Brintellix® (Vortioxetine)

Psychopharmacologic Drugs Advisory Committee

3 February 2016
Introduction

Jonathon M. Parker, RPh, MS, PhD
Vice President, Global Regulatory Affairs, CNS
Takeda Pharmaceuticals International, Inc.
Brintellix (vortioxetine) Overview

- Indicated for the treatment of major depressive disorder (MDD)
  - Currently approved in over 60 countries

- Established as a safe and effective product in treatment of depression
  - Safety profile in new studies was consistent with that observed in the previous MDD studies

- Has demonstrated a clinically meaningful benefit in treating aspects of cognitive dysfunction related to MDD
  - Consistent effect seen across multiple studies
  - Beneficial cognitive effects included in majority of labels
Vortioxetine
Distinct Pharmacologic Profile

- Targets multiple serotonin receptors at clinically relevant doses in addition to SERT inhibition

- *In vitro* and *in vivo* data support positive impact on cognitive function

- Vortioxetine reversed cognitive deficits in animal models of cognitive dysfunction
Vortioxetine
Program Development

- There is no published guidance in this area
  - Evolving program that changed with increased understanding of the science
  - Program designed to demonstrate efficacy in MDD patient population at approved antidepressant doses

- Development of program for clinical trials relied on interactions with experts
Vortioxetine
Cognition Clinical Program

- Three large clinical studies

Hypothesis Generating Study
ELDERLY (12541A)

Pivotal Studies
FOCUS (14122A)
CONNECT (202)

Both pivotal studies met primary endpoints
Vortioxetine Cognition Clinical Program

- Consistent, statistically significant benefit in treating depression as well as cognitive dysfunction
  - Treatment of MDD as measured by MADRS
  - Aspects of cognitive dysfunction as measured by Digit Symbol Substitution Test (DSST)
Vortioxetine
Supportive Evidence

Supportive Studies
- ELDERLY
- fMRI

Functional Measures
- UPSA
- WLQ

Pharmacologic profile

Nonclinical data

Pivotal Studies
FOCUS
CONNECT
Vortioxetine Summary

- Vortioxetine is an antidepressant with beneficial effects in cognitive dysfunction
- Cognitive dysfunction is an unmet medical need
- Multiple domains are impaired in MDD
  - DSST is sensitive to domains relevant to MDD
- Meaningful data for prescribers and patients that should be reflected in the label
Section 14 – Clinical Studies

- Vortioxetine was superior to placebo on the DSST in patients with MDD in both the FOCUS and CONNECT studies.
- The DSST is an integrated measure of cognitive function that involves executive function, speed of processing and attention.
- Additionally: [Appropriate study descriptions of FOCUS and CONNECT results]
<table>
<thead>
<tr>
<th><strong>External Experts</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guy Goodwin, MD</strong></td>
</tr>
<tr>
<td>President, European College of Neuropsychopharmacology</td>
</tr>
<tr>
<td>WA Handley Professor of Psychiatry, Oxford University</td>
</tr>
<tr>
<td><strong>Philip D. Harvey, PhD</strong></td>
</tr>
<tr>
<td>Leonard M. Miller Professor of Psychiatry and Behavioral Sciences</td>
</tr>
<tr>
<td>University of Miami Miller School of Medicine</td>
</tr>
<tr>
<td><strong>Harry Croft, MD</strong></td>
</tr>
<tr>
<td>Practicing Psychiatrist</td>
</tr>
<tr>
<td>Clinical Trials of Texas, Inc.</td>
</tr>
<tr>
<td>The Croft Group</td>
</tr>
</tbody>
</table>
## Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
</table>
| Introduction                   | Jonathon Parker, RPh, MS, PhD  
Vice President, Global Regulatory Affairs, CNS  
Takeda Pharmaceuticals International, Inc. |
| Measuring Change in Cognition with DSST | Judith Jaeger, MPA, PhD  
Clinical Professor, Department of Psychiatry and Behavioral Sciences,  
Albert Einstein College of Medicine  
President and Principal Scientist, CognitionMetrics, LLC |
| Study Design and Results        | Christina Kurre Olsen, PhD  
Senior Specialist, Brintellix Clinical Science  
H. Lundbeck A/S |
| Clinical Perspective           | Maurizio Fava, MD  
Executive Vice Chair, Department of Psychiatry,  
Massachusetts General Hospital  
Executive Director, Clinical Trials Network and Institute |
| Conclusion                     | Louis Mini, MD  
Vice President, Global Medical Head, CNS  
Medical Affairs  
Takeda Pharmaceuticals International, Inc. |
Measuring Change in Cognition with DSST

Judith Jaeger, PhD, MPA
Clinical Professor, Dept of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY and
President and Principal Scientist
CognitionMetrics, LLC
Disclosures

- Receive consulting fees from Takeda and Lundbeck
- No financial interest in the outcome of this meeting
Main Points

- Objective measures are necessary for clinical trials of cognition in MDD
  - Subjective ratings influenced by depressed mood
  - Subjective and objective measures often disagree
- The DSST is an appropriate objective measure in the clinical trial setting
  - Reliable
  - Stable
  - Sensitive to change
  - Sensitive to deficits seen in MDD
- Change on the DSST corresponds to clinically meaningful change in cognition
Testing Cognition: Diagnosis versus Measuring Change (1)

- **Neuropsychological (NP) tests**
  - Objectively measure cognition
  - Task performance requires particular cognitive domains
  - All tests are at least partly polyfactorial

- **Diagnostic Neuropsychological Tests**
  - Test battery, multiple domains
  - Profile of cognitive deficits relative to norms

- **Measuring change**
  - Standard tests not designed for sensitivity to change over time
  - Polyfactorial tests may be most efficient for evaluating a drug’s effects across multiple cognitive domains
Diagnostic tests

- Focus on abnormality
- Ceiling effects not a problem
- Battery required to profile a range of cognitive domains.

Tests for change

- Normal distribution
- No floor/ceiling effects allowed
- Brief (fatigue, motivation)
- Stability
- One polyfactorial test adequate and sufficient alternative to long test battery

Optimized for detecting change

Optimized for diagnosis
Digit Symbol Coding

Digit symbol substitution test

2 9 2 9 4 9 4 9 4 9 1 8 9 3 1 7 2 3 6 4 8 3 1 7 8 2 5
4 1 5 2 6 9 9 5 6 7 6 2 9 4 8 7 2 8 6
8 6 7 3 1 6 2 1 8 7 4 3 1 6 2 9
2 5 2 6 4 9 1 8 5 7 1 5 4 5 3 9 2
3 9 3 1 6 5 9 1 3 1 3 9 8 9 7 3 4 3
DSST to Measure Cognitive Change

- As a polyfactorial test, it is a brief and efficient tool
  - Measures deficiency as well as change over a range of domains

- It is highly sensitive, but not specific
  - Impairment or change on the test can occur as a result of a change in any of the domains involved and further testing would be required to understand which domain
DSST in MDD

- **MDD is a non-focal condition**
  - disease impact on single domain not of clinical interest or importance

- **DSST is an adequate and sufficient measure of dysfunction and change in MDD**
What does the DSST measure?

- Good performance on DSST requires intact:
  - **Attention**
  - **Speed of processing**
  - **Executive functions (including working memory)**

- **In clinical populations** DSST performance correlates highly with other cognitive domains including attention and executive functions (including working memory)\(^1,2,3,4\).

---

### MCCB 3-Factor Model: Correlations with DSST

**N=186 schizophrenia outpatients; 3 Factor Solution**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Name</th>
<th>Variables</th>
<th>DSST Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Processing Speed</td>
<td>TMT-A</td>
<td>( r = .822 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BACS Symbol Coding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Category Fluency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NAB Mazes</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Attention / Working Memory</td>
<td>CPT-IP</td>
<td>( r = .810 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WMS-III Spatial Span</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Letter-Number Span</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Learning</td>
<td>HVLT-R</td>
<td>( r = .811 )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BVMT-R</td>
<td></td>
</tr>
</tbody>
</table>

"Regression analysis indicated that symbol coding performance explained the most variance in MCCB total score…"

DSST in MDD: Clinical Meaningfulness

- Relationship to disability outcome
- Benchmarking
Clinical Meaningfulness: DSST Correlates with Disability in MDD

\[ x^2 = 18.63 \]
\[ \text{Odds Ratio} = 19.95 \]
\[ (p < .0001) \]

45% disabled 6 months post-baseline

Correlation* MSIF with DSST

\{ HAM-D17, PANSS pos symptoms, Medical disability \}

*GLM, polychotomous
MSIF, Multidimensional Scale for Independent Functioning.
## MSIF Overall Global Rating Anchors

