Study of a randomised switch to DTG/RPV in subjects with HIV RNA <50c/ml and archived K103N (Wisard study): Week 96 results

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Background

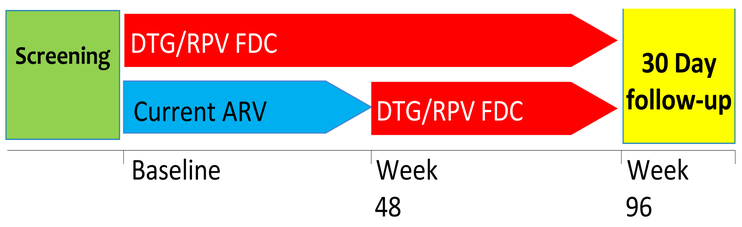
- The 2-drug regimen of DTG/RPV has been studied in switch for virologically suppressed subjects with no prior history of treatment failure or resistance (SWORD 1&2 Trials).
- Viruses with an isolated NNRTI mutation K103N retain in vitro susceptibility to RPV.
- The aim of this study is to assess the efficacy and tolerability of a dual combined therapy of Dolutegravir (DGT) 50 mg OD + Rilpivirine (RPV) 25 mg OD in virologically suppressed participants with previous virological failure with NNRTIs and documented to have had the mutation K103N
- The primary endpoint is confirmed virological failure at week 48
- This was a planned final analysis up to and including week 96.

Study Design

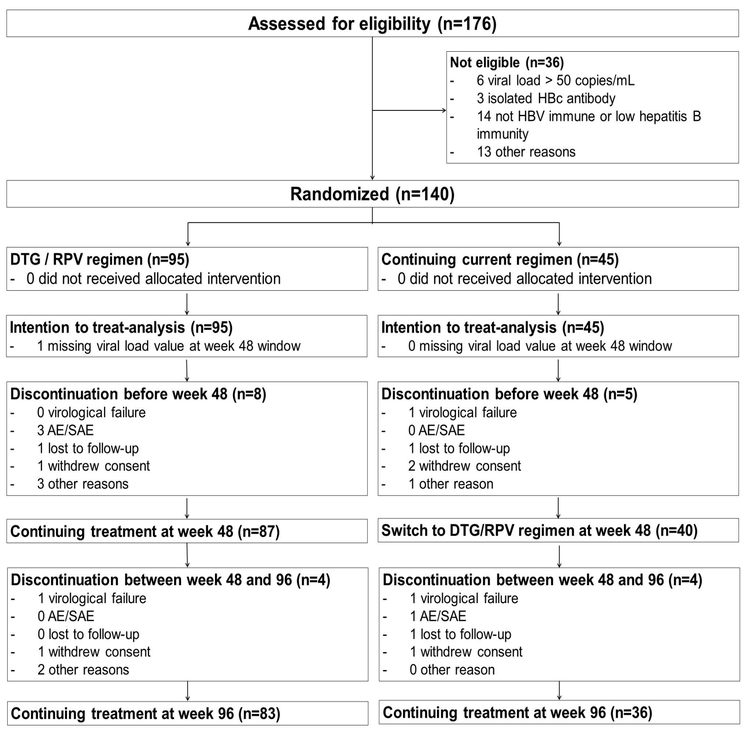
This is a 96-week European, open-label, multi-centre, exploratory study randomised 2:1 of HIV-1 participants with documented prior K103N mutation switched to DTG/RPV either immediately (DTG/RPV-I) or deferred switch until week 48 (DTG/RPV-D, previously referred to as CSR [continued suppressive regimen].
Prior PI and NRTI mutations were permitted.
Mutations known to reduce susceptibility to RPV or DTG, INSTI failure history, or contraindications to DTG or RPV were exclusions.

Experimental Arm: 100 patients switched to DTG/RPV regimen for 96 weeks

Control Arm: 50 patients continued on current regimen for 48 weeks before switching to DTG/RPV and continuing until week 96.



Study Flow Chart



Statistical Methods

- Data were summarised using median and interquartile range (IQR) for continuous variables and number and percentage for categorical variables.
- Change in laboratory parameter analyses were performed using mixed models with random intercept.
- Poisson regression model was used to compare the incidence of adverse events between the 2 groups.
- All reported p values are two-tailed with a significance level set at 5%.

Patient Demographics

	DTG/RPV-I (N=95)	DTG/RPV-D (N=45)	Total (N=140)
Age (years), median (IQR)	52 (44-58)	53 (47-56)	52 (46-57)
Gender, N(%)			
Male	79 (83.2)	35 (77.8)	114 (81.4)
Female	16 (16.8)	10 (22.2)	26 (18.6)
Child-bearing potential, N(%)	7/16 (43.8)	3/10 (30.0)	10/26 (38.5)
Ethnicity, N(%)			
White caucasian	69 (72.6)	29 (64.4)	98 (70.0)
White mixed	2 (2.1)	1 (2.2)	3 (2.1)
Asian	4 (4.2)	0 (0)	4 (2.9)
Black	7 (7.4)	7 (15.6)	14 (10)
African	3 (3.2)	3 (6.7)	6 (4.3)
Caribbean	1 (1.1)	1 (2.2)	2 (1.4)
Other	9 (9.5)	4 (8.9)	13 (9.3)
Time since HIV diagnosis (years), median (IQR)	17.1 (7.3-26.3)	22.4 (13.1-26.5)	19.7 (8.8-26.4)
Duration on ART (years), median (IQR)	16.0 (6.3-23.0)	17.7 (10.5-23.0)	16.5 (7.3-23.0)

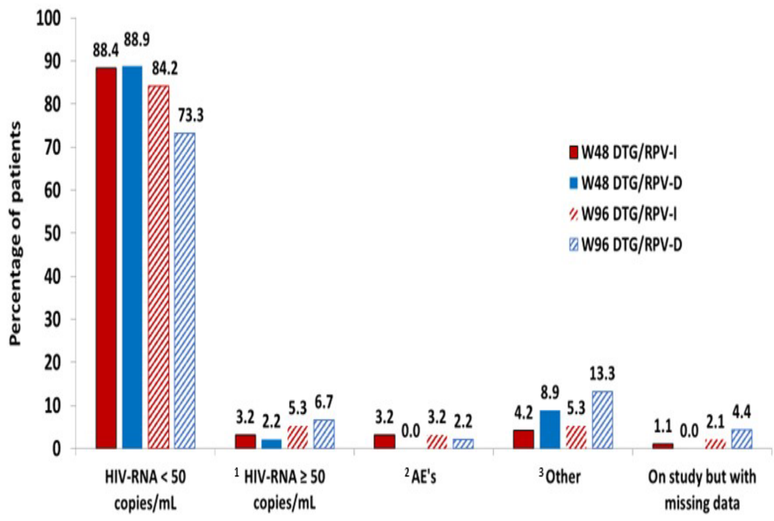
Protocol defined confirmed virological failure (CVF): week 48 and week 96

Table 1 : Protocol defined confirmed virological failure (CVF) at week 48 and week 96

	DTG/RPV-I Immediate switch at Baseline N=95		CSR[1]; DTG/RPV-D[2] Deferred switch until Week 48 N=45	
	N	% (95% CI)	N	% (95% CI)
Week 0 to Week 48	**3/95**	**3.2 (0.7-9.0)**	**1/45**	**2.2 (0.1-11.8)**
Switch to DTG/RPV occured at Week 48				
Week 0 to Week 96	**5/95**	**5.3 (1.7-11.9)**	**3/45**	**6.7 (1.4-18.3)**
Week 48 to Week 96	**2/87**	**2.3 (0.3-8.1)**	**2/40**	**5.0 (0.6-16.9)**

Confirmed Virological failure (CVF) = 2 consecutive viral loads >50 copies at least 2 weeks apart
1 - known as continued suppressive regimen (CSR) from week 0 to week 48
2 - known as the DTG/RPV deferred switch (DTG/RPV-D) from week 48 to week 96

Primary Efficacy Endpoint (week 48) and week 96 efficacy: FDA Snapshot



1 - HIV-RNA ≥ 50 copies/mL includes: patients who changed any component of background therapy to a new drug class, changed background components that were not permitted per protocol, or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48; patients who discontinued study drug or study before Week 48 for lack or loss of efficacy and patients who are equal to or above 50 copies/mL in the 48-week window.

2 - AE/SAE includes: patients who discontinued because of adverse event (AE) or death at any time point from baseline through the time window if this resulted in no virologic data during the specified window.

3 - Other Reasons includes: withdrew consent, loss to follow-up, moved, among others.

Virological Response at Week 96

	DTG/RPV-I N=95		DTG/RPV-D N=45	
	N	**% (95% CI)**	**N**	**% (95% CI)**
HIV-RNA < 50 copies/mL	80	84.2 (75.3-90.9)	33	73.3 (58.1-85.4)
HIV-RNA ≥ 50 copies/mL	5	5.3 (1.7-11.9)	3	6.7 (1.4-18.3)
• **Data in window not below 50 copies/mL**	0	0.0 (0.0-3.8)	0	0.0 (0.0-7.9)
• **Discontinued for lack of efficacy**	5	5.3 (1.7-11.9)	3	6.7 (1.4-18.3)
• **Change in backgroud therapy**	0	0.0 (0.0-3.8)	0	0.0 (0.0-7.9)
No virologic data at week 96	10	10.5 (5.2-18.5)	9	20.0 (9.6-34.6)
• **Discontinuation due to AE/SAE**	3	3.2 (0.7-9.0)	1	2.2 (0.0-11.8)
• **Discontinuation due for other reason**	5	5.3 (1.7-11.9)	6	13.3 (5.0-26.8)
• **On study but missing data in window**	2	2.1 (0.2-7.4)	2	4.4 (0.5-15.1)

Conclusions

Week 96 data continues to show that switching to DTG/RPV maintains virological suppression in the majority of participants. (84.2%)
No resistance emergence to DTG/RPV was observed.

Results

Week 48 primary endpoint confirmed virological failure (CVF) has previously been published for 140 randomised subjects in The Lancet HIV (Volume 11, Issue 3, e156 - e166) and presented at IAS 2022.

By week 96, in both the DTG/RPV-I and DTG/RPV-D arms, 2 further patients had CVF, totalling 4 CVF between week 48 and week 96.

Of the 8 CVFs from baseline through to week 96, HIV-1 RNA was <200 copies/ml in 4 participants; **only 2 samples amplified, no DTG or RPV resistance mutations observed**.

Week 96 treatment success proportion (HIV1 -RNA<50 copies/mL) by ITT FDA Snapshot was 84.2% in the DTG/RPV-I arm vs 73.3% in the DTG/RPV-D arm (+10.9% 95% CI -4 to +25.8).

DTG/RPV-I drug-related AE rate was 38 events in 22 participants (23.2%) (1 grade 3-4) between baseline/week 48; 2 events (0 grade 3-4) between week 48/96.

There were 11 drug-related AEs in 5 (12.5%) DTG/RPV-D participants (0 grade 3-4) between week 48/96. No fatalities reported.

Between week 48/96, 1 DTG/RPV-I (4 in first 48 weeks) and 1 DTG/RPV-D permanently discontinued due to AE/SAEs.

Adverse Events Week 48 - 96

Incidence of adverse events from W48 to W96

	DTG/RPV-I (N=87) 79.3 person-years		DTG/RPV-D (N=40) 34.4 person-years		P-value*	P-value**
	N of events	N of pts (%)	N of events	N of pts (%)		
Any adverse events (AEs)	141	54 (62.1)	70	28 (70.0)	0.356	0.430
Grade 1	87	36 (41.4)	46	18 (45.0)	0.278	0.704
Grade 2	38	20 (23.0)	19	12 (30.0)	0.613	0.510
Grade 3-4	6	5 (5.7)	5	5 (12.5)	0.281	0.285
Missing grade	10	7 (8.0)	0	0 (0.0)	0.0272	0.097
Drug related AEs	2	1 (1.1)	11	5 (12.5)	0.001	0.012
Drug related grade 3-4 AEs	0	0 (0.0)	0	0 (0.0)		
AE leading to the study drugs interruption (permanent or temporary)	1	1 (1.1)	3	2 (5.0)	0.094	0.233
Diarrhea	0		1			
H. Pylori in stool	1		0			
Helicobacter Infection Gut	0		1			
Sleep disorder	0		1			
Serious adverse events (SAE)	6	5 (5.7)	1	1 (2.5)	0.376	0.664
partial resection of the prostate	1		0			
prostatic adenocarcinoma	1		0			
voluntar drug intoxication	1		0			
Pachymeningitis	1		0			
Legionellosis pneumonia	1		0			
suspected rectum carcinoma	1		0			
Penile intraepithelial neoplasia	0		1			

Details of Protocol defined virological failures from week 48 to week 96

ARV at screening	Treatment group	HIV-RNA VL WK48	HIV-RNA VL WK52	HIV-RNA VL WK60	HIV-RNA VL WK72	HIV-RNA VL WK96	HIV-RNA VL at Early Termination	DRMs prior to baseline	DRMs after Viroloigcal failure
Cobicistat/Darunavir (DRV) monotherapy	DTG/RPV-D	<50 (17-DEC-2020)	111967 (04-MAR-2021) || 254 (24-MAR-2021)					**PI:** M36I, A71T, L90M **NRTI:** K70R; M184V **NNRTI:** K103N	Test failed to amplify
Darunavir (DRV)/Ritonavir (RTV)/emtricitabine and tenofovir	DTG/RPV-D	38 (13-FEB-2020)	<20 (12-MAR-2020)		128 (30-JUL-2020) || 88 (17-AUG-2020)	<20 (21-JAN-2021)		**NNRTI:** K103KN; V179T	VL< 400c/ml, no resistance test undertaken
Cobicistat/Abacavir (ABC)/Atazanavir (ATV)/Lamivudine (3TC)	DTG/RPV-I	60 (17-NOV-2020) || 0 (01-DEC-2020)			315 (06-MAY-2021) || 85 (20-MAY-2021)	<20 (04-NOV-2021)	<20 (17-JUN-2021)	**NNRTI:** K103KN	Test failed to amplify
Cobicistat, elvitegravir, emtricitabine, and tenofovir	DTG/RPV-I	39 (17-NOV-2020)	25 (17-DEC-2020)		33200 (17-MAY-2021)		33200 (17-MAY-2021)	**PI:** L33V **NNRTI:** K103N	LTFU

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