STABILITY

Stabilization of Atherosclerotic plaque By
Initiation of darapLadIb TherapY

Harvey D White
on behalf of
The STABILITY Investigators
Lipoprotein-associated Phospholipase A$_2$ (Lp-PLA$_2$) activity: Background

Contrasting histopathological characteristics of a stable versus a vulnerable or ruptured plaque

**Stable Plaque**
- Low Lp-PLA₂ content (dark staining)
- May have significant stenosis
- Thick fibrous cap / high collagen content
- Modest lipid pool
- Few inflammatory cells

**Vulnerable or ruptured Plaque**
- High Lp-PLA₂ content (dark staining)
- May have minimal stenosis
- Thin fibrous cap / low collagen content
- Large lipid pool
- Many inflammatory cells

Lp-PLA₂ and CHD risk: The Lp-PLA₂ Studies Collaboration; compared with conventional risk factors

79,036 participants from 32 prospective studies

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR (95% CI) per 1-SD higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp-PLA₂ activity</td>
<td>1.11 (1.05-1.16)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.10 (1.00-1.21)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1.34 (1.19-1.51)</td>
</tr>
<tr>
<td>Non HDL cholesterol</td>
<td>1.10 (1.02-1.18)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.15 (1.06-1.24)</td>
</tr>
</tbody>
</table>

Adjusted for non-lipid and lipid conventional risk factors

LSC Lancet 2010; 375:1536
STABILITY: Background

**Association studies**

**EPIDEMIOLOGY**
Higher Lp-PLA₂ levels predict CV events

**GENETICS**
Deficiency in Lp-PLA₂ due to null allele results in decreased CHD

**PATHOLOGY**
Up-regulation of Lp-PLA₂ in vulnerable plaques

Darapladib is a selective oral inhibitor that decreases Lp-PLA₂ by 60%

**Intervention with darapladib**

**PRECLINICAL**
Reduces Lp-PLA₂ in plaque and necrotic core area (pig)

**HUMAN ATEROMA**
Reduces carotid plaque Lp-PLA₂ activity

**CORONARY IMAGING**
IBIS-2
Halts progression of coronary artery necrotic plaque core volume
STABILITY Trial
Stabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY

Patients with chronic CHD
(prior MI >1 mth, prior coronary revascularization, multivessel CAD)

Enrichment criteria: ≥60 years of age, diabetes mellitus, low HDL, current smoking, significant renal dysfunction, polyvascular disease

15,828 patients randomized

Darapladib 160mg  Placebo

Optimized guideline-mandated treatment

median follow-up 3.7 years, 1588 events

Primary endpoint: composite of CV death, MI, stroke
Secondary endpoints: major coronary events, total coronary events
Key Exclusion Criteria

- Planned coronary revascularization
- Current liver disease or severe renal impairment
- Current severe heart failure
- Poorly controlled hypertension
- Severe asthma that is poorly controlled
- History of anaphylaxis, anaphylactoid reactions, or severe allergic responses
- Concomitant cytochrome P-450 inhibitor use
- Lp-PLA$_2$ activity $\leq$20.0 nmol/min/mL
Recruitment into STABILITY Trial (N=15,828)

North America (25%)
- USA 3102
- Canada 780
- Mexico 141

South America
- Argentina 542
- Brazil 384
- Chile 195
- Peru 78

Western Europe (22%)
- Belgium 202
- Denmark 102
- France 250
- Greece 187
- Germany 1089
- Italy 256
- Netherlands 444
- Norway 113
- Spain 474
- Sweden 299
- UK 184

Eastern Europe (22%)
- Bulgaria 222
- Cz Republic 774
- Estonia 77
- Hungary 410
- Poland 510
- Romania 411
- Russia 654
- Slovakia 120
- Ukraine 353

