Dolutegravir (Tivicay)

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Dolutegravir (Tivicay)

- Treatment Naïve: 50 mg once daily with or without food
- Coadministered with certain UGT1A or CYP3A inducers: 50 mg twice daily with or without food
- INSTI-experienced with certain substitutions: 50 mg twice daily with or without food
- Clinically suspected INSTI resistance: 50 mg twice daily with or without food
Dolutegravir (Tivicay)

- **Class**: integrase strand transfer inhibitor (INSTI)
- **Approval Status**: approved for persons 12 and older
- **Dose (with or without food)**:
  - Treatment Naïve: 50 mg once daily
  - Treatment Experienced, INSTI-Naive: 50 mg once daily
  - INSTI Resistant: 50 mg twice daily
  - Coadministration of Certains Inducers: 50 mg twice daily
- **Metabolism**: glucuronidation via UGT 1A1
- **Adverse Events**:
  - Small increases in serum creatinine (benign inhibition of creatinine secretion)
## Recommended Dolutegravir Dosing

<table>
<thead>
<tr>
<th>Adult Population</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve or Treatment-experienced INSTI-naïve</td>
<td>50 mg once daily</td>
</tr>
<tr>
<td>Coadministered with potent UGT1A/CYP3A inducer: Efavirenz, Fosamprenavir/ritonavir, Tipranavir/ritonavir, Rifampin</td>
<td>50 mg twice daily</td>
</tr>
<tr>
<td>INSTI-experienced with certain INSTI mutations* or Clinically suspected INSTI resistance</td>
<td>50 mg twice daily</td>
</tr>
<tr>
<td>Poor virologic response associated with Q148 Substitution plus ≥2 INSTI mutations</td>
<td></td>
</tr>
</tbody>
</table>

*Note: INSTI-experienced with certain INSTI mutations are defined as those with certain INSTI resistance mutations that are associated with reduced dolutegravir efficacy.*
## Dolutegravir
### Summary of Key Studies

- **Phase 2b Trials in Treatment Naïve**
  - SPRING-1: Dose-ranging Dolutegravir vs. Efavirenz + 2NRTIs

- **Phase 3 Trials in Treatment Naïve**
  - SPRING 2: Dolutegravir + 2NRTIs vs Raltegravir + 2NRTIs
  - FLAMINGO: Dolutegravir vs. Ritonavir-boosted Darunavi
  - GS-380-1489: Dolutegravir + TAF-FTC versus Bictegravir-TAF-FTC
  - ING 116070: Dolutegravir CSF levels and virologic response in CSF

- **Phase 2a Trial in Treatment Naïve & Experienced**
  - ING 111521: 10-Day, dose-ranging, dolutegravir monotherapy trial
  - IMPAACT P1093: Dolutegravir in infants, children, and adolescents
# Dolutegravir

## Summary of Key Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 2b Trials in Treatment Experienced</strong></td>
<td></td>
</tr>
<tr>
<td>VIKING 1 &amp; 2</td>
<td>Dolutegravir 50 mg QD added to failing regimen</td>
</tr>
<tr>
<td>VIKING 2</td>
<td>Dolutegravir 50 mg BID added to failing regimen</td>
</tr>
<tr>
<td><strong>Phase 3 Trials in Treatment Experienced</strong></td>
<td></td>
</tr>
<tr>
<td>SAILING</td>
<td>Dolutegravir 50 mg QD vs. Raltegravir in salvage regimen</td>
</tr>
<tr>
<td>VIKING 3</td>
<td>Dolutegravir 50 mg BID in patients with INSTI resistance</td>
</tr>
<tr>
<td>VIKING-4</td>
<td>Dolutegravir 50 mg BID in patients with INSTI resistance</td>
</tr>
<tr>
<td></td>
<td>(with placebo-controlled 7-day monotherapy phase)</td>
</tr>
<tr>
<td><strong>Phase IV Switch Studies</strong></td>
<td></td>
</tr>
<tr>
<td>NEAT 022</td>
<td>CV Risk Switching from boosted PI to Dolutegravir</td>
</tr>
<tr>
<td>DOMONO</td>
<td>Dolutegravir 50 mg QD Monotherapy vs. 3-drug treatment</td>
</tr>
</tbody>
</table>
INITIAL THERAPY

Dolutegravir
Dolutegravir vs. Efavirenz in Antiretroviral Naive

SPRING-1 Study
Dolutegravir versus Efavirenz in ARV-Naïve SPRING-1: Study Design

**Study Design: SPRING-1**

**Background**: Dose-ranging, partially-blinded phase 2b trial in antiretroviral-naïve persons with HIV to select a dolutegravir dose for phase 3 trials.

