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Original Article

HIV-1 resistance rarely observed in subjects using darunavir once-daily regimens across clinical studies

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Background: Darunavir 800 mg once daily (QD) is indicated for HIV-1–infected treatment-naïve and treatment-experienced (without darunavir resistance-associated mutations [RAMs]) individuals, and has been evaluated in phase 2/3 studies with durations between 48 and 192 weeks.

Objective: To summarize the development (or identification) of post-baseline resistance (RAMs and antiretroviral phenotypic susceptibility) among subjects receiving darunavir QD dosing.

Methods: Seven phase 2/3 studies with available genotypes/phenotypes for subjects treated with ritonavir- or cobicistat-boosted darunavir 800 mg QD regimens were assessed: ARTEMIS (NCT00258557; n = 343), GS-US-299-0102 (NCT01565850; n = 153), GS-US-216-0130 (NCT01440569; n = 313), ODIN (NCT00524368; n = 294), INROADS (NCT01199939; n = 54), MONET (NCT00458302; n = 256), and PROTEA (NCT01448707; n = 273). Genotypic analyses were conducted at baseline (except switch studies enrolling virologically suppressed subjects [MONET, PROTEA]). Criteria for post-baseline resistance testing and evaluation of the development (or identification [switch studies]) of RAMs (respective IAS-USA mutations) varied slightly across studies.

Results: Among 1686 subjects treated with darunavir 800 mg QD regimens, 184 had protocol-defined virologic failure; 182 had post-baseline genotypes analyzed. Overall, 4/1686 (0.2%) developed (or had identified [switch studies]) primary protease inhibitor and/or darunavir RAMs (ARTEMIS, n = 1; GS-US-216-0130, n = 1; ODIN, n = 1; MONET, n = 1). Only 1/1686 (<0.1%) subject lost darunavir phenotypic susceptibility (ODIN; possibly related to prior ritonavir-boosted lopinavir virologic failure). Among 1103 subjects using a nucleos(t)ide reverse transcriptase inhibitor (N(t)RTI) backbone, 10 (0.9%) developed ≥1 N(t)RTI RAM (8 had the emtricitabine RAM M184I/V).

Conclusions: Darunavir has a high genetic barrier to resistance. Across a diverse population of HIV-1–infected subjects treated with darunavir 800 mg QD regimens, the development of darunavir resistance was rare (<0.1%).

Keywords: Darunavir once daily, Human Immunodeficiency virus-1, Resistance, Genotypic resistance, Resistance-associated mutations, Phenotypic resistance, Antiretroviral

Introduction

Human immunodeficiency virus (HIV)-1 drug resistance testing can provide important information to guide antiretroviral (ARV) treatment strategy because resistance-associated mutations (RAMs) harbored by the virus may restrict treatment options. To minimize the risk of developing RAMs, the use of ARV agents with a high genetic barrier to resistance, such as protease inhibitors (PIs), are desirable. In the case of boosted darunavir, potent antiviral activity against wild-type and multidrug-resistant HIV-1 and a high genetic barrier to the development of resistance have been demonstrated. Darunavir dosed once daily (QD) has been studied extensively across diverse populations in clinical trials, demonstrating excellent efficacy and safety. These studies of varying duration have enrolled both treatment-naïve and treatment-experienced subjects and included a range of combination therapies and monotherapy. Boosted darunavir 800 mg, in combination with 2 nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs), is a recommended initial ARV treatment option in certain clinical situations for HIV-1 infection per guidelines from the United States Department of Health and Human Services (US DHHS; with ritonavir or cobicistat). Boosted darunavir 800 mg, in combination with 2 N(t)RTIs, is also a recommended initial regimen per the European AIDS
Clinical Society (EACS; with ritonavir or cobicistat). Darunavir QD is indicated for HIV-1–infected individuals who are treatment-naive or treatment-experienced without darunavir RAMs. Eleven HIV-1 protease (PR) mutations associated with darunavir resistance were previously identified based on an analysis of a pooled dataset of studies in highly treatment-experienced subjects (subjects had received treatment with darunavir 600 mg and ritonavir 100 mg twice daily). Consistent with darunavir having a high genetic barrier to the development of resistance, its virologic efficacy has been shown to be compromised only in the presence of 3 or more darunavir RAMs in the background of a high number (median of 14 or 15, respectively) of International Antiviral Society–USA (IAS-USA) PI RAMs.

The current report is an analysis of the development (or identification) of post-baseline resistance, including primary PI, darunavir, N(t)RTI, and non-nucleoside reverse transcriptase inhibitor (NNRTI) RAMs, as well as loss of ARV phenotypic susceptibility, among HIV-1–infected subjects in the darunavir 800 mg QD dosing arms from seven completed clinical studies at their respective final analysis time points.

**Methods**

**Study designs**

This analysis was based on data from seven company-sponsored, phase 2 and 3 studies that investigated darunavir 800 mg QD–containing ARV regimens and had available genotype and phenotype data (ARTEMIS [ClinicalTrials.gov Identifier: NCT00258557], GS-US-299-0102 [NCT01565850], GS-US-216-0130 [NCT01440569], ODIN [NCT00524368], INROADS [NCT01199939], MONET [NCT00458302], and PROTEA [NCT01448707]); detailed study designs have been published for each study. Only the darunavir 800 mg QD treatment arms were included in this analysis. As shown in Figure 1, the studies differed in clinical phase, sample size, and final analysis time point. The subject populations also varied in regards to treatment experience (i.e. treatment-naive or treatment-experienced) and, for treatment-experienced subjects, history of ARV use and viral suppression status (i.e. viral load of ≥50 or <50 HIV-1 RNA copies/mL at screening). Treatment varied in terms of boosting agent (ritonavir or cobicistat) and background regimen.

### DRV study

**ARTEMIS**

- **Study design**: Phase 3; 142 weeks
- **Patient population**: TN adults
- **Study summary**
  - N = 689
  - DRV + rtv + FTC/TDF (n = 343)

**GS-US-299-0102**

- **Study design**: Phase 2; 48 weeks
- **Patient population**: TN adults
- **Study summary**
  - N = 153
  - DRV/cobi/FTC/TAF (n = 103)
  - DRV + cobi + FTC/TDF (n = 50)

**GS-US-216-0130**

- **Study design**: Phase 3b; 48 weeks
- **Patient population**: TN and TE adults
- **Study summary**
  - N = 313
  - DRV + cobi + 2 N(t)RTIs; TN (n = 295)
  - DRV + cobi + 2 N(t)RTIs; TE (n = 18)

**ODIN**

- **Study design**: Phase 3; 48 weeks
- **Patient population**: TE adults
- **Study summary**
  - N = 590
  - DRV + rtv + 2 N(t)RTIs (n = 294)

**INROADS**

- **Study design**: Phase 2b; 48 weeks
- **Patient population**: TE and TN (with transmitted resistance) adults
- **Study summary**
  - N = 54
  - DRV + rtv + ETR; TE (n = 42)
  - DRV + rtv + ETR; TN with transmitted resistance (n = 12)

**MONET**

- **Study design**: Phase 3; 144 weeks
- **Patient population**: Virologically suppressed adults
- **Study summary**
  - N = 256
  - DRV monotherapy + rtv (n = 127)
  - DRV + rtv + 2 N(t)RTIs (n = 129)

**PROTEA**

- **Study design**: Phase 3b; 96 weeks
- **Patient population**: Virologically suppressed adults
- **Study summary**
  - N = 273
  - DRV monotherapy + rtv (n = 137)
  - DRV + rtv + 2 N(t)RTIs (n = 136)

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**Figure 1** Study summaries of darunavir 800 mg QD–containing treatment arms

Notes: QD, once daily; DRV, darunavir; HIV-1, human immunodeficiency virus-1; TN, treatment-naïve; rtv, ritonavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; cobi, cobicistat; TAF, tenofovir alafenamide; TE, treatment-experienced; N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; ETR, etravirine; ARV, antiretroviral. For each ARV regimen, agents combined in the same tablet are separated by a ‘/’ and those in different tablets are separated by a ‘+’.
Three of the seven studies (ARTEMIS, GS-US-216-0130, and ODIN) were pivotal phase 3 studies that evaluated the safety and efficacy of darunavir QD treatment (with N(t)RTIs). ARTEMIS was a 192-week, phase 3 study of treatment-naïve adults; among the 689 enrolled subjects, 343 were included in this analysis (i.e. were treated with darunavir 800 mg QD) and had received ritonavir-boosted darunavir with emtricitabine and tenofovir disoproxil fumarate. GS-US-299-0102 was a 48-week, phase 2 study of treatment-naïve adults; all 153 subjects were included in this analysis and had received cobicistat-boosted darunavir and emtricitabine, with either tenofovir disoproxil fumarate or tenofovir alafenamide. GS-US-216-0130 was a 48-week, phase 3 study of both treatment-naïve and treatment-experienced adults; all 313 subjects received cobicistat-boosted darunavir and 2 N(t)RTIs. ODIN was a 48-week, phase 3 study of treatment-experienced adults; of 390 enrolled subjects, 294 were included in this analysis and had received ritonavir-boosted darunavir and emtricitabine. ARTEMIS was a 192-week study of treatment-naïve adults; among the 689 enrolled subjects, 343 were included in this analysis (i.e. were treated with darunavir 800 mg QD) and had received ritonavir-boosted darunavir with emtricitabine and tenofovir disoproxil fumarate. GS-US-299-0102 was a 48-week, phase 2b study of treatment-experienced adults and treatment-naïve adults with transmitted resistance; all 54 subjects were included in this analysis and had received ritonavir-boosted darunavir and etravirine. MONET was a 144-week, phase 3 study of vireologically suppressed adults; all 256 enrolled subjects were included in this analysis and had received ritonavir-boosted darunavir monotherapy or ritonavir-boosted darunavir and 2 N(t)RTIs. INROADS was a 48-week, phase 2 study of treatment-experienced adults; of 590 enrolled subjects, 294 were included in this analysis and had received ritonavir-boosted darunavir with emtricitabine. Studies varied in regards to excluded RAMs and the requirement of genotypic or phenotypic ARV susceptibility. Three studies included eligibility criteria that limited history of previous virologic failures.

### Evaluation of resistance

Genotypic and phenotypic analyses were conducted at screening (GS-US-299-0102, GS-US-216-0130) or screening/baseline (ARTEMIS, ODIN, INROADS), except for switch studies that enrolled vireologically suppressed subjects (MONET, PROTEA). The criteria for protocol-defined virologic failure (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 viral load threshold was tested). When feasible, resistance testing was performed at the time of (confirmed [preferable] or unconfirmed) virologic failure and/or at later time points. Post-baseline virologic failure 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 (PR-reverse transcriptase [RT]) assays. The viral load

<table>
<thead>
<tr>
<th>Study</th>
<th>Viral load at screening (copies/mL)</th>
<th>Excluded RAMs</th>
<th>Genotypic or phenotypic susceptibility</th>
<th>Virologic failure history</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTEMIS</td>
<td>≥5000</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GS-US-299-0102</td>
<td>≥5000</td>
<td>–</td>
<td>DRV, FTC, TDF –</td>
<td>–</td>
</tr>
<tr>
<td>GS-US-216-0130</td>
<td>≥1000</td>
<td>DRV</td>
<td>DRV, 2 N(t)RTIs –</td>
<td>–</td>
</tr>
<tr>
<td>ODIN</td>
<td>&gt;1000</td>
<td>DRV</td>
<td>DRV, optimized N(t)RTI background –</td>
<td>–</td>
</tr>
<tr>
<td>INROADS</td>
<td>&gt;500</td>
<td>DRV, ETR –</td>
<td>DRV, ETR –</td>
<td>≥2 previous virologic failures while on PI-containing ARV therapy</td>
</tr>
<tr>
<td>MONET</td>
<td>&lt;50</td>
<td>Primary PI –</td>
<td>–</td>
<td>No history of virologic failure while on previous/current ARV therapy</td>
</tr>
<tr>
<td>PROTEA</td>
<td>&lt;50</td>
<td>Primary PI –</td>
<td>–</td>
<td>No history of virologic failure while on previous/current ARV therapy</td>
</tr>
</tbody>
</table>

Notes: RAM, resistance-associated mutation; DRV, darunavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; ETR, etravirine; PI, protease inhibitor; ARV, antiretroviral; HIV-1, human immunodeficiency virus-1; NNRTI, non-nucleoside reverse transcriptase inhibitor; IAS-USA, International Antiviral Society–USA.

*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*Treatment-naïve subjects who were 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 NNRTIs were not eligible to enroll.

^IAS-USA primary PI mutations were based on historical genotypes.
cut-off for attempting resistance testing was as low as 50 copies/mL for some studies (ARTEMIS, ODIN, INROADS, and MONET) and 400 copies/mL for other studies (GS-US-299-0102, GS-US-216-0130, and PROTEA; Table 2).

Evaluation of the development of RAMs (or identification of RAMs, in the case of switch studies) was based on PI, N(t)RTI, and NNRTI IAS-USA mutation lists defined in each study (Figure 2). RAMs were considered to have developed if they were detected post-baseline but not at baseline or screening. Mutations that were identified among subjects with virologic failure in the switch studies could not be compared with screening/baseline sequences to evaluate whether they developed during the study due to being virologically suppressed at screening and, therefore, lacking genotypes. If available, loss of phenotypic susceptibility to ARVs was defined as fold change (FC) in the 50% effective concentration (EC50; in cell-based assays) below or equal to the lower clinical cut-off or biological cut-off at baseline, but above the cut-off value post-baseline.

### Results

#### Resistance at baseline

Across the seven studies, a total of 2328 subjects were enrolled and 1686 of these were treated with darunavir 800 mg QD–based regimens. Among non-virologically suppressed subjects at baseline, the majority in each study cut-off for attempting resistance testing was as low as 50 copies/mL for some studies (ARTEMIS, ODIN, INROADS, and MONET) and 400 copies/mL for other studies (GS-US-299-0102, GS-US-216-0130, and PROTEA; Table 2).

Evaluation of the development of RAMs (or identification of RAMs, in the case of switch studies) was based on PI, N(t)RTI, and NNRTI IAS-USA mutation lists defined in each study (Figure 2). RAMs were considered to have developed if they were detected post-baseline but not at baseline or screening. Mutations that were identified among subjects with virologic failure in the switch studies could not be compared with screening/baseline sequences to evaluate whether they developed during the study due to being virologically suppressed at screening and, therefore, lacking genotypes. If available, loss of phenotypic susceptibility to ARVs was defined as fold change (FC) in the 50% effective concentration (EC50; in cell-based assays) 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

<table>
<thead>
<tr>
<th>Study</th>
<th>PDVF</th>
<th>VL cut-off for resistance testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTEMIS, ODIN, and INROADS*</td>
<td>Rebounder: on-study at Week 12 and achieved 2 consecutive VL &lt;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 &lt;50 copies/mL</td>
<td>≥50 copies/mL</td>
</tr>
<tr>
<td>GS-US-299-0102 and GS-US-216-0130</td>
<td>Rebounder: VL &lt;50 copies/mL followed by 2 consecutive VL ±400 copies/mL, or 2 consecutive &gt;1 log10 increase in VL from nadir or Suboptimal virologic response: VL &lt;1 log10 reduction from baseline at Week 8 visit, confirmed at Week 12</td>
<td>≥400 copies/mL</td>
</tr>
<tr>
<td>MONET</td>
<td>2 consecutive VL ≥50 copies/mL</td>
<td>≥50 copies/mL (at any time)</td>
</tr>
<tr>
<td>PROTEA</td>
<td>2 consecutive VL ≥400 copies/mL</td>
<td>&gt;400 copies/mL (at any time)</td>
</tr>
</tbody>
</table>

Note: PDVF, protocol-defined virologic failure; VL, viral load; TLOVR, time to loss of virologic response.

*TLOVR (non-virologic failure censored) algorithm.

### Figure 2

**RAM lists**

Notes: RAM, resistance-associated mutation; PI, protease inhibitor; DRV, darunavir; N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; ins, insertion; NNRTI, non-nucleoside reverse transcriptase inhibitor; IAS-USA, International Antiviral Society–USA. *Mutation lists varied between studies; the IAS-USA 2008 (December) list was used in ODIN and MONET, IAS-USA 2009 list in ARTEMIS, IAS-USA 2010 list in PROTEA, IAS-USA 2011 list 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). 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). 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). The N83D mutation was considered a primary PI RAM in ARTEMIS, INROADS and PROTEA (considered a secondary PI RAM in ARTEMIS, GS-US-299-0102, GS-US-216-0130, ODIN, and MONET)
harbored HIV-1 subtype B (Table 3). In general, baseline RAMs tended to be more common among treatment-experienced subjects (ODIN and INROADS) than treatment-naive subjects (ARTEMIS, GS-US-299-0102, and most subjects in GS-US-216-0130). All three studies that enrolled treatment-experienced subjects excluded individuals with darunavir RAMs at screening, but notably, three subjects receiving darunavir QD-based regimens in ODIN had ≥1 darunavir RAM at baseline. For studies of treatment-experienced subjects, previous use of PIs, N(t) RTIs, and NNRTIs was common (Table 4).

Baseline phenotypic susceptibility data were available in two studies of treatment-experienced subjects. In ODIN, 100% (291/291) of subjects with available data were susceptible to darunavir; susceptibility to N(t)RTI 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 used in their background regimen. INROADS, 100% (54/54) of subjects were susceptible to both study drugs (darunavir and etravirine).

**Development of resistance**

Of the 1686 subjects included in this analysis, 184 had PDVF and 182 had post-baseline genotypes analyzed (Table 5). Overall, only 4 of 1686 (0.2%) subjects developed (or, in the case of switch studies, had identified) primary PI and/or darunavir RAMs post-baseline (4 of 184 [2.2%] subjects with PDVF).

Among the four subjects, one (ARTEMIS) developed V11I, a darunavir (and secondary PI) RAM, after treatment was discontinued due to noncompliance; no loss of phenotypic susceptibility to darunavir or any PI was observed.

A second subject (treatment-experienced, GS-US-216-0130) developed I84I/V, a primary PI and darunavir RAM, detected at Week 12 with a viral load of 63 copies/mL, but was resuppressed at subsequent visits. The subject lost phenotypic susceptibility to darunavir; moreover, it is possible that the mutation was already present at baseline (no sequence available due to suppressed viral load).

A third subject (ODIN), at Week 48, developed M46I, a primary PI and darunavir RAM at baseline. For studies of treatment-experienced subjects, previous use of PIs, N(t) RTIs, and NNRTIs was common (Table 4).

A fourth subject (ritonavir-boosted darunavir monotherapy treatment arm of MONET) had L33F, a primary PI and DRV RAM, detected at Week 12 with a viral load of 63 copies/mL, but was resuppressed at subsequent visits until Week 144. The darunavir RAM did not confer phenotypic resistance to darunavir; moreover, it is possible that the mutation was already present at baseline (no sequence available due to suppressed viral load).

Among subjects treated with ritonavir-boosted darunavir monotherapy, only 1 of 264 (0.4%) had a post-baseline darunavir RAM. Overall, among all 1686 subjects treated with any regimen containing darunavir QD in the analysis, only 1 (<0.1%) lost phenotypic susceptibility to darunavir.

Ten of the 1103 (0.9%) non-virologically suppressed subjects who used an N(t)RTI backbone developed N(t)RTI RAMs; 9 of these subjects also lost phenotypic susceptibility to ≥1 of the N(t)RTI included in their regimen (Table 5). Four subjects from ARTEMIS, all of whom used emtricitabine and tenofovir disoproxil fumarate, developed RAMs (M184I/V, n = 3; M184V and K70E, n = 2). Among subjects who achieved a viral load of <50 copies/mL, 3 subjects had ≥1 DRV RAM at baseline.