E & SE Asia
- China 369
- Hong Kong 117
- Korea 503
- Taiwan 200
- Japan 318

South Africa 386

Asia-Pacific/Latina (31%)
- Australia 306
- New Zealand 202
- Philippines 219
- Thailand 207
- Taiwan 200
- Vietnam 250
- USA 3102
- Canada 780
- Mexico 141
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=7904)</th>
<th>Darapladib (N=7924)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> Median in years</td>
<td>65.0</td>
<td>65.0</td>
</tr>
<tr>
<td>&lt;65 years (%)</td>
<td>49%</td>
<td>48%</td>
</tr>
<tr>
<td>65-74 years (%)</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>&gt;=75 years (%)</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Race or Ethnic Group (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78%</td>
<td>79%</td>
</tr>
<tr>
<td>Black</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Central/South/South East Asian</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>East Asian/Japanese</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>2%</td>
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</tbody>
</table>
### Chronic Coronary Heart Disease Qualifying Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (N=7904)</th>
<th>Darapladib (N=7924)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>59%</td>
<td>59%</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>PCI</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>CABG</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Multi-vessel CAD</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>
## Enrichment Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Placebo (N=7904)</th>
<th>Darapladib (N=7924)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60 years</td>
<td>73%</td>
<td>73%</td>
</tr>
<tr>
<td>Diabetes req. pharmacotherapy</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>HDL &lt; 40 mg/dL (1.03 mmol/L)</td>
<td>35%</td>
<td>33%</td>
</tr>
<tr>
<td>Current smoker or former smoker within 3 months (≥5 cigs/day)</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Significant renal dysfunction (eGFR 30 to 59 mL/min/1.73 m² or urine ACR ≥3 mg albumin/g creatinine)</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Polyvascular disease (cerebrovascular disease or peripheral arterial disease)</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>
## Baseline LDL

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Placebo (N=7904)</th>
<th>Darapladib (N=7924)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Interquartile range)</td>
<td>80 (63 – 101)</td>
<td>80 (63 – 101)</td>
</tr>
<tr>
<td>&lt;70 (&lt;1.8mmol/L)</td>
<td>36%</td>
<td>35%</td>
</tr>
<tr>
<td>70 – 100 (1.8-2.6 mmol/L)</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>≥100 (≥2.6 mmol/L)</td>
<td>26%</td>
<td>26%</td>
</tr>
</tbody>
</table>
## Concomitant Medication Usage

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Time Point</th>
<th>Placebo (N=7904)</th>
<th>Darapladib (N=7924)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Baseline</td>
<td>93%</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>Study end</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td>Statins</td>
<td>Baseline</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td>Study end</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Baseline</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>Study end</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>P2Y12 Inhibitors</td>
<td>Baseline</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td>Study end</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Baseline</td>
<td>56%</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>Study end</td>
<td>54%</td>
<td>54%</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker</td>
<td>Baseline</td>
<td>23%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>Study end</td>
<td>27%</td>
<td>26%</td>
</tr>
</tbody>
</table>
# Standard of Care Measures

<table>
<thead>
<tr>
<th></th>
<th>Time Point</th>
<th>Placebo (N=7890)</th>
<th>Darapladib (N=7912)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-Cholesterol (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Interquartile range)</td>
<td>Baseline Study end</td>
<td>80 (63 – 101)</td>
<td>79 (62 – 100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79 (62 – 100)</td>
<td>80 (63 – 101)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78 (61 – 99)</td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Baseline Study end</td>
<td>132/79 mmHg</td>
<td>132/79 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>131/77 mmHg</td>
<td>132/77 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Subject Status Overview

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=7904)</th>
<th>Darapladib (N=7924)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP Discontinuation</td>
<td>26.8%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Study Withdrawal</td>
<td>273 (3.5%)</td>
<td>278 (3.5%)</td>
</tr>
<tr>
<td>Complete CV Endpoint Follow-up</td>
<td>7628 (96.5%)</td>
<td>7641 (96.4%)</td>
</tr>
<tr>
<td>Complete Vital Status Follow-up</td>
<td>7845 (99.3%)</td>
<td>7877 (99.4%)</td>
</tr>
</tbody>
</table>

Median follow-up time was 3.7 years for both treatment groups

Adherence (≥ 80%) was 91.3% for placebo and 89.3% for darapladib
Primary Endpoint:
Time to First Occurrence CV Death, MI, Stroke

HR (95% CI) = 0.94 (0.85, 1.03)
P-value = 0.199
Placebo events = 819
Darapladib 160mg events = 769
Subgroup Analyses for CV Death, MI, Stroke

**Baseline Status**

![Graph showing subgroup analyses with hazard ratios and number of events](image)

**Variables**

- **Age ≥60:**
  - No
  - Yes
  - HR (95% CI): 0.98 (0.80, 1.20)
  - P-value: 0.613

- **Gender:**
  - Male
  - Female
  - HR (95% CI): 0.92 (0.83, 1.03)
  - P-value: 0.500

- **Race collapsed:**
  - White
  - Non-White
  - HR (95% CI): 0.90 (0.80, 1.00)
  - P-value: 0.077

- **Prior myocardial infarction:**
  - No
  - Yes
  - HR (95% CI): 0.87 (0.74, 1.03)
  - P-value: 0.295

- **Prior coronary revascularization:**
  - No
  - Yes
  - HR (95% CI): 0.95 (0.80, 1.14)
  - P-value: 0.837

- **Multivessel CHD:**
  - No
  - Yes
  - HR (95% CI): 0.92 (0.82, 1.03)
  - P-value: 0.395

- **Diabetes req. pharmacotherapy:**
  - No
  - Yes
  - HR (95% CI): 0.91 (0.80, 1.03)
  - P-value: 0.422

- **HDL-C level <40 mg/dL:**
  - No
  - Yes
  - HR (95% CI): 0.94 (0.83, 1.07)
  - P-value: 0.951

- **Smoker:**
  - No
  - Yes
  - HR (95% CI): 0.99 (0.89, 1.11)
  - P-value: 0.044

- **Renal dysfunction:**
  - No
  - Yes
  - HR (95% CI): 0.87 (0.77, 0.99)
  - P-value: 0.104

- **Polyvascular Disease:**
  - No
  - Yes
  - HR (95% CI): 0.93 (0.83, 1.04)
  - P-value: 0.796
Subgroup Analyses for CV Death, MI, Stroke

Pre-Study CHD Event:
- Recent -
- Remote -

Statin use:
- No -
- Yes -

eGFR:
- <60 ml/min/1.73m² -
- ≥60 ml/min/1.73m² -

Baseline LDL:
- <70 mg/dL -
- ≥70 - <100 mg/dL -
- ≥100 mg/dL -

hs C-reactive protein:
- <1.0 mg/L -
- 1.0 - 3.0 mg/L -
- >3.0 mg/L -

Region:
- North America -
- Eastern Europe -
- Western Europe -
- South America -
- Asia/Pacific -

Hazard Ratio

Favors Darapladib
Favors Placebo

HR (95% CI)  Interaction P-value  Number of Events (%)  Placebo  Darapladib
0.88 (0.72, 1.08)  0.481  194 (10.2%)  173 (9.1%)
0.96 (0.86, 1.07)  0.544  623 (10.4%)  596 (9.9%)
0.79 (0.46, 1.38)  0.863  29 (13.0%)  22 (10.7%)
0.94 (0.85, 1.04)  0.863  790 (10.3%)  747 (9.7%)
0.90 (0.73, 1.10)  0.575  191 (17.0%)  165 (15.2%)
0.96 (0.86, 1.07)  0.604  625 (9.2%)  604 (8.9%)
1.03 (0.87, 1.23)  0.238  245 (8.7%)  251 (9.0%)
0.95 (0.81, 1.12)  0.291  291 (9.6%)  278 (9.1%)
0.84 (0.71, 1.00)  0.281  281 (13.7%)  240 (11.6%)
1.00 (0.83, 1.22)  0.604  209 (7.6%)  209 (7.6%)
0.89 (0.75, 1.05)  0.283  283 (10.8%)  253 (9.7%)
0.90 (0.75, 1.08)  0.249  249 (13.6%)  225 (12.2%)
0.90 (0.74, 1.09)  0.863  213 (10.6%)  190 (9.5%)
0.94 (0.77, 1.15)  0.193  193 (10.9%)  181 (10.2%)
0.89 (0.73, 1.09)  0.207  207 (10.5%)  187 (9.3%)
1.02 (0.74, 1.41)  0.73  73 (12.2%)  74 (12.3%)
1.03 (0.81, 1.31)  0.133  133 (8.6%)  137 (8.9%)
# Cardiovascular and Mortality Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>P-Val</th>
<th>Placebo</th>
<th>Darap</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, MI, Stroke</td>
<td>0.94</td>
<td>0.199</td>
<td>10.4%</td>
<td>9.7%</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.96</td>
<td>0.59</td>
<td>4.7%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.89</td>
<td>0.11</td>
<td>5.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.01</td>
<td>0.92</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>All-Cause Mortality, MI, Stroke</td>
<td>0.96</td>
<td>0.40</td>
<td>12.2%</td>
<td>11.7%</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>1.01</td>
<td>0.87</td>
<td>7.3%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