<table>
<thead>
<tr>
<th>RATING</th>
<th>ANCHORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Essentially normal</td>
</tr>
<tr>
<td></td>
<td>Essentially normal role functioning</td>
</tr>
<tr>
<td>2</td>
<td>Very mild disability</td>
</tr>
<tr>
<td></td>
<td>(Could still be at low end of normal range). Somewhat below normal functioning with no or minimal support. Functioning normally with some support.</td>
</tr>
<tr>
<td>3</td>
<td>Somewhat disabled</td>
</tr>
<tr>
<td></td>
<td>Performing adequately with regular support in mainstream environments.</td>
</tr>
<tr>
<td></td>
<td>Performing with some difficulty with no supports in mainstream environments.</td>
</tr>
<tr>
<td>4</td>
<td>Moderately disabled</td>
</tr>
<tr>
<td></td>
<td>Performing well in non-mainstream, specialized environments.</td>
</tr>
<tr>
<td></td>
<td><strong>Performing with some difficulty in spite of regular supports in mainstream environment.</strong></td>
</tr>
<tr>
<td></td>
<td>Performing with significant difficulty with no supports in mainstream environments.</td>
</tr>
<tr>
<td>5</td>
<td>Significantly disabled</td>
</tr>
<tr>
<td></td>
<td>Generally unable to function at all without supports. Performing with some difficulty in non-mainstream, specialized environments.</td>
</tr>
<tr>
<td></td>
<td><strong>Performing with significant difficulty even with significant supports in mainstream environments.</strong></td>
</tr>
<tr>
<td>6</td>
<td>Extremely disabled</td>
</tr>
<tr>
<td></td>
<td>Generally unable to function in mainstream environments, even w/supports. Performing with significant difficulty or at extremely limited capacity in non-mainstream, specialized environments. Performing well and showing some independent functioning in comprehensive care environments.</td>
</tr>
<tr>
<td>7</td>
<td>Totally disabled</td>
</tr>
<tr>
<td></td>
<td>Virtually total care provided in institutional or specialized environments with no independent functioning</td>
</tr>
</tbody>
</table>
# MSIF Overall Global Rating Anchors

<table>
<thead>
<tr>
<th>RATING</th>
<th>ANCHORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Essentially normal role functioning</td>
</tr>
<tr>
<td>2</td>
<td>Very mild disability (Could still be at low end of normal range).</td>
</tr>
<tr>
<td></td>
<td>Functioning normally with some support.</td>
</tr>
<tr>
<td>3</td>
<td>Somewhat disabled (Performing adequately with regular support in mainstream environments.)</td>
</tr>
<tr>
<td>4</td>
<td>Moderately disabled (Performing well in non-mainstream, specialized environments. Performing with some difficulty in mainstream environments.)</td>
</tr>
<tr>
<td>5</td>
<td>Significantly disabled (Generally unable to function at all without supports. Performing with some difficulty in non-mainstream, specialized environments. Performing with significant difficulty even with significant supports in mainstream environments.)</td>
</tr>
<tr>
<td>6</td>
<td>Extremely disabled (Generally unable to function in mainstream environments, even w/supports. Performing with significant difficulty or at extremely limited capacity in non-mainstream, specialized environments. Performing well and showing some independent functioning in comprehensive care environments.)</td>
</tr>
<tr>
<td>7</td>
<td>Totally disabled (Virtually total care provided in institutional or specialized environments with no independent functioning)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RATING</th>
<th>DSST Effect Size</th>
<th>Standard Deviation</th>
<th>Odds of 1 pt MSIF Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.5</td>
<td>19.95</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.25</td>
<td>4.47</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.25</td>
<td>2.11</td>
<td></td>
</tr>
</tbody>
</table>

Note: The table above provides the DSST Effect Size, Standard Deviation, and Odds of 1 pt MSIF Difference for each rating level.
DSST in MDD: Magnitude of Dysfunction

- Meta-analysis: Overall cognitive dysfunction in MDD vs. Healthy controls about 0.5 SD’s

- DSST effect size relative to healthy controls (Snyder, 2013)
  - 22 studies, 1904 subjects on DSST
  - Effect size decrement on DSST: 0.55 (p<0.001) (CI=0.34-0.75)
Clinical Meaningfulness: Benchmarking DSST Impairment in MDD

Effect Size (Cohen’s d) on DSST Performance

- Lorazepam (2 mg) (Pompeia, 2008)
- Diphenhydramine 150 mg (Roth et al, 1987)
- Alcohol BAC 0.088 (Mattila, 1997)
- MDD, relative to healthy controls (Snyder, 2013)
How can one 90 second test be this useful? Is it enough?

