspecified					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			

CenterNr: 30 **Number of SAEs: 3**

07.03.2016	**300008-01**	**0008**	**Arm B**	**53**	**female**	**initial + follow-up**	**closed**	**09.03.2016**		**not related**	**no**
Reaction: hospitalization due to hemorrhoids, Antrumgastritis					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			
05.09.2016	**300008-02**	**0008**	**Arm B**	**54**	**female**	**initial + follow-up**	**closed**	**08.09.2016**	**no**	**not related**	**no**
Reaction: Syncope unknown origin					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved			
05.09.2016	**300008-03**	**0008**	**Arm B**	**54**	**female**	**initial**	**closed**	**17.10.2016**	**not done**	**not related**	**no**
Reaction: cervical spine protrusion					SAE-Criteria: Inpatient hospitalization or prolongation			Outcome: Recovered/Resolved with sequel			

Total Number of SAEs: 21