**Inclusion Criteria (n = 205)**
- Age ≥18
- Antiretroviral-naïve
- CD4 >200 cells/mm³
- HIV RNA >1,000 copies/mL
- No NNRTI mutations

**Treatment Arms**
- Dolutegravir: 2, 10, or 50 mg daily + 2 NRTIs*
- Efavirenz: 600 mg daily + 2 NRTIs*

*2 NRTIs = Tenofovir DF-Emtricitabine or Abacavir-Lamivudine

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Dolutegravir versus Efavirenz in ARV-Naïve SPRING-1: Results

Week 48 Virologic Response (TLOVR)

Dolutegravir versus Efavirenz in ARV-Naïve SPRING-1: Results

Week 16, 24, and 48 Virologic Response (TLOVR)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>DTG 10 mg</th>
<th>DTG 25 mg</th>
<th>DTG 50 mg</th>
<th>DTG Subtotal</th>
<th>EFV 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
<td>8 (5%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (13%)</td>
<td>6 (12%)</td>
<td>6 (12%)</td>
<td>19 (12%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
<td>12 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (4%)</td>
<td>0</td>
<td>3 (6%)</td>
<td>5 (3%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>10 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>5 (3%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>0</td>
<td>3 (6%)</td>
<td>3 (2%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (4%)</td>
<td>0</td>
<td>0</td>
<td>2 (1%)</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>

**Interpretation**: “Dolutegravir was effective when given once daily without a pharmacokinetic booster and was well tolerated at all assessed doses. Our findings support the assessment of once daily 50 mg dolutegravir in phase 3 trials.”

Dolutegravir vs. Raltegravir
SPRING-2 Study
Study Design: SPRING-2

- **Background**: Randomized, double-blind study, phase 3 trial comparing dolutegravir versus raltegravir, both with 2NRTI backbone in persons with HIV.

- **Inclusion Criteria (n = 822)**
  - Antiretroviral-naïve
  - Age ≥18
  - HIV RNA ≥1,000 copies/mL
  - No active CDC AIDS condition

- **Treatment Arms**
  - Dolutegravir + 2NRTIs
  - Raltegravir + 2NRTIs
  - Fixed dose 2NRTIs* = TDF-FTC or ABC-3TC

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**Dolutegravir**: 50 mg QD
Fixed-dose NRTI backbone*  
(n = 411)

**Raltegravir**: 400 mg BID
Fixed-dose NRTI backbone*  
(n = 411)

Dolutegravir versus Raltegravir
SPRING-2: Results

Week 48: Virologic Response, by Baseline HIV RNA

Dolutegravir versus Raltegravir
SPRING-2: Results

Week 48: Virologic Response, by NRTI Component

Interpretation: “The non-inferior efficacy and similar safety profile of dolutegravir compared with raltegravir means that if approved, combination treatment with once-daily dolutegravir and fixed-dose nucleoside reverse transcriptase inhibitors would be an effective new option for treatment of HIV-1 in treatment-naive patients.”

Dolutegravir vs. Raltegravir

SPRING-2 Study: Week 96 Data
### Dolutegravir + 2NRTIs versus Raltegravir + 2NRTIs

#### SPRING-2 (Week 96): Results

**Week 96 Virologic Response: Background Dual NRTI Therapy**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>81/332 (411)</td>
<td></td>
</tr>
<tr>
<td>Abacavir-Lamivudine</td>
<td>76/314 (411)</td>
<td></td>
</tr>
<tr>
<td>Tenofovir DF-Emtricitabine</td>
<td>74/125 (169)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>76/124 (164)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>77/190 (247)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86/207 (242)</td>
<td></td>
</tr>
</tbody>
</table>
Dolutegravir versus Raltegravir
SPRING-2 (Week 96): Conclusions

**Interpretation**: “At week 96, once-daily dolutegravir was non-inferior to twice-daily raltegravir in treatment-naive, patients with HIV-1. Once-daily dosing without requirement for a pharmacokinetic booster makes dolutegravir-based therapy an attractive treatment option for HIV-1-infected treatment-naive patients.”

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs

FLAMINGO
Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Study Design

**Study Design: FLAMINGO**

- **Background**: Randomized, open label phase 3b study comparing dolutegravir to darunavir-ritonavir with fixed-dose NRTI backbone in antiretroviral-naïve persons with HIV.

- **Inclusion Criteria** (n = 484 analyzed)
  - Antiretroviral-naïve
  - Age ≥18
  - HIV RNA ≥1,000 copies/mL
  - No active class C conditions
  - No resistance to NRTIs or protease inhibitors

- **Treatment Arms** (once daily)
  - Dolutegravir 50 mg + 2 NRTIs*
  - Darunavir 800 mg + Ritonavir 100 mg + 2 NRTIs*

*2 NRTIs = tenofovir-emtricitabine or abacavir-lamivudine (with negative HLA-B*5701 testing).

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs
FLAMINGO: Results

Week 48 Virologic Response, by Baseline HIV RNA Level

<table>
<thead>
<tr>
<th>Baseline HIV RNA</th>
<th>Dolutegravir + 2NRTIs</th>
<th>Darunavir + RTV + 2NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>217/242</td>
<td>200/242</td>
</tr>
<tr>
<td>≤100,000 copies/mL</td>
<td>160/181</td>
<td>157/181</td>
</tr>
<tr>
<td>&gt;100,000 copies/mL</td>
<td>57/61</td>
<td>43/61</td>
</tr>
</tbody>
</table>

HIV RNA <50 copies/mL (%)

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs

FLAMINGO: Results

48 Week Virologic Outcomes (Modified Intent-to-Treat Analysis)

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs

**FLAMINGO: Results**

*Week 48 Virologic Response, by Background Dual NRTI Therapy*

<table>
<thead>
<tr>
<th>NRTI BackBone</th>
<th>Overall</th>
<th>ABC-3TC</th>
<th>TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV RNA &lt;50 copies/mL (%)</td>
<td>HIV RNA &lt;50 copies/mL (%)</td>
<td>HIV RNA &lt;50 copies/mL (%)</td>
</tr>
<tr>
<td>Dolutegravir + 2 NRTIs</td>
<td>90/217/242</td>
<td>90/71/79</td>
<td>90/146/163</td>
</tr>
<tr>
<td>Darunavir + RTV + 2 NRTIs</td>
<td>83/200/242</td>
<td>85/68/80</td>
<td>81/132/162</td>
</tr>
</tbody>
</table>

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs

**FLAMINGO: Common Adverse Events**

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events in ≥ 5% of Subjects in Either Arm</th>
<th>DTG + 2 NRTIs (n = 242)</th>
<th>DRV + RTV + 2 NRTIs (n= 242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>17%</td>
<td>29%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>18%</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Cough</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Dolutegravir + 2 NRTIs versus Darunavir + RTV + 2 NRTIs

FLAMINGO: Common Adverse Events (continued)

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events in ≥ 5% of Subjects in Either Arm</th>
<th>DTG + 2 NRTIs (n = 242)</th>
<th>DRV + RTV + 2 NRTIs (n = 242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Rash</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Depression</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Interpretation**: “Once-daily dolutegravir was superior to once-daily darunavir plus ritonavir. Once-daily dolutegravir in combination with fixed-dose NRTIs represents an effective new treatment option for HIV-1-infected, treatment-naive patients.”
Dolutegravir + ABC-3TC and CSF HIV-1 RNA Levels

ING116070 Study
Dolutegravir + ABC-3TC and Impact on CSF HIV RNA Levels
ING116070 Study: Design

### Study Design: ING116070

- **Background**: Single arm, phase 3b, open-label, multi-center trial to evaluate the distribution and antiviral activity of dolutegravir + abacavir-lamivudine in CSF in persons with HIV.

