EBBINGHAUS:

- A Cognitive Study of Patients Enrolled in the FOURIER Trial

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Late-Breaking Clinical Trial
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Cognition and Statins

– Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits

– In 2012 FDA added risk of adverse cognitive effects to label of all statins

– However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects.

*The National Lipid Association
Brain synthesizes cholesterol locally

mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

FOURIER: Summary Results

FOURIER Study Population: 27,564 stable patients with CV disease, age 40-85 years; additional CV risk factor(s), LDL ≥ 70 mg/dL (or non-HDL ≥ 100)

Evolocumab on background of statin c/w placebo:

• ↓ LDL-C by 59%
• ↓ CV outcomes on background of statin therapy
• Safe and well-tolerated

EBBINGHAUS: Hypothesis

The addition of evolocumab to statin therapy in patients with clinically evident cardiovascular disease does not adversely affect cognitive function.

Trial Organization

Executive Committee
Robert P. Giugliano (Chair)  François Mach  Brian R. Ott

TIMI Study Group
Marc S. Sabatine (Chairman)  Marc P. Bonaca (Safety Desk)  Estella Kanevsky
Sabina Murphy (Director of Stats)  Kelly Im (Assoc Dir Stats)

Cambridge Cognition: Kenton Zavitz (non-voting member of EC)

Sponsor: Amgen
Christopher Kurtz  Scott M. Wasserman  Narimon Honarpour
Kelly Hanlon  Beat Knusel  Thomas Liu
Jingjing Schneider  Huei Wang

Participating Countries (N=30)
Australia  Belgium  Canada  Czech Republic  Denmark
Estonia  Finland  France  Germany  Greece
Hong Kong  Hungary  Italy  Japan  Latvia
Lithuania  Malaysia  Netherlands  New Zealand  Norway
Poland  Portugal  Russia  Slovakia  South Africa
Spain  Sweden  Turkey  United Kingdom  USA
**Trial Design**

**Randomized Double Blind**

**Evolocumab SC**
- 140 mg Q2W or 420 mg QM

**Placebo SC**
- Q2W or QM

**2442 patients screened for EBBINGHAUS**

**1974 Enrolled (Full Analysis Pop)**
- Median F/U 19.8 months

**Primary Analysis Cohort (N=1204)**
- Baseline cognitive testing on/before 1st dose of study drug and had f/u cognitive testing post dosing*
- Additional 770 pts w/ baseline assessment before week 12 visit

**Major Exclusions**
1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study

### Baseline Characteristics (Full Population)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>, years, mean (SD)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Male sex</td>
<td>72</td>
</tr>
<tr>
<td><strong>Education</strong>, years, mean (SD)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>20</td>
</tr>
<tr>
<td>Non-stroke neurologic disease</td>
<td>14</td>
</tr>
<tr>
<td>Atrial fibrillation at any time</td>
<td>9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24</td>
</tr>
<tr>
<td>Hypertension</td>
<td>84</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>34</td>
</tr>
<tr>
<td>High intensity statin use</td>
<td>71</td>
</tr>
<tr>
<td><strong>LDL-C</strong>, mg/dL, median [25th, 75th]</td>
<td>92 [80-108]</td>
</tr>
</tbody>
</table>

Data shown are % unless otherwise indicated

Pooled data; no differences between treatment arms

Median time from most recent event ~3.5 yrs;
Endpoints

1. Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform. Assessed at baseline, 6, 12, 24, 48 mos and study end.
   – **Primary:** Spatial working memory strategy index of executive function
   – **Secondary:** Spatial working memory between errors
     Paired associates learning
     Reaction time
   – **Exploratory:** Global score (combines above 4 tests)

2. **Patient survey of everyday cognition** at study end

3. **Investigator report of cognitive AEs**

*Memory and executive function domains

Owen 1990 PMID: 2267054; Sahakian 1988, PMID: 3382917; Owen 1996 PMID: 8714706; Kollins PMID: 21476931

Statistical Considerations

• **Primary Endpoint Analysis – Non-inferiority**
  – NI margin = 20% of placebo SD (Cohen's d=0.2)
  – Upper 95%CI of change from baseline in primary endpoint (SWM strategy index Z-score) is compared to non-inferiority (NI) margin

• **Other Analyses:**
  - Other 3 CANTAB tests
  – Global score = average of 4 Z-scores of CANTAB tests
  – CANTAB tests post nadir LDL-C achieved
CANTAB - Spatial Working Memory (SWM)

- Search for the blue token hidden within a red box
- Number of red boxes increases each round (3, 4, 6, 8).
- Critical instruction: *Do not return to a box where a blue token was found.*

SWM strategy index: = # inefficient searches started. Range 4-28.

