Boosted Darunavir

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Disclosures

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Boosted Darunavir Basics

• **Medication**
  – Oral protease inhibitor (PI)

• **Administration**
  – Co-administered with Ritonavir (DRV/r) OR
  – Co-administered with Cobicistat as a fixed dose combination tablet (DRV/c)
  – Several drug-drug interactions due to ritonavir and cobicistat CYP3A inhibition

• **Indication**
  – Once daily DRV/r or DRV/c is indicated for the treatment of HIV-1 in adult and pediatric patients
  – Twice daily DRV/r can be used in treatment-experienced adults with certain PI resistance mutations

Source: Darunavir Prescribing Information and Darunavir-Cobicistat Prescribing Information.
Boosted Darunavir Basics

• Testing Prior to Initiation
  – Liver function tests if using DRV/r
  – Renal function if using DRV/c
  – Genotype especially for treatment experienced individuals

• With Renal Impairment
  – DRV/c is not recommended for severe renal impairment

• With Hepatic Impairment
  – DRV/c is not recommended for severe hepatic impairment
  – Close monitoring of liver function tests are recommended if using DRV/r

Source: Darunavir Prescribing Information and Darunavir-Cobicistat Prescribing Information.
Darunavir

Dosing: Once daily with food

800 mg Darunavir + 100 mg Ritonavir

600 mg Darunavir + 100 mg Ritonavir

Dosing: Twice daily with food

Booster
Darunavir-Cobicistat

Darunavir: 800 mg
Cobicistat: 150 mg

Dosing: Once daily with food
# Recommended Darunavir Dosing in Adult Patients

## Treatment-Naïve and Treatment Experienced with no Darunavir Resistance-Associated Mutations

<table>
<thead>
<tr>
<th>Darunavir + Ritonavir</th>
<th>Darunavir-Cobicistat</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg + 100 mg</td>
<td>800 mg-150 mg</td>
</tr>
</tbody>
</table>

- **Dosing:** Once daily with food

## Treatment Experienced with ≥1 Darunavir Resistance-Associated Mutations

<table>
<thead>
<tr>
<th>Darunavir + Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 mg + 100 mg</td>
</tr>
</tbody>
</table>

- **Dosing:** Twice daily with food

*Source: Darunavir Prescribing Information and Darunavir-Cobicistat Prescribing Information.*
Darunavir: Mechanism of Action
HIV Protease and Polypeptide Cleavage
Protease Inhibitors: Mechanism of Action

Active Site

HIV Protease

Darunavir
Resistance
### HIV Protease and Darunavir Amino Acid Mutations

**Darunavir Resistance-Associated Mutations**

<table>
<thead>
<tr>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>V11I</td>
</tr>
<tr>
<td>V32I</td>
</tr>
<tr>
<td>L33F</td>
</tr>
<tr>
<td>I47V</td>
</tr>
<tr>
<td>I50V</td>
</tr>
<tr>
<td>I54L</td>
</tr>
<tr>
<td>I54M</td>
</tr>
<tr>
<td>T74P</td>
</tr>
<tr>
<td>L76V</td>
</tr>
<tr>
<td>I84V</td>
</tr>
<tr>
<td>L89V</td>
</tr>
</tbody>
</table>

Illustration: David H. Spach, MD and Cognition Studio, Inc.
Key Clinical Trials
### Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Study Design

**Background**: Randomized, open-label phase 3 trial comparing the efficacy and safety of once-daily darunavir + ritonavir with lopinavir-ritonavir in treatment-naïve persons with HIV

**Inclusion Criteria** (n = 689)
- Age >18 years
- Antiretroviral-naïve
- HIV RNA ≥5000 copies/mL
- No AIDS-defining illness

**Treatment Arms**
- DRV 800 mg QD + RTV 100 mg QD + TDF-FTC
- LPV/r 800/200 mg QD (or 400 mg bid) + TDF-FTC

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**Darunavir + Ritonavir + TDF-FTC**  
(n = 343)

**Lopinavir-ritonavir + TDF-FTC**  
(n = 346)

Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Results at 48 Weeks

Week 48: Virologic Response (Intent-to-Treat Analysis)

Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Results at 96 Weeks

Week 96: Virologic Response (Intent-to-Treat Analysis)

Once Daily Darunavir/r versus Lopinavir/r in Treatment-Naïve ARTEMIS: Results at 96 Weeks

Week 96: Analysis of Lipids

Boosted Darunavir
Summary of Key Studies

• Trials in Treatment Naïve Adults
  - 1,2 ARTEMIS: DRV/r versus LPV/r
    • Once-daily DRV/r was superior in virologic response to LPV/r, with a more favorable safety, gastrointestinal and lipid profile, in antiretroviral-naïve patients

Efficacy of Darunavir-cobicistat is based on clinical trials establishing the efficacy of using DRV/r once daily in treatment naïve individuals

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Study Design

**Background**: Two randomized, phase 2b trials to compare the efficacy and safety of ritonavir-boosted darunavir with other protease inhibitors in treatment-experienced adults with HIV and PI resistance.