### Table 3 Baseline virus characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>HIV-1 subtype, n (%)</th>
<th>Protease</th>
<th>Reverse transcriptase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Non-B</td>
<td>Primary PI</td>
</tr>
<tr>
<td>ARTEMIS (n = 342)</td>
<td>210 (61)</td>
<td>132 (39)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>GS-US-299-0102 (n = 153)</td>
<td>149 (97)</td>
<td>4 (3)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>GS-US-216-0130 (n = 313)</td>
<td>301 (96)</td>
<td>12 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>ODIN (n = 294)</td>
<td>179 (61)</td>
<td>115 (39)</td>
<td>47 (16)</td>
</tr>
<tr>
<td>INROADS (n = 54)</td>
<td>52 (96)</td>
<td>2 (4)</td>
<td>5 (9)</td>
</tr>
</tbody>
</table>

Notes: RAM, resistance-associated mutation; HIV-1, human immunodeficiency virus-1; PI, protease inhibitor; DRV, darunavir; N(t)RTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

*Data were not available for 1 subject.
*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

<table>
<thead>
<tr>
<th>Study</th>
<th>≥1 PI</th>
<th>≥2 N(t)RTIs</th>
<th>≥1 NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-US-216-0130 (n = 18)</td>
<td>9 (50)</td>
<td>16 (89)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>ODIN (n = 294)</td>
<td>159 (54)</td>
<td>291 (99)</td>
<td>258 (88)</td>
</tr>
<tr>
<td>INROADS (n = 42)</td>
<td>29 (69)</td>
<td>42 (100)</td>
<td>32 (76)</td>
</tr>
<tr>
<td>MONET (n = 256)</td>
<td>191 (75)</td>
<td>256 (100)</td>
<td>146 (57)</td>
</tr>
<tr>
<td>PROTEA (n = 273)</td>
<td>219 (80)</td>
<td>273 (100)</td>
<td>117 (43)</td>
</tr>
</tbody>
</table>

Notes: ARV, antiretroviral; PI, protease inhibitor; N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; DRV, darunavir.

aData are presented as n (%).

ONE hundred and four (38%) subjects had a history of DRV use.

Results

A total of one thousand sixty-three (9%) subjects were included in this study. Two hundred and eighty-nine (27%) subjects developed a primary PI RAM or lost phenotypic susceptibility to ≥1 N(t)RTI in their background regimen.

Among these 1103 (0.9%) non-virologically suppressed subjects who used an N(t)RTI backbone developed N(t)RTI RAMs; the most common, the emtricitabine RAM M184I/V, was found in 8 subjects. Nine of these 10 subjects lost phenotypic susceptibility to ≥1 N(t)RTI in their background regimen.

Discussion

Across a diverse population of HIV-1–infected subjects taking a darunavir 800 mg QD–based regimen, only 4 of 1686 (0.2%) subjects developed (or had identified) a post-baseline primary PI and/or darunavir RAMs, and only 1 subject lost darunavir phenotypic susceptibility. The extremely low prevalence of the development of darunavir RAMs and darunavir phenotypic resistance is consistent with the known high genetic barrier to resistance of darunavir. Notably, among treatment-naïve subjects treated with darunavir QD, none developed a primary PI RAM or lost phenotypic susceptibility to darunavir. Among those subjects who were treatment-experienced but PI-naïve, none developed phenotypic darunavir resistance. Importantly, the 1 treatment-experienced subject who lost darunavir phenotypic susceptibility had a prior history of virologic failure with ritonavir-boosted lopinavir treatment, which may have contributed cross-resistant PI RAMs.14,15 The fact that many of this subject’s developing mutations were lopinavir RAMs suggests the possibility that archived resistance variants may have rapidly reemerged upon exposure to darunavir.

The development of resistance to N(t)RTIs in subjects’ backbone therapies was also rare in these studies. Ten of 1103 (0.9%) non-virologically suppressed subjects who used an N(t)RTI backbone developed N(t)RTI RAMs; the most common, the emtricitabine RAM M184I/V, was found in 8 subjects. Nine of these 10 subjects lost phenotypic susceptibility to ≥1 N(t)RTI in their background regimen.