Lower scores represent better performance.
Primary Endpoint
Spatial Working Memory Strategy Index

Mean Number of boxes

Placebo  Evolocumab

Baseline  Post baseline  Change

Raw Scores

17.8 17.8 17.6 17.5

-0.29 -0.21

P_{\text{non-inferiority}} < 0.001

Non-inferiority boundary 0.19

Treatment Difference in Z score (Placebo minus Evolocumab)

Favors Evolocumab  Favors Placebo

P_{\text{NI}} is from fixed estimate
# Secondary Endpoints

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Task description</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial Working Memory Between Errors Score</td>
<td>Find the hidden blue token</td>
<td># times a box is revisited in which a blue token had already been found</td>
</tr>
<tr>
<td>Paired Associates Learning</td>
<td>Memory matching game (Concentration)</td>
<td># times errors made in finding a match</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>Touch yellow dot quickly after it appears on screen</td>
<td>Time in milliseconds until dot touched</td>
</tr>
</tbody>
</table>

Lower scores (fewer errors, faster time) are better
Secondary Endpoint Results

Spatial Working Memory Between Errors Score

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21.0</td>
<td>20.9</td>
</tr>
<tr>
<td>Post baseline</td>
<td>20.1</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Paired Associates Learning

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>25.2</td>
<td>26.5</td>
</tr>
<tr>
<td>Post baseline</td>
<td>23.6</td>
<td>24.9</td>
</tr>
</tbody>
</table>

Median 5-Choice Reaction Time

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>355</td>
<td>357</td>
</tr>
<tr>
<td>Post baseline</td>
<td>356</td>
<td>362</td>
</tr>
</tbody>
</table>

Trt diff of Δ in Z-scores

- Spatial Working Memory: Placebo vs. Evolocumab
  - Baseline: 0.033, P_{superiority} = 0.36
  - Post baseline: 0.023, P_{superiority} = 0.49

- Median 5-Choice Reaction Time: Placebo vs. Evolocumab
  - Baseline: 0.073, P_{superiority} = 0.06

Lower raw scores (fewer errors, faster time) are better.
Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)

Primary CANTAB Endpoint*: Average Change from Baseline

Nadir LDL-Achieved (mg/dL)
- <25 mg/dL
- 25-39 mg/dL
- ≥ 40 mg/dL

P=NS across LDL values achieved and also between treatments

Composite Global Score: Average Change from Baseline

Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=781)</th>
<th>Evolocumab (N=800)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>1.16 (0.39)</td>
<td>1.17 (0.39)</td>
<td>0.81</td>
</tr>
<tr>
<td>Executive functioning total score</td>
<td>1.11 (0.32)</td>
<td>1.12 (0.32)</td>
<td>0.28</td>
</tr>
<tr>
<td>Planning</td>
<td>1.08 (0.31)</td>
<td>1.10 (0.32)</td>
<td>0.20</td>
</tr>
<tr>
<td>Organization</td>
<td>1.09 (0.32)</td>
<td>1.10 (0.33)</td>
<td>0.57</td>
</tr>
<tr>
<td>Divided attention</td>
<td>1.15 (0.42)</td>
<td>1.16 (0.41)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td>1.13 (0.33)</td>
<td>1.14 (0.33)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Patient self-report at end of study as compared to randomization, graded as:

1. Better or no change
2. Questionable / occasionally worse
3. Consistently a little worse
4. Consistently much worse

Lower scores represent better cognition

Results shown are in the full study population.
Investigator Reported Cognitive Adverse Events

Data shown are % of patients with at least 1 event

*1 patient who did not take study drug is excluded from the evolocumab group
Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. No differences btw evolocumab vs placebo
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL