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Introduction

- In the primary analysis of the GEMINI-1 & -2 studies at Week 48, the 2-drug regimen (2DR) of dolutegravir (DTG) + lamivudine (3TC) was non-inferior to the 3-drug regimen (3DR) of DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in HIV-1–infected, ART-naïve adults, leading to the approval of the 2DR as a once-daily single-tablet regimen by the US FDA and the EMA¹
- At the 96-week analysis, non-inferiority was maintained²
- Eleven participants on 2DR and seven on 3DR met protocol-defined confirmed virologic withdrawal (CVW) criteria through Week 96
- We present a detailed description of these CVWs

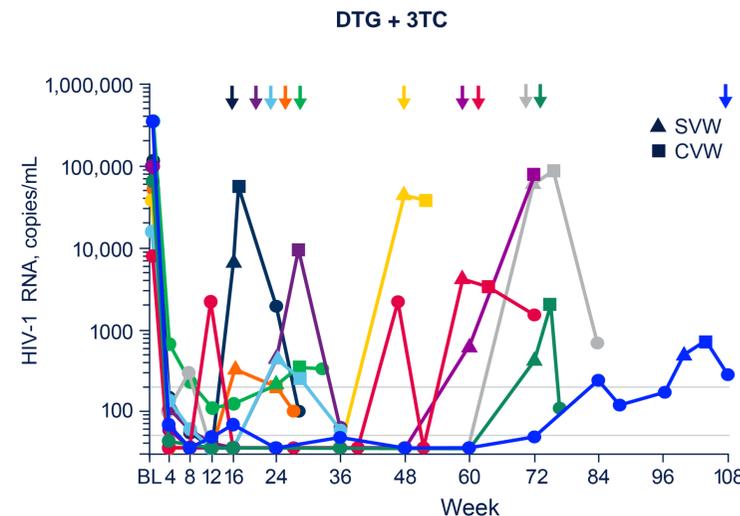
Methods

- Treatment-naïve adults were eligible if screening HIV-1 RNA viral loads (VLs) were between 1000-500,000 c/mL, HIV-1 genotype showed no major RT/PR resistance mutations, and were HBV negative
- CVW was defined as 2 consecutive VLs (suspected virologic withdrawal [SVW] result followed by CVW result) meeting virologic non-response (VL ≥200 c/mL after Week 24 or <1.0 log decline in VL by Week 12 unless HIV-1 RNA is <200 c/mL) or virologic rebound criteria (≥200 c/mL after prior confirmed suppression to <200 c/mL)
- Monogram Biosciences performed integrase and RT/PR genotypic and phenotypic resistance testing on Day 1 and SVW samples
- We evaluated CVW participant baseline (BL) VL and CD4+ cell count characteristics, resistance, VL progression, potential adherence issues, and study drug interruption (based on investigator reporting) through the study course

Results

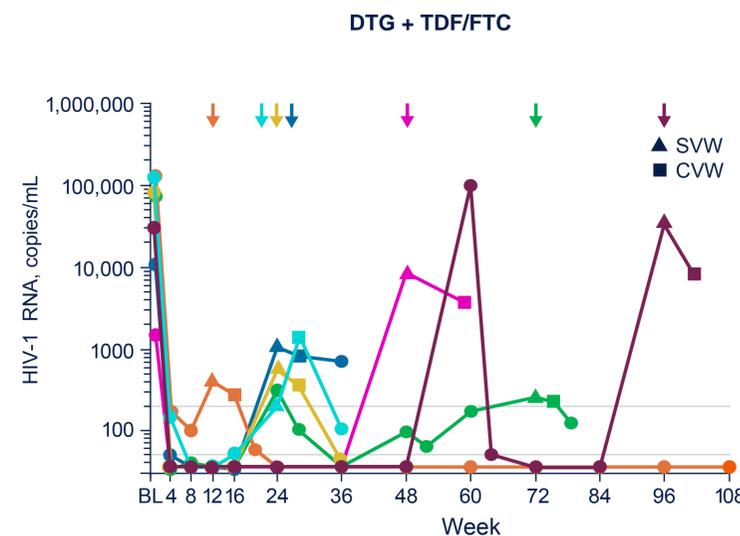
- In GEMINI-1 & -2, of 1974 participants screened, 3 (0.15%) failed screening due to transmitted M184V resistance
- Overall, 11 participants on DTG + 3TC and 7 on DTG + TDF/FTC met CVW criteria through Week 96
- All CVWs experienced virologic rebound, 2 CVWs in each arm experienced at least one VL elevation ≥200 c/mL after suppression to <50 c/mL and none of the 18 CVWs had VL blips (defined as a single VL between ≥50 to <200 c/mL with adjacent values <50 c/mL) that preceded CVW
- One DTG + 3TC participant did not achieve suppression prior to withdrawal at Week 24 (Figures 1 and 2)

Figure 1. Individual HIV-1 RNA Viral Load Progression by Visit for Participants Meeting CVW Criteria in the DTG + 3TC Arm



Arrows represent the week in which CVW occurred. The color of the arrow corresponds to the color assigned to each participant.