- **Inclusion Criteria (n = 13)**
  - Antiretroviral-naïve
  - Age ≥18 years
  - HIV RNA ≥5,000 copies/mL
  - CD4 count ≥200 cells/mm³
  - No active CDC AIDS condition (except KS)

- **Treatment Arm (n = 12)**
  - Dolutegravir (QD) + Abacavir-lamivudine

Dolutegravir + ABC-3TC and Impact on CSF HIV RNA Levels

ING116070 Study: Design

<table>
<thead>
<tr>
<th>Cerebrospinal Fluid (CSF) Parameter</th>
<th>Week 2</th>
<th>Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CSF DTG Concentration total, ng/mL</td>
<td>16.2</td>
<td>12.6</td>
</tr>
<tr>
<td>CSF/Total Plasma Ratio for DTG Concentration</td>
<td>0.47</td>
<td>0.55</td>
</tr>
<tr>
<td>CSF HIV-1 RNA &lt;50 copies/mL</td>
<td>11/12 (92%)</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>CSF HIV-1 RNA &lt;2 copies/mL</td>
<td>ND</td>
<td>11/12 (92%)</td>
</tr>
</tbody>
</table>

**Conclusions:** “The dolutegravir concentrations in CSF were similar to unbound plasma concentrations and exceeded the in vitro 50% inhibitory concentration for wild-type HIV (0.2 ng/mL), suggesting that dolutegravir achieves therapeutic concentrations in the central nervous system. The HIV-1 RNA reductions were similar in CSF and plasma.”
TREATMENT-NAÏVE AND TREATMENT EXPERIENCED

Dolutegravir
Dolutegravir 10-Day, Dose-Ranging, Monotherapy Study
ING111521
## Dolutegravir Dose-Ranging Monotherapy
### ING111521 Study: Design

### Study Design: ING111521

- **Background**: Randomized, double-blind, dose-ranging, 10-day, phase 2a study to evaluate antiviral activity, safety, and pharmacokinetics and pharmacodynamics of dolutegravir in persons with HIV.

- **Inclusion Criteria (n = 35)**
  - Antiretroviral-naïve and antiretroviral-experienced
  - Integrase strand transfer inhibitor-naïve
  - Age ≥18 and ≤65 years
  - CD4 ≥100 cells/mm³
  - HIV RNA ≥5,000 copies/mL
  - No AIDS conditions

- **Treatment Arms**
  - Dolutegravir 2, 10, or 50 mg daily, or placebo

### Dolutegravir: 2 mg QD
- (n = 9)

### Dolutegravir: 10 mg QD
- (n = 9)

### Dolutegravir: 50 mg QD
- (n=10)

### Placebo
- (n=7)

Dolutegravir Dose-Ranging Monotherapy ING111521 Study: Results

Baseline to Day 11: Change in Baseline HIV RNA Level

Regimen (once daily dosing)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Change in HIV RNA from Baseline (Log10 copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.05</td>
</tr>
<tr>
<td>Dolutegravir: 2 mg</td>
<td>-1.51</td>
</tr>
<tr>
<td>Dolutegravir: 10 mg</td>
<td>-2.03</td>
</tr>
<tr>
<td>Dolutegravir: 50 mg</td>
<td>-2.46</td>
</tr>
</tbody>
</table>

Dolutegravir Dose-Ranging Monotherapy
ING111521 Study: Results

Baseline to Day 11: Patients with Suppressed Viral Load at Nadir

Conclusion: “Dolutegravir demonstrated potent antiviral activity, good short-term tolerability, low pharmacokinetic variability, and a predictable pharmacokinetics/pharmacodynamics relationship, which support once daily dosing without a pharmacokinetic booster in integrase-naive patients in future studies.”

Dolutegravir in Treatment-Experienced Adolescents

IMPAACT P1093
Dolutegravir in Treatment-Experienced Adolescents
IMPAACT P1093: Study Design

**Study Design: IMPAACT P1093**

- **Background:** Open-label, non-randomized phase I/II study treatment-experienced adolescents with HIV

- **Inclusion Criteria (n = 23)**
  - Age 12 to <18 years of age
  - Antiretroviral-experienced
  - Naïve to integrase inhibitors
  - HIV RNA >1,000 copies/mL
  - Genotype showing sensitivity to at least one other active antiretroviral agent

- **Treatment Arms**
  - Dolutegravir monotherapy, then dolutegravir with optimized background regimen

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### Stage I
Intensive PK group n=10

<table>
<thead>
<tr>
<th>Functional monotherapy or monotherapy phase</th>
<th>Optimize therapy continuation phase 48 week DTG + OBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 5-10 Intensive PK visit Week 48</td>
</tr>
</tbody>
</table>

### Stage II: opens after dose/safety criteria met in stage I; n=13

- DTG and OBR from day 1

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Dolutegravir in Treatment-Experienced Adolescents
IMPAACT P1093: Results

Week 48: Virologic Response

Week 48: Patient-Reported Adherence

**Conclusions**: “Dolutegravir achieved target PK exposures in adolescents. Dolutegravir was safe and well tolerated, providing good virologic efficacy through week 48.”
TREATMENT EXPERIENCED

Dolutegravir
Dolutegravir in Patients with Raltegravir-Resistant HIV

VIKING (Cohorts I & II)


## Dolutegravir in Patients with Raltegravir Resistance

### VIKING Study (Cohorts I & II): Study Design

**Day 1**

<table>
<thead>
<tr>
<th><strong>Functional Monotherapy Phase</strong></th>
<th><strong>Continuation Phase</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort I</strong>: Dolutegravir: 50 mg QD</td>
<td><strong>Cohort I</strong>: Dolutegravir: 50 mg QD + OBR</td>
</tr>
<tr>
<td><strong>Cohort II</strong>: Dolutegravir: 50 mg BID</td>
<td><strong>Cohort II</strong>: Dolutegravir: 50 mg BID + OBR</td>
</tr>
</tbody>
</table>

**Week 24**

**Study Design: VIKING**

- **Background**: Single-arm, phase 2b trial evaluating efficacy of once daily or twice daily dolutegravir in patients with integrase resistance.

- **Inclusion Criteria (n=51)**
  - Age ≥18 years
  - HIV RNA > 1,000 copies/mL
  - Documented resistance ≥3 ARV classes, including integrase inhibitors

- **Treatment Arms**
  - Cohort I*: dolutegravir 50 mg once daily
  - Cohort II*: dolutegravir 50 mg twice daily

*Failing regimen continued during day 1-10, then replaced with OBR through week 24.

Dolutegravir in Patients with Raltegravir Resistance VIKING Study (Cohorts I & II): Results

Week 24 Virologic Response

![Bar chart showing viral suppression thresholds for Cohorts I and II.]

- **HIV RNA <400 copies/mL**
  - **Cohort I**: 14/27 (52%)
  - **Cohort II**: 20/24 (83%)

- **HIV RNA <50 copies/mL**
  - **Cohort I**: 11/27 (41%)
  - **Cohort II**: 18/24 (75%)

Conclusion: “Dolutegravir 50 mg twice daily with an optimized background provided greater and more durable benefit than the once-daily regimen. These data are the first clinical demonstration of the activity of any integrase inhibitor in subjects with HIV-1 resistant to raltegravir.”

Dolutegravir versus Raltegravir in Treatment Experienced
SAILING Study
Dolutegravir versus Raltegravir in Treatment Experienced SAILING: Study Design


<table>
<thead>
<tr>
<th>Study Design: SAILING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong>: Randomized, double-blind, active-control phase 3 trial evaluating efficacy, safety, and emergent resistance with dolutegravir versus raltegravir in antiretroviral-experienced, integrase inhibitor-naïve patients with at least 2-class resistance</td>
</tr>
<tr>
<td><strong>Inclusion Criteria</strong> (n = 715)</td>
</tr>
<tr>
<td>- Age ≥18</td>
</tr>
<tr>
<td>- Resistance to ≥2 ARV classes</td>
</tr>
<tr>
<td>- Integrase inhibitor-naïve</td>
</tr>
<tr>
<td>- 2 consecutive HIV RNA ≥400 copies/mL (unless &gt;1000 copies/mL at screening)</td>
</tr>
<tr>
<td><strong>Treatment Arms</strong></td>
</tr>
<tr>
<td>- Dolutegravir + up to 2 background ARTs</td>
</tr>
<tr>
<td>- Raltegravir + up to 2 background ARTs</td>
</tr>
</tbody>
</table>

