Low HIV-1 Resistance in Subjects Using Darunavir Once-daily Regimens Across Studies

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Introduction

- Darunavir (DRV) has very potent antiviral activity against wild-type and multidrug-resistant human immunodeficiency virus (HIV)-1, with a high genetic barrier to the development of resistance[1,2]
- Boosted DRV 800 mg, in combination with 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs), is a Recommended initial antiretroviral (ARV) treatment option for HIV-1 infection per guidelines from the US Department of Health and Human Services (DHHS; with ritonavir [rtv]; considered an Alternative regimen with cobicistat [cobi]) and is also a Recommended initial regimen per the European AIDS Clinical Society (EACS; with rtv or cobi)[3,4]
- DRV dosed once daily (QD) has been studied extensively across diverse populations in clinical trials, demonstrating excellent efficacy and safety[5–11]; these studies of varying duration have enrolled both treatment-naïve (TN) and treatment-experienced (TE) subjects and included a range of combination therapies
- DRV QD treatment is indicated for HIV-1–infected individuals who are TN or TE without DRV resistance-associated mutations (RAMs)[12]
  - Eleven HIV-1 protease mutations associated with DRV resistance were previously identified based on an analysis of a pooled dataset of studies in highly TE subjects (who received treatment with DRV 600 mg and rtv 100 mg twice daily); the virologic efficacy of DRV is compromised in the presence of ≥3 DRV RAMs[13,14]
- In a recent phase 2 study[6] and 2 ongoing phase 3 studies (AMBER [ClinicalTrials.gov Identifier: NCT02431247] and EMERALD [NCT02269917]), the QD, single-tablet regimen containing DRV 800 mg, cobi 150 mg, emtricitabine (FTC) 200 mg, and tenofovir alafenamide (TAF) 10 mg is being evaluated

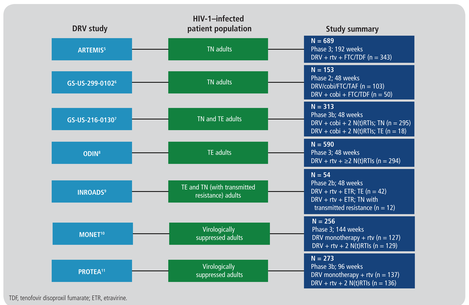
Objective

- To evaluate treatment-emergent resistance (RAMs and loss of phenotypic ARV susceptibility) for subjects in the DRV QD dosing arms from 7 completed clinical studies at the final analysis time point (48-192 weeks)

Methods

Study Designs

- Sponsored phase 2/3 studies investigating DRV 800 mg QD–containing ARV regimens with available genotypes/phenotypes were included in this analysis (**Figure 1** and **Table 1**)



TDF, tenofovir disoproxil fumarate; ETR, etravirine.

Figure 1. Study summaries of DRV QD–containing treatment arms.

Table 1. Key Resistance Eligibility Criteria at Screening

Study	VL at screening (copies/mL)	Excluded RAMs	Genotypic or phenotypic susceptibility	VF history
ARTEMIS	≥5,000	–	–	–
GS-US-299-0102	≥5,000	–	DRV, FTC, TDF[a]	–
GS-US-216-0130	≥1,000	DRV	DRV, 2 N(t)RTIs[a]	–
ODIN	>1,000	DRV	DRV, optimized N(t)RTI background[a]	–
INROADS	>500	DRV, ETR[b]	DRV, ETR[a,b]	≤2 previous VFs while on PI-containing ARV therapy
MONET	<50	Primary PI[c]	–	No history of VF while on previous/current ARV therapy
PROTEA	<50	Primary PI[c]	–	No history of VF while on previous/current ARV therapy

VL, viral load; VF, virologic failure; PI, protease inhibitor.
[a]For GS-US-299-0102, GS-US-216-0130, and ODIN: susceptibility was based on genotype at screening. For INROADS: susceptibility was based on phenotype at screening.
[b]TN subjects eligible to enroll in INROADS were required to have HIV-1 with transmitted primary drug resistance that conferred genotypic or phenotypic resistance to either efavirenz or nevirapine; those with multiclass transmitted resistance or with transmitted resistance to only classes other than non-nucleoside reverse transcriptase inhibitors were not eligible to enroll.
[c]IAS-USA primary PI mutations were based on historical genotypes.

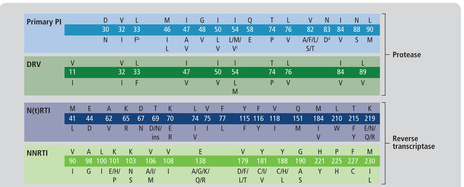
Evaluation of Resistance

- Genotypic/phenotypic analyses were conducted at screening (GS-US-299-0102, GS-US-216-0130) or screening/baseline (ARTEMIS, ODIN, INROADS), except for switch studies enrolling virologically suppressed subjects (MONET, PROTEA)
- Criteria for protocol-defined VF (PDVF) varied slightly across studies (**Table 2**)
- Resistance testing was performed on samples from subjects experiencing PDVF (except MONET and PROTEA, for which any sample that exceeded the VL threshold was tested). When feasible, resistance testing was performed at the time of confirmed VF and/or at later time points
  - Post-baseline VF plasma samples were sequenced (population sequencing) and phenotyped at Virco BVBA (Mechelen, Belgium) using the Virco®TYPE HIV-1 and Antivirogram® assays, or at Monogram Biosciences (South San Francisco, CA, USA) using the GenoSure® MG and PhenoSense® GT (protease [PR]-reverse transcriptase [RT]) assays
- Evaluation of treatment-emergent RAMs or the presence of on-treatment (in the case of switch studies) RAMs was based on PI, N(t)RTI, and non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation lists defined in each study (**Figure 2**)
  - RAMs were considered treatment-emergent if they were detected post-baseline but not at baseline or screening
- Loss of phenotypic susceptibility to ARVs was defined as fold change in the 50% effective concentration (in cell-based assays; EC_{50}) below or equal to the lower clinical cut-off or biological cut-off at baseline, but above the cut-off value post-baseline

Table 2. Viral Load Criteria for Post-baseline Resistance Testing

Study	PDVF	VL cut-off for resistance testing
ARTEMIS, ODIN, and INROADS[a]	Rebounder: on-study at Week 12 and achieved 2 consecutive VL <50 copies/mL, followed by 2 consecutive VL ≥50 copies/mL or discontinuation with a last observed on-treatment VL ≥50 copies/mL or Suboptimal virologic response: on-study at Week 12 and never achieved 2 consecutive VL <50 copies/mL	≥50 copies/mL
GS-US-299-0102 and GS-US-216-0130	Rebounder: VL <50 copies/mL followed by 2 consecutive VL ≥400 copies/mL, or 2 consecutive >1 log_{10} increase in VL from nadir or Suboptimal virologic response: VL <1 log_{10} reduction from baseline at Week 8 visit, confirmed at Week 12	≥400 copies/mL
MONET	2 consecutive VL ≥50 copies/mL	>50 copies/mL (at any time)
PROTEA	2 consecutive VL ≥400 copies/mL	>400 copies/mL (at any time)

TLOVR, time to loss of virologic response.
[a]TLOVR (non-VF censored) algorithm.



ins, insertion.
[a]Mutation lists varied between studies; the IAS-USA 2008 (December) list[14] was used in ODIN and MONET, IAS-USA 2009 list[15] in ARTEMIS, IAS-USA 2010 list[13] in PROTEA, IAS-USA 2011 list[16] in INROADS, and adapted IAS-USA lists in GS-US-299-0102 and GS-US-216-0130 (primary PI RAMs: identical to IAS-USA 2009 list except that L33F and I54V were considered primary PI RAMs instead of secondary; N(t)RTI RAMs: IAS-USA 2011 list used in GS-US-299-0102 and a modified list used in GS-US-216-0130).
[b]The L33F mutation was considered a primary PI RAM in GS-US-299-0102, GS-US-216-0130, ODIN, and MONET (considered a secondary PI RAM in ARTEMIS, INROADS, and PROTEA).
[c]The I54V mutation was considered a primary PI RAM in GS-US-299-0102 and GS-US-216-0130 (considered a secondary PI RAM in ARTEMIS, ODIN, INROADS, MONET, and PROTEA).
[d]The N83D mutation was considered a primary PI RAM in INROADS and PROTEA (considered a secondary PI RAM in ARTEMIS, GS-US-299-0102, GS-US-216-0130, ODIN, and MONET).

Figure 2. RAM lists.*

Results

Resistance at Baseline

- Characteristics of the virus at baseline (for non–virologically suppressed subjects; **Table 3**) and ARV histories at baseline (for TE subjects; **Table 4**) are summarized

Table 3. Baseline Virus Characteristics

	HIV-1 subtype, n (%)		≥1 RAM, n (%)			
			Protease		Reverse transcriptase	
Study	B	Non-B	Primary PI	DRV	N(t)RTI	NNRTI
ARTEMIS (n = 342)[a]	210 (61)	132 (39)	16 (5)	5 (1)	29 (8)	60 (18)
GS-US-299-0102 (n = 153)	149 (97)	4 (3)	8 (5)	6 (4)	15 (10)	30 (20)
GS-US-216-0130 (n = 313)	301 (96)	12 (4)	10 (3)	0	43 (14)	87 (28)
ODIN (n = 294)	179 (61)	115 (39)	47 (16)	3 (1)[b]	219 (75)	210 (71)
INROADS (n = 54)	52 (96)	2 (4)	5 (9)	0	25 (46)	31 (57)

[a]Data were not available for 1 subject.
[b]The presence of DRV RAMs at screening was not allowed for ODIN; however, 3 subjects had ≥1 DRV RAM at baseline.

Table 4. Previous ARV Use[a]

Study	≥1 PI	≥2 N(t)RTIs	≥1 NNRTI
GS-US-216-0130 (n = 18)	9 (50)	16 (89)	12 (67)
ODIN (n = 294)	159 (54)	291 (99)	258 (88)
INROADS (n = 42)	29 (54)	42 (78)	32 (59)
MONET (n = 256)	191 (75)	256 (100)	146 (57)
PROTEA (n = 273)	219 (80)[b]	273 (100)	117 (43)

[a]Data are presented as n (%).
[b]104 (38%) subjects had a history of DRV use.

Table 5. Treatment-emergent RAMs and Loss of ARV Phenotypic Susceptibility Across Studies

					Subjects with ≥1 (emergent) RAM, n (%)		
					Protease	Reverse transcriptase	
Study	Treatment	Subjects, n	Subjects with PDVF, n (%)	Subjects evaluated for resistance, n	Primary PI/DRV	N(t)RTI	NNRTI
ARTEMIS (Week 192)	DRV + rtv + FTC/TDF	343	55 (16)	43	V11I; n = 1[c,*]	M184I/V; n = 3[b] M184V + K70E; n = 1[b]	–
GS-US-299-0102 (Week 48)	DRV/cobi/FTC/TAF	103	4 (4)	4	0	0	–
	DRV + cobi + FTC/TDF	50	1 (2)	1	0	0	–
GS-US-216-0130 (Week 48)	DRV + cobi + 2 N(t)RTIs	313	15 (5)	15	I84I/V; n = 1[c,*]	M184V; n = 2[d]	–
ODIN (Week 48)	DRV + rtv + ≥2 N(t)RTIs	294	65 (22)	60	V32I + M46I + L76V + I84V; n = 1[e]	M184V; n = 1[f] V75I + M184V; n = 1[f] T215F; n = 1[c,*] T215Y; n = 1[f]	–
INROADS (Week 48)	DRV + rtv + ETR	54	7 (13)	2	0	–	E138K + M230L; n = 1[g] L100I/I + E138E/G + Y181Y/C; n = 1[g,*]
MONET[h] (Week 144)	DRV monotherapy + rtv	127	21 (17)	31	L33F; n = 1[c,*]	–	–
	DRV + rtv + 2 N(t)RTIs	129	13 (10)	23	0	0	–
PROTEA[h] (Week 96)	DRV monotherapy + rtv	137	1 (1)	2	0	–	–
	DRV + rtv + 2 N(t)RTIs	136	2 (1)	1	0	0	–
Total		1,686	184 (11)	182	**4**	**10**	**2**
Pivotal phase 3 studies (ARTEMIS, ODIN, and GS-US-216-0130)[i]		950	135 (14)	118	**3**	**10**	**–**

***Indicates no loss of phenotypic susceptibility for the corresponding ARVs.**
[a]Subject developed V11I, a secondary PI RAM, after treatment stop (discontinuation due to noncompliance), with no loss of DRV or PI phenotypic susceptibility observed.
[b]For all 4 subjects, there was a loss of FTC susceptibility.
[c]One TE subject developed I84I/V, which was both a primary PI RAM and a DRV RAM; DRV and PI phenotypic susceptibility were not lost.
[d]Both subjects (1 TN and 1 TE) used an FTC and TDF N(t)RTI backbone and lost susceptibility to FTC.
[e]One subject (DRV QD arm) developed 4 primary PI RAMs, 3 of which were also DRV RAMs (V32I, L76V, and I84V); DRV, amprenavir, atazanavir, indinavir, and nelfinavir phenotypic susceptibility were lost, possibly related to previous VF with lopinavir + rtv treatment.
[f]For 3 of these subjects, development of N(t)RTI RAMs was associated with loss of susceptibility to an N(t)RTI in the optimized background regimen; 2 subjects (1 who developed M184V and 1 who developed V75I + M184V) each lost susceptibility to abacavir and lamivudine, and 1 subject (who developed T215Y) lost susceptibility to zidovudine.
[g]The subject who developed E138K + M230L lost susceptibility to ETR. The subject who developed L100I/I + E138E/G + Y181Y/C became partially susceptible to ETR.
[h]On-treatment RAMs are reported for the 2 switch studies (MONET and PROTEA). One MONET subject (DRV + rtv +2 N(t)RTIs arm) who had detectable primary PI and N(t)RTI RAMs was excluded because these mutations were already present at the start of the study as a result of a previous VF.
[i]One subject had L33F, both a primary PI RAM and a DRV RAM, detected at Week 12 with HIV-1 RNA of 63 copies/mL, but was resuppressed at subsequent visits until Week 144.
*Combined data from the 3 pivotal phase 3 studies of DRV QD.

- Baseline phenotypic susceptibility data were available in 2 studies of TE subjects
  - ODIN: 100% (291/291) of subjects with available data were susceptible to DRV; susceptibility to N(t)RTIs in the optimized background regimen was as follows: 18% (53/290) of subjects were susceptible to 1 N(t)RTI, 75% (218/290) to ≥2 N(t)RTIs, and 7% (19/290) were not susceptible to any N(t)RTIs
  - INROADS: 100% (54/54) of subjects were susceptible to both study drugs (DRV and ETR)

Development of Resistance

- Within the 7 studies, a total of 2,328 subjects were enrolled; 1,686 subjects were treated with DRV QD–based regimens and, among these, 184 had PDVF and 182 had post-baseline genotypes analyzed (**Table 5**)
- Overall, 4/1,686 (0.2%) subjects developed treatment-emergent (or had on-treatment [switch studies]) primary PI and/or DRV RAMs
  - Only 1 (<0.1%) subject lost phenotypic susceptibility to DRV; this was possibly related to a prior VF with lopinavir + rtv (all of the developing primary PI RAMs and most of the secondary PI RAMs were also lopinavir RAMs)
- Among subjects treated with DRV monotherapy + rtv, only 1/264 (0.4%) had an on-treatment DRV RAM; this RAM (L33F) was detected at Week 12 (VL of 63 copies/mL) and the subject was resuppressed at subsequent visits until Week 144
- Among all subjects who used an N(t)RTI backbone, 10/1,103 (0.9%) developed treatment-emergent N(t)RTI RAMs to their background regimen (including 8 subjects with the FTC RAM M184I/V)
  - Nine of these subjects lost phenotypic susceptibility to ≥1 N(t)RTI in their background regimen

Conclusions

- **Across a diverse population of HIV-1–infected subjects (N = 1,686) treated with a DRV 800 mg QD–based regimen, the development of resistance was rare**
  - **Only 4 (0.2%) subjects were observed to have treatment-emergent or on-treatment primary PI and/or DRV RAMs**
  - **Only 1 (<0.1%) subject lost DRV phenotypic susceptibility; importantly, this subject had a prior history of lopinavir + rtv VF**
- **DRV dosed QD has a very high genetic barrier to the development of resistance**

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