Figure 2. Individual HIV-1 RNA Viral Load Progression by Visit for Participants Meeting CVW Criteria in the DTG + TDF/FTC Arm



Arrows represent the week in which CVW occurred. The color of the arrow corresponds to the color assigned to each participant.

Table 1. CVWs by Baseline CD4+ Cell Count and Baseline HIV-1 RNA

Baseline subgroups	DTG + 3TC	DTG + TDF/FTC
BL CD4+ cell count, % (n/N)		
≤200 cells/mm ³	4.8 (3/63)	3.6 (2/55)
>200 cells/mm ³	1.2 (8/653)	0.8 (5/662)
BL HIV-1 RNA, % (n/N)		
≤100,000 c/mL	1.0 (6/576)	0.7 (4/564)
>100,000 c/mL	3.6 (5/140)	2.0 (3/153)

- There were low and comparable CVWs across treatment arms by baseline VL or CD4+ cell count (Table 1)

Table 2. Summary of CVWs in DTG + 3TC Arm

Participant	Sub-type	BL CD4+ (cells/mm ³)	CVW visit (week)	BL VL (c/mL)	SVW VL (c/mL)	CVW VL (c/mL)	WD VL (c/mL)	Adherence/treatment interruption
A	BF	212	W16	124,492	6648	56,435	95	Unknown
B	B	284	W24	50,263	348	206	96	Adherent
C	B	529	W24	17,232	461	251	59	Unknown
D	B	213	W24	96,277	451	9602	67	Treatment interruption
E	F	19	W24	368,439	212	376	362	Adherent
F	B	414	W48	37,701	43,908	38,457	ND	Unknown; concurrent SAE (psychosis)
G	B	567	W60	7654	3972	3131	1513	Non-adherent
H	B	347	W60	101,671	703	85,556	ND	Treatment interruption
I	B	50	W72	63,817	422	2154	115	Non-adherent
J	B	74	W72	112,812	61,076	87,794	671	Non-adherent
K*	B	317	W96	341,818	396	726	280	Non-adherent

*Participant K SVW visit occurred within the Week 96 window for the Snapshot analysis. WD, withdrawal.

Resistance Analysis

- Resistance data to determine treatment emergence were available for all samples except 2 cases on DTG + TDF/FTC where testing failed with HIV-1 VL below the assay cut-off. No treatment-emergent genotypic or phenotypic resistance in IN or RT was observed in any CVWs on either treatment arm
- All fold change (FC) at withdrawal visit were below the Monogram phenotypic clinical or biological cut-offs. Maximum FC at withdrawal was 1.13 and 1.74 for DTG and 3TC, respectively, for CVWs in the DTG + 3TC arm, and 1.38, 1.07, and 1.28 for DTG, TDF, and FTC for CVWs, respectively, in the DTG + TDF/FTC arm

Table 3. Summary of CVWs in DTG + TDF/FTC Arm

Participant type	Sub-type	BL CD4+ (cells/mm ³)	CVW visit (week)	BL VL (c/mL)	SVW VL (c/mL)	CVW VL (c/mL)	WD VL (c/mL)	Adherence/treatment interruption
L*	B	22	W12	136,753	393	276	NA	Unknown
M	B	226	W24	10,930	1136	809	647	Unknown
N	B	251	W24	76,325	569	362	46	Unknown
O	B	201	W24	156,701	213	1559	97	Unknown
P	B	602	W48	1568	8384	3653	3011	Unknown
Q	B	253	W72	66,881	254	232	121	Unknown
R	B	144	W96	28,905	30,316	7793	ND	Non-adherent

*Participant L met CVW criteria at Week 12; not withdrawn from study due to central laboratory data reporting error and continued to remain suppressed to Week 108. WD, withdrawal.

- For participants with VLs at withdrawal, VL decreased ≥2 fold for 8 of 9 participants in the DTG + 3TC arm and 3 of 5 in the DTG + TDF/FTC arm between the CVW and withdrawal time points (Tables 2 and 3)
- 6/11 CVWs in the DTG + 3TC arm and 1/7 in the DTG + TDF/FTC arm appeared to be associated with adherence or treatment interruption issues

Conclusions

- In GEMINI-1 & -2, there were low and comparable numbers of participants meeting CVW criteria through 96 weeks in the DTG + 3TC and DTG + TDF/FTC arms with low and comparable CVWs across treatment arms by baseline VL or CD4+ cell count
- There were no emergent genotypic or phenotypic resistance to INI or NRTIs observed through 96 weeks among CVWs
- VL progressions for CVWs generally show a steep increase in viral load followed by a decrease at withdrawal visit, consistent with non-adherence/treatment interruption and subsequent re-adherence
- These data further support the durability and high barrier to resistance of the 2DR DTG + 3TC

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