**Inclusion Criteria (n = 155)**
- Age ≥18 years
- HIV RNA >1000 copies/mL
- On PI-containing regimen
- Took >1 NRTI, and ≥1 NNRTI as part of failing regimen
- At least 1 primary PI mutation at screening

**Treatment Arms**
- Darunavir 600 mg BID + Ritonavir 100 mg bid + OBR*
- Investigator-selected control PI + OBR*

*OBR = Optimized background regimen: ≥2 NRTIs +/- enfuvirtide

Darunavir/r versus other PIs in Treatment-Experienced
POWER 1 and 2: Result

Week 48: Virologic Response

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Result

Week 48: Virologic Response (ITT-TLOVR)

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Result

Week 48: Virologic Response, by Primary PI Mutations at Baseline

Darunavir/r versus other PIs in Treatment-Experienced POWER 1 and 2: Result

Week 48: Virologic Response, by DRV Resistance-Associated Mutations at Baseline

Once-daily versus Twice-daily Darunavir in Treatment-Experienced ODIN: Study Design

- **Background**: Randomized, open-label phase 3 trial to compare once daily versus twice-daily dosing of ritonavir-boosted darunavir in treatment-experienced patients with HIV

- **Inclusion Criteria (n = 590)**
  - Age ≥18 years
  - On stable antiretroviral regimen for >12 weeks
  - HIV RNA >1000 copies/mL
  - CD4 count >200 cells/mm$^3$
  - No darunavir resistance-associated mutations

- **Treatment Arms**
  - Darunavir 800 mg QD + RTV 100 mg QD + OBR*
  - Darunavir 600 mg BID + RTV 100 mg BID + OBR

*OBR = Optimized background regimen: ≥2 nucleoside reverse transcriptase inhibitors, investigator-selected

Once Daily versus Twice Daily Darunavir in ARV-Experienced ODIN: Result

Week 48: Virologic Response (ITT-TLOVR)

Once-Daily versus Twice Daily Darunavir in ARV-Experienced ODIN: Result (Impact on Lipids)

Week 48: Changes in Lipids from Baseline

Once Daily versus Twice Daily Darunavir in ARV-Experienced ODIN: Result

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DRV + RTV + Once Daily + OBR (n = 294)</th>
<th>DRV + RTV + Twice Daily + OBR (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10.9%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9.9%</td>
<td>15.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.1%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Rash</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>1.4%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Boosted Darunavir: Summary of Key Studies

• Trials in Treatment Naïve Adults
  - 1,2 ARTEMIS: DRV/r versus LPV/r
    • Once-daily DRV/r was superior in virologic response to LPV/r, with a more favorable safety, gastrointestinal and lipid profile, in antiretroviral-naive patients

• Trials In Treatment Experienced Adults with PI resistance
  - 3 POWER 1 and 2: Switch to DRV-COBI-TAF-FTC or stay on PI + TDF-FTC
    • Using DRV/r 600/100 mg twice daily with OBR, had more effective virologic response plus favorable safety and tolerability, up to week 48, in treatment-experienced patients
  - 4 ODIN: Switch to DRV-COBI-TAF-FTC or stay on PI + TDF-FTC
    • Once-daily DRV/r 800/100 mg was non-inferior in virologic response to twice-daily DRV/r 600/100 mg at 48 weeks in treatment-experienced patients with no DRV RAMs

Source:
Boosted Darunavir: Adverse Effects

• **Gastrointestinal**
  - Diarrhea and nausea

• **Hepatotoxicity**
  - Risk increased with pre-existing liver dysfunction, including chronic HBV or HCV

• **Skin Reactions**
  - Darunavir contains a sulfonamide moiety
  - Rash in approximately 8%
  - Stevens-Johnson syndrome in 0.1% of persons taking darunavir with cobicistat

• **Prior Sulfonamide Allergy**
  - Incidence and severity of rash similar with or without a history of sulfonamide allergy
  - History of sulfonamide allergy not a contraindication but monitoring recommended
Boosted Darunavir: Editor’s Summary

• Oral PI available to be given with ritonavir or, in a fixed dose combination with cobicistat

• High genetic barrier to resistance

• DRV/c should not be used in patients with severe renal or severe hepatic impairment, but DRV/r remains an option

• Mostly associated with gastrointestinal adverse effects, such as diarrhea and nausea

• As an inhibitor of CYP3A, Cobicistat and Ritonavir can cause problematic interactions with drugs metabolized by CYP3A or drugs that induce or inhibit CYP3A
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