- **Dolutegravir 50 mg QD + ≤2 Background ART Drugs** (n = 354)
- **Raltegravir 400 mg BID + ≤2 Background ART Drugs** (n = 361)
Dolutegravir versus Raltegravir in Treatment Experienced SAILING: Results

Week 48 Virologic Response, By Baseline HIV RNA Level

Dolutegravir versus Raltegravir in Treatment-Experienced
SAILING: Results

Week 48 Virologic Failure

**Interpretation:** “Once-daily dolutegravir, in combination with up to two other antiretroviral drugs, is well tolerated with greater virological effect compared with twice-daily raltegravir in this treatment-experienced patient group.”
Dolutegravir in Patients with Integrase-Resistant HIV

VIKING-3
**Study Design: VIKING-3**

- **Background**: Single arm, open-label, phase 3 trial to determine the efficacy of twice daily dolutegravir in patients with integrase resistance.

- **Inclusion Criteria** (n=183)
  - Age ≥18
  - Antiretroviral experienced, resistance to raltegravir and/or elvitegravir
  - Resistance to 2 classes of ARVs (in addition to integrase resistance)
  - HIV RNA ≥500 copies/mL
  - At least one fully active drug for optimized background regimen
  - Dolutegravir naïve

- **Treatment arm**: Dolutegravir 50 mg twice daily, with OBR added on day 7

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Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-3: Results

24 Week Virologic Response, by Baseline HIV RNA Level

Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-3: Results

24 Week Virologic Response, by Baseline Genotype

<table>
<thead>
<tr>
<th>Baseline Genotype</th>
<th>HIV RNA &lt;50 copies/mL (%)</th>
<th>100/126</th>
<th>79</th>
<th>58</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Q148 Mutation*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q148 + 1 Mutation^</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q148 + ≥2 Mutations^</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or only historical evidence of resistance
^Secondary mutations from G140A/C/S, E138A/K/T or L74I.

Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-3: Results

24 Week Virologic Response, by Baseline Phenotype

**Conclusions**: “Dolutegravir 50 mg BID-based therapy was effective in this highly treatment-experienced population with integrase inhibitor-resistant virus.”

Dolutegravir in Patients with Integrase-Resistant HIV

VIKING-4
Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-4: Study Design

### Day 1

**Functional Monotherapy Phase**

**Dolutegravir: 50 mg BID or Placebo**

### Day 8

**Continuation Phase**

**Dolutegravir: 50 mg BID + OBR**

### Week 48

**Study Design: VIKING-4**

- **Background:** Single-arm, open-label, phase 3 trial to evaluate short-term antiviral efficacy of dolutegravir in persons with HIV who have integrase resistance

- **Inclusion Criteria**
  - Age ≥18 years old
  - ARV experienced, dolutegravir naïve,
  - Documented Resistance to ≥3 ARV classes, including raltegravir or elvitegravir
  - HIV RNA ≥1,000 copies/mL

- **Treatment Arms (n = 30 randomized)**
  - Day 0 to 7: Dolutegravir: 50 mg BID or Placebo
  - Day 8 to Week 24: Dolutegravir 50 mg BID + optimized background regimen

Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-4: Results

Baseline to Day 8: Change in Viral Load (in Functional Monotherapy Phase)

Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-4: Results

Week 24 and 48 Virologic Response in Dolutegravir-Treated Patients

Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-4: Results

Week 24 Virologic Response, by Baseline Genotype

*Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or historical evidence of resistance.

^Secondary mutations from G140A/C/S, E138A/K/T and L74I.

Dolutegravir in Patients with Integrase Inhibitor Resistance VIKING-4: Results

Week 48 Virologic Response, by Baseline Genotype

<table>
<thead>
<tr>
<th>Baseline Dolutegravir Fold Change (Phenotype)</th>
<th>HIV RNA &lt;50 copies/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>40</td>
</tr>
<tr>
<td>No Q148 Mutation*</td>
<td>11/30</td>
</tr>
<tr>
<td>Q148 + 1 Mutation^</td>
<td>57</td>
</tr>
<tr>
<td>Q148 + ≥2 Mutations^</td>
<td>25</td>
</tr>
</tbody>
</table>

- *Included primary INI-resistance mutations N155H, Y143C/H/R, T66A or E92Q or historical evidence of resistance.
- ^Secondary mutations from G140A/C/S, E138A/K/T and L74I.

Dolutegravir in Patients with Integrase Inhibitor Resistance

VIKING-4: Results

Week 24 Virologic Response, by Baseline Phenotype*

<table>
<thead>
<tr>
<th>HIV RNA &lt;50 copies/mL (%)</th>
<th>Overall</th>
<th>0 to 2.5</th>
<th>&gt; 2.5 to 4</th>
<th>&gt; 4 to 8</th>
<th>&gt; 10 to 20</th>
<th>&gt; 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>47</td>
<td>55</td>
<td>60</td>
<td>22</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>14/30</td>
<td>6/11</td>
<td>3/5</td>
<td>2/9</td>
<td>1/2</td>
<td>1/2</td>
</tr>
</tbody>
</table>

*Missing phenotypic resistance data on 1 subject

Week 48 Virologic Response, by Baseline Phenotype

*Missing phenotypic resistance data on 1 subject

Conclusions: “The observed day 8 antiviral activity in this highly treatment-experienced population with INI-resistant HIV-1 was attributable to dolutegravir. Longer-term efficacy (after considering baseline ART resistance) and safety during the open-label phase were in-line with the results of the larger VIKING-3 study.”
SWITCH STUDIES

Dolutegravir
Switch from Boosted PI to Dolutegravir

NEAT 022
Switching from a Boosted PI to Dolutegravir

NEAT 022: Design

Study Design

- **Background**: Randomized, open-label, multicenter trial in Europe evaluating the impact of switching from a boosted PI to dolutegravir in virologically suppressed persons with older age or elevated cardiovascular risk.

- **Inclusion Criteria**
  - Age ≥50 years or Framingham 10-year estimated cardiovascular event risk >10%
  - HIV RNA <50 copies/mL
  - On 2 NRTI’s + boosted PI
  - No prior virologic failure and no genotypic resistance mutations

48 weeks (primary endpoint), after which all participants switch to DTG + 2 NRTI’s

**Switch Regimen**
Dolutegravir + 2 NRTI’s
(n = 205)

**Maintenance Regimen**
Boosted PI + 2 NRTI’s
(n = 210)

### Switching from a Boosted PI to Dolutegravir

#### NEAT 022: Baseline Regimens

<table>
<thead>
<tr>
<th>NRTI Backbone</th>
<th>DTG + 2 NRTI’s (n = 205)</th>
<th>PI/r + 2 NRTI’s (n = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF-Lamivudine</td>
<td>134 (65.4%)</td>
<td>135 (64.3%)</td>
</tr>
<tr>
<td>Abacavir-Lamivudine</td>
<td>63 (30.7%)</td>
<td>67 (31.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (3.9%)</td>
<td>8 (3.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Boosted PI</th>
<th>DTG + 2 NRTI’s (n = 205)</th>
<th>PI/r + 2 NRTI’s (n = 210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir + ritonavir</td>
<td>105 (51.5%)</td>
<td>107 (51.0%)</td>
</tr>
<tr>
<td>Atazanavir + ritonavir</td>
<td>77 (37.7%)</td>
<td>74 (35.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>22 (10.7%)</td>
<td>29 (13.8%)</td>
</tr>
</tbody>
</table>

Switching from a Boosted PI to Dolutegravir
NEAT 022: Results

Week 48: Virologic Response by FDA Snapshot Analysis (ITT)

Week 48: Virologic Response by FDA Snapshot Analysis (ITT)

HIV RNA <50 copies/mL (%)

- Dolutegravir + 2 NRTI's: 93.1%
- Ritonavir-Boosted PI + 2 NRTI's: 95.2%

Switching from a Boosted PI to Dolutegravir
NEAT 022: Results

Mean Percentage Change in Lipids at 48 Weeks

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Dolutegravir + 2 NRTI's</th>
<th>Ritonavir-Boosted PI + 2 NRTI's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>-8.7</td>
<td>0.7</td>
</tr>
<tr>
<td>LDL</td>
<td>-7.7</td>
<td>2.0</td>
</tr>
<tr>
<td>HDL</td>
<td>-5.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-18.4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Switching from a Boosted PI to Dolutegravir
NEAT 022: Conclusion

**Interpretation:** “Switching to a dolutegravir regimen in virologically suppressed HIV type 1 patients with high cardiovascular disease risk was noninferior, and significantly improved lipid profiles.”

Dolutegravir as Maintenance Monotherapy

DOMONO
Dolutegravir as Maintenance Monotherapy
DOMONO: Design

**Study Design: DOMONO**

- **Background**: Randomized, open-label, phase 2, non-inferiority trial conducted at 2 centers in Netherlands to determine if dolutegravir monotherapy is noninferior to combination antiretroviral therapy in maintaining viral suppression.

- **Inclusion Criteria**:
  - Age ≥18 years old
  - On 3-drug ART
  - HIV RNA <50 copies/mL for ≥6 months
  - HIV RNA zenith <100,000 copies/mL
  - CD4 count nadir >200 cells/mm³
  - No baseline HIV drug resistance
  - No history of virologic failure
  - No HBV co-infection

- **Dolutegravir Regimen**
  - Dolutegravir 50 mg once daily

**Immediate Switch to Monotherapy**
- Dolutegravir (n = 51)

**Continue 3-Drug ART**
- Continue 3-Drug ART (n = 53)

**Delayed Monotherapy**
- Dolutegravir (n = 47)
  - 6/53 did not switch

**Separate Control Group**
- 3-Drug ART (n = 152)

## Dolutegravir as Maintenance Monotherapy

### DOMONO: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Immediate Switch to DTG Monotherapy (n = 51)</th>
<th>Delayed Switch to DTG Monotherapy (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, years)</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Male, %</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>MSM, %</td>
<td>80</td>
<td>77</td>
</tr>
<tr>
<td>Caucasian ethnicity, %</td>
<td>86</td>
<td>79</td>
</tr>
<tr>
<td>On TDF before switch, %</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>On NNRTI + 2 NRTI’s before switch, %</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>On PI + 2 NRTI’s before switch, %</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>On INSTI + 2 NRTI’s before switch, %</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Receiving a STR before switch, %</td>
<td>63</td>
<td>77</td>
</tr>
<tr>
<td>Time on ART (median, months)</td>
<td>35</td>
<td>43</td>
</tr>
<tr>
<td>HIV RNA zenith (median, copies/mL)</td>
<td>29,300</td>
<td>44,877</td>
</tr>
<tr>
<td>CD4 T-cell nadir (median, cells/mm³)</td>
<td>320</td>
<td>380</td>
</tr>
</tbody>
</table>

**Source:** Wijting I, et al. Lancet HIV. 2017;4;e547-54.
Dolutegravir as Maintenance Monotherapy
DOMONO: 24-Week Results

Week 24 Virologic Suppression

Dolutegravir as Maintenance Monotherapy
DOMONO: 48-Week Results

Week 48 Virologic Suppression (Entire Study Population)

- Study stopped early; 8 virologic failures in dolutegravir arm, 3 with INSTI resistance (N155H, R263K, S230R)
- RNA at failure 678-4,990 copies/mL with one exception (71,600 copies/mL); all reported >95% adherence and all suppressed with re-initiation of cART

Interpretation: “Dolutegravir monotherapy was non-inferior to combination ART at 24 weeks. However, virological failure continued to occur thereafter and led to dolutegravir resistance. Dolutegravir should not be used as maintenance monotherapy.”
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