Boosted-darunavir monotherapy is not recommended in guidelines from the US DHHS, and is an option only for exceptional persons who are not candidates for dual therapies per EACS guidelines, due to reduced efficacy compared with combination regimens1; however, numerous studies have evaluated monotherapy as an ARV regimen simplification strategy in virologically suppressed individuals. Such studies allow for insights into the true genetic barrier to the development of resistance when subjects are treated with only boosted darunavir 800 mg QD. In the current analysis, among those receiving ritonavir-boosted darunavir monotherapy (in MONET and PROTEA), only 1 of 264 (0.4%) subjects was observed to have a darunavir RAM, (which, by itself, does not confer resistive phenotype to darunavir).14,15 Across six additional studies of ritonavir-boosted darunavir monotherapy (818 subjects in total), no post-baseline darunavir RAMs were detected and only 2 (0.2%) subjects had a post-baseline primary PI RAM.18–24 Taken together, findings from studies of boosted-darunavir monotherapy further illustrate its high genetic barrier to resistance. This is in contrast to integrase inhibitor monotherapy, which has resulted in high rates of resistance development.25,26

The rare development of darunavir resistance upon virologic failure, as seen in the current analysis, is consistent with findings based on a database analysis of US clinical samples.5,27 Samples (from patients receiving varying ARV/PI regimens and with different treatment experiences and histories of resistance [no prior treatment information was available]) had been submitted for resistance testing (combined genotypic and phenotypic resistance testing) to Monogram Biosciences and were collected from 2006 through 2015.5,27 The overall prevalence of darunavir RAMs among these submitted samples decreased over time; a corresponding decrease in darunavir phenotypic resistance was also observed.5,27 The prevalence of darunavir phenotypic resistance remained lower than that of other PIs for each year during the analysis period.5,27
Table 5  Development (and identification) of post-baseline RAMs and loss of ARV phenotypic susceptibility across studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Subjects, n</th>
<th>Subjects with PDVF, n (%)</th>
<th>Subjects evaluated for resistance, n</th>
<th>Subjects with ≥1 RAM, n</th>
<th>Primary PI/DRV</th>
<th>N(t)RTI</th>
<th>NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTEMIS (Week 192)</td>
<td>DRV + rtv + FTC/TDF</td>
<td>343</td>
<td>55 (16)</td>
<td>43</td>
<td>V11I; n = 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>M184V/V; n = 3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>GS-US-299-0102 (Week 48)</td>
<td>DRV/cobi/FTC/TAF</td>
<td>103</td>
<td>4 (4)</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>GS-US-216-0130 (Week 48)</td>
<td>DRV + cobi + FTC/TDF</td>
<td>50</td>
<td>1 (2)</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>ODIN (Week 48)</td>
<td>DRV + rtv + ≥2 N(t)RTIs</td>
<td>313</td>
<td>15 (5)</td>
<td>15</td>
<td>V84I; n = 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>M184V; n = 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>INROADS (Week 48)</td>
<td>DRV + rtv + ETR</td>
<td>54</td>
<td>7 (13)</td>
<td>2</td>
<td>0</td>
<td>–</td>
<td>E138K + M230L; n = 1&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>MONET&lt;sup&gt;a&lt;/sup&gt; (Week 144)</td>
<td>DRV monotherapy + rtv</td>
<td>129</td>
<td>21 (17)</td>
<td>31</td>
<td>L33F; n = 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>PROTEA&lt;sup&gt;b&lt;/sup&gt; (Week 96)</td>
<td>DRV monotherapy + rtv</td>
<td>137</td>
<td>13 (10)</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1486</td>
<td>184 (13)</td>
<td>182</td>
<td>4 (0.2)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>10 (0.7)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>2 (0.7)&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Pivotal phase 3 studies (ARTEMIS, GS-US-216-0130, and ODIN)&lt;sup&gt;m&lt;/sup&gt;</td>
<td></td>
<td>950</td>
<td>135 (14)</td>
<td>118</td>
<td>3 (0.3)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>10 (1.1)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Bolded values highlight the n (%) of subjects with ≥1 RAM in the total population. RAM, resistance associated-mutation; ARV, antiretroviral; PDVF, protocol-defined virologic failure; PI, protease inhibitor; DRV, darunavir; N(t)RTI, nucleoside/tide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; rtv, ritonavir; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; cobi, cobicistat; TAF, tenofovir alafenamide; ETR, etravirine; QD, once daily; TE, treatment-experienced; TN, treatment-naïve.