Hazard Ratio: 0.5, 1.0, 1.5, 2.0

Favors Darap  Favors Placebo
Time to First Occurrence Major Coronary Events (CHD Death, MI, Urgent Coronary Revascularization)

HR (95% CI) = 0.90 (0.82, 1.00)
P-value = 0.045
Placebo events = 814
Darapladib 160mg events = 737
Time to First Occurrence Total Coronary Events
(CHD Death, MI, Any Coronary Revascularization, Hospitalization for Unstable Angina)

HR (95% CI) = 0.91 (0.84, 0.98)
P-value = 0.019
Placebo events = 1269
Darapladib events = 1159
Coronary-Specific Endpoints

1 - Component of pre-specified composite, but not a pre-specified endpoint
2 - Component of pre-specified composite, pre-specified as an endpoint of interest
Diarrhea/Odor Adverse Events Leading to Study Drug Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=7890)</th>
<th></th>
<th>Darapladib (N=7912)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Rate per 100 PY</td>
<td>n (%)</td>
<td>Rate per 100 PY</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (0.8%)</td>
<td>0.21</td>
<td>254 (3%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Abnormal feces</td>
<td>5 (&lt;0.1%)</td>
<td>0.02</td>
<td>177 (2%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Abnormal skin odor</td>
<td>4 (&lt;0.1%)</td>
<td>0.01</td>
<td>174 (2%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Abnormal urine odor</td>
<td>1 (&lt;0.1%)</td>
<td>&lt;0.01</td>
<td>113 (1%)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
# Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=7890)</th>
<th>Darapladib (N=7912)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Rate per 100 PY</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>3448 (44%)</td>
<td>16.02</td>
</tr>
<tr>
<td>Any adverse event leading to study drug discontinuation</td>
<td>1067 (14%)</td>
<td>3.98</td>
</tr>
<tr>
<td>Asthma</td>
<td>64 (0.8%)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Renal Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>89 (1.1%)</td>
<td>0.32</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²): Mean (SD) change from baseline at end of treatment period</td>
<td>1.7 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Treatment difference (95% CI)</td>
<td></td>
<td>-2.5 (-3.0, -2.1)</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New cancer</td>
<td>529 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Adjudicated new GI cancer</td>
<td>105 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Liver Events</td>
<td>52 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>7 (&lt;0.1%)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

Darapladib in patients with stable CHD followed for 3.7 years on a background of optimal medical therapy

- Did not significantly reduce the incidence of the primary composite endpoint of CV death, MI or stroke
- There was no effect on stroke or total mortality
- Reduced the prespecified coronary-specific secondary endpoints of major coronary events (1% absolute) and total coronary events (1.5% absolute) with nominal significance (p<0.05)
Implications

The STABILITY trial is the first large scale randomized global trial to test a novel mechanism of inhibition of inflammation in the atherosclerotic plaque

- Further analyses of the trial results in subgroups based on biomarkers, including Lp-PLA\textsubscript{2} levels, and genetics will explore if darapladib might be useful in specific patient subsets
- The STABILITY trial results indicate that darapladib warrants further evaluation in other clinical settings
Study Acknowledgements

We would like to acknowledge all the study investigators, research staff and study patients, without whom this study would not be possible

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