<sup>a</sup>Indicates no loss of phenotypic susceptibility for the corresponding ARVs.

<sup>b</sup>Subject developed V11I, a secondary PI RAM, after treatment stop (discontinuation due to noncompliance), with no loss of phenotypic susceptibility to DRV or any PI.

<sup>c</sup>For all four subjects, there was a loss of FTC phenotypic susceptibility.

<sup>d</sup>One TE subject developed I84I/V, a primary PI and DRV RAM, after treatment stop (discontinuation due to noncompliance), with no loss of phenotypic susceptibility to DRV or any PI.

<sup>e</sup>For all four subjects, there was a loss of FTC phenotypic susceptibility.

<sup>f</sup>Subject developed V11I, a secondary PI RAM, after treatment stop (discontinuation due to noncompliance), with no loss of phenotypic susceptibility to DRV or any PI.

<sup>g</sup>Both subjects lost FTC phenotypic susceptibility.

<sup>h</sup>Subject developed four primary PI RAMs, three of which were also DRV RAMs (V32I, L76V, and I84V), with loss of phenotypic susceptibility to DRV, amprenavir, atazanavir, indinavir, and nelfinavir (possibly related to a previous virologic failure with rtv-boosted lopinavir treatment); see main text for additional information.

<sup>i</sup>The subject who developed M184V used an N(t)RTI backbone consisting of lamivudine, tenofovir disoproxil fumarate, and zidovudine; this subject did not lose phenotypic susceptibility to any of the background ARV agents. The subject who developed T215Y used an N(t)RTI backbone consisting of lamivudine, tenofovir disoproxil fumarate, and zidovudine; this subject lost phenotypic susceptibility to ETR etravirine.

<sup>j</sup>The subject who developed E138K and M230L lost ETR etravirine phenotypic susceptibility. The subject who developed L100L/I, E138E/G, and Y181Y/C had reduced susceptibility to ETR at the endpoint.

<sup>k</sup>The subject who developed L33F, a primary PI and DRV RAM, after treatment stop (discontinuation due to noncompliance), with no loss of phenotypic susceptibility to DRV or any PI.

<sup>l</sup>RAMs that were identified during the 2 switch studies (MONET and PROTEA) are reported. 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 virologic failure.

<sup>m</sup>Combined data from the three pivotal phase 3 studies of DRV QD.
Of note, there is another darunavir 800 mg QD–based regimen that is currently in clinical development. It is the first single-tablet regimen containing darunavir and combines darunavir 800 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg. This agent was evaluated in GS-US-299-0102 through 48 weeks7 (included in the current analysis and showing no resistance to darunavir, emtricitabine, or tenofovir alafenamide) and is being evaluated in 2 ongoing phase 3 studies (AMBER [NCT02431247] and EMERALD [NCT02269917]29); it was approved in Europe in September 2017 and submitted for regulatory approval in the United States in 2017. This potential regimen includes tenofovir alafenamide, a novel prodrug of tenofovir that provides comparable efficacy at one-tenth of the dose of tenofovir disoproxil fumarate, resulting in a ~90% lower tenofovir plasma concentration and fewer adverse effects, particularly renal and bone adverse effects.7,29,30 Moreover, strategies to simplify ARV regimens and decrease pill burden, such as single-tablet regimens, may help improve treatment adherence, which may in turn lead to higher virologic suppression rates and further reduce the potential for development of drug resistance.31–33

In summary, HIV-1 resistance to darunavir was rarely observed in the seven clinical studies of darunavir 800 mg QD–based treatment regimens that were included in this analysis; only 1 of 1686 (<0.1%) subjects lost darunavir phenotypic susceptibility. These findings are consistent with those from previous studies1–5 and demonstrate that darunavir dosed QD, which is indicated in treatment-naïve and treatment-experienced (without darunavir RAMs) patients, has a very high genetic barrier to the development of resistance.

Contributors

E.L., E.Y.W., D.L., S.S., S.D.M., and K.B. contributed to the conception and design of the analysis, interpretation of the data, and drafting and revision of the article.

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References