- Reliable and valid
- Longer batteries add burden; not necessarily more informative
- Highly correlated with much longer batteries
- Broadly sensitive to CNS change and dysfunction
- Effect size on DSST in MDD is 0.55 (comparable to longer batteries)
- Correlates with disability
- Change on DSST is clinically meaningful
<table>
<thead>
<tr>
<th>Section</th>
<th>Speaker</th>
<th>Institution/Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Jonathon Parker, RPh, MS, PhD</td>
<td>Vice President, Global Regulatory Affairs, CNS Takeda Pharmaceuticals International, Inc.</td>
</tr>
<tr>
<td>Measuring Change in Cognition with DSST</td>
<td>Judith Jaeger, MPA, PhD</td>
<td>Clinical Professor, Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine President and Principal Scientist, CognitionMetrics, LLC</td>
</tr>
<tr>
<td>Study Design and Results</td>
<td>Christina Kurre Olsen, PhD</td>
<td>Senior Specialist, Brintellix Clinical Science H. Lundbeck A/S</td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td>Maurizio Fava, MD</td>
<td>Executive Vice Chair, Department of Psychiatry, Massachusetts General Hospital Executive Director, Clinical Trials Network and Institute</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Louis Mini, MD</td>
<td>Vice President, Global Medical Head, CNS Medical Affairs Takeda Pharmaceuticals International, Inc.</td>
</tr>
</tbody>
</table>
Study Designs and Results

Christina Kurre Olsen, PhD
Senior Specialist, Brintellix Clinical Science
H. Lundbeck A/S
Presentation Overview

- Rationale
- Study and methodology overview
- Individual studies
  - Study 12541A (ELDERLY)
  - Study 14122A (FOCUS)
  - Study 202 (CONNECT)
- Summary of the evidence
Vortioxetine differs from SSRIs/SNRIs due to direct effects at 5-HT receptors
Precedent from Literature (Raskin 2007)

Individual Cognitive Score

- Duloxetine, 60 mg/day
  - N=197
  - N=195
  - N=98
  - N=98

- Placebo

![Graph showing cognitive scores for Duloxetine and Placebo groups.](image)

- Learning trials
- Delayed recall
- Verbal Learning and Recall Test
- Symbol Digit Substitution Test
- Two-Digit Cancellation Test
- Letter-Number Sequencing Test

\[ d \ p=0.03 \ vs \ placebo \]
\[ e \ p=0.02 \ vs \ placebo \]
Cognition Development Program

- **ELDERLY**
  - Depression study exploring the effect of vortioxetine on cognitive performance (DSST, RAVLT) – included active reference

- **FOCUS and CONNECT**
  - Designed to confirm effect of vortioxetine on cognitive dysfunction in adult MDD

- Nonclinical studies conducted to extend the understanding of vortioxetine’s distinct cognition-enhancing effects

- Clinical fMRI study designed to explore brain activity during cognitive performance

Hypothesis generating

2 pivotal studies with cognitive dysfunction as primary endpoint

Supportive evidence
**Study Design Overview**

- All 3 studies were 8-week placebo-controlled and included subjects with moderate to severe MDD (MADRS ≥ 26)

<table>
<thead>
<tr>
<th></th>
<th>ELDERLY</th>
<th>FOCUS</th>
<th>CONNECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, N</td>
<td>453</td>
<td>602</td>
<td>602</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Depression</td>
<td>Cognitive dysfunction</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td>Age</td>
<td>≥65 years</td>
<td>18-65 years</td>
<td>18-65 years</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>5 mg</td>
<td>10 and 20 mg</td>
<td>10/20 mg</td>
</tr>
<tr>
<td>Region</td>
<td>EU/CA/US</td>
<td>EU/US/RoW</td>
<td>EU/US</td>
</tr>
<tr>
<td>Active reference</td>
<td>Duloxetine</td>
<td>–</td>
<td>Duloxetine</td>
</tr>
</tbody>
</table>

- **Duloxetine as active reference**
  - Antidepressant for assay (MADRS) sensitivity
  - Effect on some measures of cognitive function (learning and memory)
Key Exclusion Criteria
Pivotal Studies

- Exclusions consistent with the NDA MDD studies
  - Mental disorder that might interfere with the diagnosis and/or conduct of study
  - Any current psychiatric disorder other than MDD
  - Use of medications - with potential CNS effect/interactions
  - Cognitive or behavioral psychotherapy
## Pivotal FOCUS and CONNECT Studies

<table>
<thead>
<tr>
<th></th>
<th>Similar Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOCUS</strong></td>
<td>Cognitive dysfunction vs placebo in adult (18-65 years) MDD</td>
</tr>
<tr>
<td></td>
<td>Cognitive performance</td>
</tr>
<tr>
<td></td>
<td>▪ Objective neuropsychological tests</td>
</tr>
<tr>
<td><strong>CONNECT</strong></td>
<td>Patient’s perception</td>
</tr>
<tr>
<td></td>
<td>▪ Subjective measures of cognitive function</td>
</tr>
</tbody>
</table>
# Pivotal FOCUS and CONNECT Studies

<table>
<thead>
<tr>
<th></th>
<th>Study-specific Design Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOCUS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Substantiate the findings in <strong>ELDERLY</strong> (composite DSST, RAVLT score; Week 8)</td>
</tr>
<tr>
<td></td>
<td>Investigate early (Week 1) treatment effects on cognitive dysfunction</td>
</tr>
<tr>
<td><strong>CONNECT</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Replicate <strong>FOCUS</strong> (DSST; Week 8)</td>
</tr>
<tr>
<td></td>
<td>Distinct effect via including an active reference (similar to <strong>ELDERLY</strong>)</td>
</tr>
<tr>
<td></td>
<td>Support clinical relevance (functionality)</td>
</tr>
</tbody>
</table>
## Primary Prespecified Endpoints

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>ELDERLY</th>
<th>FOCUS</th>
<th>CONNECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Depression</td>
<td>Cognitive dysfunction</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>HAM-D$_{24}$</td>
<td>Composite Z-score at Week 8 (DSST, RAVLT$<em>{acq}$, RAVLT$</em>{delay}$)</td>
<td>DSST at Week 8</td>
</tr>
</tbody>
</table>
## Key Secondary Prespecified Endpoints

<table>
<thead>
<tr>
<th>ELDERLY</th>
<th>FOCUS</th>
<th>CONNECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key secondary endpoints (multiplicity-controlled, hierarchical)</td>
<td>HAM-D$_{24}$ (Weeks 6,4,2,1)</td>
<td>DSST, RAVLT$<em>{acq}$, RAVLT$</em>{delay}$</td>
</tr>
</tbody>
</table>
### Additional Prespecified Endpoints

<table>
<thead>
<tr>
<th></th>
<th><strong>ELDERLY</strong></th>
<th><strong>FOCUS</strong></th>
<th><strong>CONNECT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional endpoints (depression, cognition, functionality)</td>
<td>MADRS</td>
<td>MADRS</td>
<td>MADRS</td>
</tr>
<tr>
<td></td>
<td>CGI-I/CGI-S</td>
<td>CGI-I/CGI-S</td>
<td>CGI-S</td>
</tr>
<tr>
<td></td>
<td>..</td>
<td>TMT-A/B</td>
<td>TMT-A/B</td>
</tr>
<tr>
<td></td>
<td>..</td>
<td>Stroop Con/Incon</td>
<td>Stroop Con/Incon</td>
</tr>
<tr>
<td></td>
<td>DSST</td>
<td>CRT/SRT</td>
<td>CRT/SRT</td>
</tr>
<tr>
<td></td>
<td>RAVLT</td>
<td>PDQ</td>
<td>One-Back</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GMLT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPFQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>UPSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WLQ</td>
</tr>
</tbody>
</table>
Prespecified Statistical Methodology

Pivotal Studies

- **Statistical Analyses**
  - Endpoints assessed more than once post Baseline: MMRM
  - Endpoints assessed only once post Baseline: ANCOVA, LOCF
  - Path analysis: ANCOVA, LOCF
Prespecified Testing Strategy

- Analyses of primary and key secondary endpoints under full multiplicity control for vortioxetine
  - Prespecified hierarchical test order
  - Bonferroni adjustment for multiple doses (FOCUS)
  - Statistical significance indicated by symbol *

- Additional endpoints for vortioxetine and results for active reference presented with nominal p-values
  - Nominal significance indicated by symbol †
### Measurements of Cognitive Function, Functional Capacity and Work Limitations Across Studies

<table>
<thead>
<tr>
<th></th>
<th>ELDERLY</th>
<th>FOCUS</th>
<th>CONNECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Performance-Based</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychological test performance</td>
<td>DSST, RAVLT</td>
<td>DSST, RAVLT, TMT, Stroop, CRT/SRT</td>
<td>DSST, TMT, Stroop, CRT/SRT, One-Back, GMLT</td>
</tr>
<tr>
<td>Functional capacity</td>
<td>NA</td>
<td>NA</td>
<td>UPSA</td>
</tr>
<tr>
<td><strong>Subjective Patient-Reported</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive symptoms</td>
<td>NA</td>
<td>PDQ</td>
<td>PDQ, CPFQ</td>
</tr>
<tr>
<td>Work productivity</td>
<td>NA</td>
<td>NA</td>
<td>WLQ</td>
</tr>
</tbody>
</table>

NA - not assessed
In All 3 Studies, Vortioxetine Improved Depressive Symptoms

- The active reference duloxetine also improved depressive symptoms

**Mean Change from Baseline in MADRS Total Score**

<table>
<thead>
<tr>
<th>ELDERLY</th>
<th>FOCUS</th>
<th>CONNECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO 145</td>
<td>VOR 5 mg</td>
<td>DUL 155</td>
</tr>
<tr>
<td>VOR 148</td>
<td>PBO 194</td>
<td>VOR 10 mg</td>
</tr>
<tr>
<td>DUL 148</td>
<td>VOR 193</td>
<td>VOR 20 mg</td>
</tr>
<tr>
<td>5 mg 175</td>
<td>10 mg 193</td>
<td>10/20 mg 187</td>
</tr>
<tr>
<td>10 mg 167</td>
<td>20 mg 204</td>
<td></td>
</tr>
<tr>
<td>20 mg 167</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† p<0.05; †† p<0.01; ††† p<0.001 vs placebo
ELDERLY Study

Hypothesis-Generating Study
ELDERLY Study
Cognitive Performance Efficacy Data

Standardized Effect Size vs Placebo

- Vortioxetine
- Duloxetine

† p<0.05; †† p<0.01 vs placebo

Polyfactorial (processing speed, attention, executive function)

Verbal learning and memory
FOCUS Study

Pivotal Study
FOCUS Study
Primary Endpoint

The effect size on the MADRS ranged from 0.58 (VOR 10 mg) and 0.68 (VOR 20 mg)

***p<0.001 vs placebo
## FOCUS Study
### Key Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>VOR 10 mg</th>
<th></th>
<th>VOR 20 mg</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∆ Placebo</td>
<td>p-value</td>
<td>Effect Size</td>
<td>∆ Placebo</td>
</tr>
<tr>
<td>DSST</td>
<td>4.20</td>
<td>p&lt;0.0001</td>
<td>0.51</td>
<td>4.26</td>
</tr>
<tr>
<td>RAVLT&lt;sub&gt;acquisition&lt;/sub&gt;</td>
<td>1.02</td>
<td>p=0.029</td>
<td>0.23</td>
<td>0.59</td>
</tr>
<tr>
<td>RAVLT&lt;sub&gt;delayed recall&lt;/sub&gt;</td>
<td>0.71</td>
<td>p=0.003</td>
<td>0.31</td>
<td>0.65</td>
</tr>
</tbody>
</table>
**FOCUS Study**
*Across Neuropsychological Tests*

![Graph showing standardized effect sizes across various neuropsychological tests for Vortioxetine 10 mg and Vortioxetine 20 mg compared to placebo.]

- **DSST**
  - Vortioxetine 10 mg: ***p<0.001 vs placebo; nominal***
  - Vortioxetine 20 mg: ***p<0.001 vs placebo; nominal***

- **RAVLT Acq**
  - Vortioxetine 10 mg: ⬆ p<0.05

- **RAVLT Delay**
  - Vortioxetine 10 mg: ⬆ p<0.05
  - Vortioxetine 20 mg: ⬆ p<0.05

- **TMT-B**
  - Vortioxetine 10 mg: ⬆ p<0.05
  - Vortioxetine 20 mg: ⬆ p<0.05

- **STROOP Con**
  - Vortioxetine 10 mg: ⬆ p<0.05
  - Vortioxetine 20 mg: ⬆ p<0.05

- **STROOP Incon**
  - Vortioxetine 10 mg: ⬆ p<0.05
  - Vortioxetine 20 mg: ⬆ p<0.05

- **TMT-A**
  - Vortioxetine 10 mg: ⬆ p<0.05
  - Vortioxetine 20 mg: ⬆ p<0.05

- **SRT**
  - Vortioxetine 10 mg: ⬆ p<0.05
  - Vortioxetine 20 mg: ⬆ p<0.05

- **CRT**
  - Vortioxetine 10 mg: ⬆ p<0.05
  - Vortioxetine 20 mg: ⬆ p<0.05

***p<0.001 vs placebo; nominal ⬆ p<0.05; ⬆ p<0.01; ⬆ p<0.001 vs placebo
FOCUS Study
Subjective Patient-reported Cognitive Function

Perceived Deficits Questionnaire (PDQ)

VOR 10 mg
n=181

VOR 20 mg
n=188

††† p<0.001 vs placebo

††† p<0.001 vs placebo

Standardized Effect Size
CONNECT Study

Pivotal Study
- The effect size on the MADRS ranged from 0.25 for vortioxetine and 0.37 for duloxetine

*p<0.05 vs placebo
## CONNECT Study
### Key Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vortioxetine</th>
<th>Duloxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \Delta ) Placebo</td>
<td>p-value</td>
</tr>
<tr>
<td>PDQ subscore</td>
<td>-2.6</td>
<td>p=0.001</td>
</tr>
<tr>
<td>CGI-I score</td>
<td>-0.29</td>
<td>p=0.017</td>
</tr>
</tbody>
</table>
**CONNECT Study**

Across Neuropsychological Tests

*p<0.05 vs placebo ; nominal ††† p<0.001 vs placebo

*Standardized Effect Size vs Placebo*

- DSST
- TMT-A
- TMT-B
- STROOP Con
- STROOP Incon
- OBT
- GMLT
- SRT
- CRT

**Bars:**
- Vortioxetine
- Duloxetine

---

*p<0.05 vs placebo ; nominal ††† p<0.001 vs placebo*
## CONNECT Study
### Overall Composite Score

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Standardized Effect Size</th>
<th>SE</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>Nominal p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vortioxetine</td>
<td>149</td>
<td>0.25</td>
<td>0.05</td>
<td>0.01</td>
<td>0.21</td>
<td>0.0337</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>156</td>
<td>0.13</td>
<td>0.05</td>
<td>-0.04</td>
<td>0.16</td>
<td>0.2443</td>
</tr>
</tbody>
</table>

Prespecified analysis of the Composite Z-score for all 9 neuropsychological tests (equally weighted; FAS, ANCOVA, LOCF).
CONNECT: DSST, TMT-A, TMT-B, Stroop con, Stroop incon, OBT, GMLT, SRT, CRT
CONNECT Study
Functional Capacity

UCSD Performance-based Skills Assessment (UPSA)

Difference vs Placebo in Composite Total Scores

Vortioxetine
n=175

Duloxetine
n=187

††† p<0.001 vs placebo
CONNECT Study
Work Productivity

Work Limitation Questionnaire (WLQ) in Working Patients (~ 40%)

Change from Baseline at Week 8 vs Placebo

- Time Management: n=72, n=74
- Physical Demand: n=71, n=74
- Mental Demand: n=73, n=77
- Output Demand: n=70, n=75

† p<0.05 vs placebo
Summary of the Evidence
Consistent Results Across Studies
Effect on DSST Cognitive Performance

![Graph showing standardized effect size vs placebo for Vortioxetine and Duloxetine in ELDERLY, FOCUS, CONNECT, and ELDERLY CONNECT studies.](image)

- Vortioxetine:
  - 5 mg: Standardized Effect Size vs Placebo
  - 10 mg: Standardized Effect Size vs Placebo
  - 20 mg: Standardized Effect Size vs Placebo
  - 10/20 mg (flex): Standardized Effect Size vs Placebo

- Duloxetine:
  - Standardized Effect Size vs Placebo

**Secondary Endpoint (LOCF)**
- Vortioxetine:*
- Duloxetine: ns

**Multiplicity Controlled Key Secondary Endpoint (MMRM)**
- Vortioxetine: ***
- Duloxetine: ns

**Primary Endpoint (LOCF)**
- Vortioxetine: *
- Duloxetine: ns

Additional Notes:
- *p<0.05, ***p<0.001 vs placebo, nominal † p<0.05 vs placebo; ns – not significant
Effect of Vortioxetine on DSST Performance is Largely a Mood-independent Effect

-0.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8

Standardized Effect Size vs Placebo

ELDERLY
FOCUS
CONNECT
ELDERLY CONNECT

VOR 5 mg
VOR 10 mg
VOR 20 mg
VOR 10/20 mg Flex
DUL

Effect mediated through effect on MADRS (indirect)
Effect NOT mediated through effect on MADRS (direct)
Vortioxetine – Summary of the Evidence

- The pharmacological profile and animal data in models of cognitive function
  - Supporting that vortioxetine is different from SSRIs/SNRIs
- Clinical fMRI study in subjects remitted from depression indicating that vortioxetine improves neuronal efficiency during cognitive processes
- Clinical data showing improved objective cognitive function in acute MDD
  - Mood-independent effect
  - Across a broad range of cognitive domains
  - Same effect not shown with duloxetine
- Clinical data showing improvement on performance-based functional capacity, patient-reported cognitive function and work productivity measures
## Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
<th>Position/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Jonathon Parker, RPh, MS, PhD</td>
<td>Vice President, Global Regulatory Affairs, CNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Takeda Pharmaceuticals International, Inc.</td>
</tr>
<tr>
<td>Measuring Change in Cognition</td>
<td>Judith Jaeger, MPA, PhD</td>
<td>Professor of Psychiatry and Behavioral Sciences,</td>
</tr>
<tr>
<td>with DSST</td>
<td></td>
<td>Albert Einstein College of Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>President and Principal Scientist, CognitionMetrics, LLC</td>
</tr>
<tr>
<td>Study Design and Results</td>
<td>Christina Kurre Olsen, PhD</td>
<td>Senior Specialist, Brintellix Clinical Science</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H. Lundbeck A/S</td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td>Maurizio Fava, MD</td>
<td>Executive Vice Chair, Department of Psychiatry, Massachusetts General Hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Executive Director, Clinical Trials Network and Institute</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Louis Mini, MD</td>
<td>Vice President, Global Medical Head, CNS Medical Affairs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Takeda Pharmaceuticals International, Inc.</td>
</tr>
</tbody>
</table>
Clinical Perspective

Maurizio Fava, MD
Executive Vice Chair, Department of Psychiatry
Massachusetts General Hospital (MGH)
Director, Division of Clinical Research
MGH Research Institute
Executive Director
MGH Clinical Trials Network and Institute (CTNI)
Associate Dean for Clinical and Translational Research
Slater Family Professor of Psychiatry
Harvard Medical School
Disclosure

• Consultant to Takeda and Lundbeck
• Consulting fees paid to MGH, no personal compensation
Why Treating Cognition in Depression is Important

- Cognitive dysfunction in Major Depressive Disorder
  - Common symptom that is often persistent, and an important contributor to functional impairment
  - Associated with disability in functioning, greater severity of illness, and increased disease burden
  - Represents a major unmet need in clinical practice
Cognitive Impairment at Baseline: CONNECT and FOCUS

Objective Impairment

1 >1 SD below the norm on at least 2 of the following: DSST, CRT, TMT-A, or TMT-B

Subjective Only

Objective (with or without Subjective)

Scored at least markedly impaired (≥5) on at least 2 of the 4 CPFQ cognitive domains

64.3%  64.1%

81.1%

CONNECT
FOCUS
Objective
Combined

1 www.mghcme.org

2 www.mghcme.org
Effect of Vortioxetine on DSST

Vortioxetine

- Secondary Endpoint (LOCF)
- Multiplicity Controlled Key Secondary Endpoint (MMRM)
- Primary Endpoint (LOCF)

Duloxetine

- Active Reference (LOCF)

* p<0.05, *** p<0.001 vs placebo, nominal † p<0.05 vs placebo; ns – not significant
Clinical Meaningfulness

- Vortioxetine consistently improved cognitive function in MDD patients as measured by the DSST
  - Standardized effect size between 0.25 and 0.52 across studies
  - Standardized effect size for duloxetine between 0.07 and 0.18
- Vortioxetine also improved subjective measures of cognitive function (CPFQ and PDQ)
- Performance-based measure of functional capacity and work productivity used in the CONNECT study also improved with vortioxetine (UPSA and WLQ)
- No deleterious effects on other cognitive measures
Summary

- Cognitive dysfunction in MDD often **persists** and contributes to functional impairment
- Effect of vortioxetine across three studies was **consistent, distinct**, and largely **independent** of mood effect
- Cognitive improvement was associated with **improvement in functional capacity**
- Results are clinically relevant and **important information** for clinicians and patients
## Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Jonathon Parker, RPh, MS, PhD</td>
<td>Vice President, Global Regulatory Affairs, CNS Takeda Pharmaceuticals International, Inc.</td>
</tr>
<tr>
<td>Measuring Change in Cognition with DSST</td>
<td>Judith Jaeger, MPA, PhD</td>
<td>Clinical Professor, Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine President and Principal Scientist, CognitionMetrics, LLC</td>
</tr>
<tr>
<td>Study Design and Results</td>
<td>Christina Kurre Olsen, PhD</td>
<td>Senior Specialist, Brintellix Clinical Science H. Lundbeck A/S</td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td>Maurizio Fava, MD</td>
<td>Executive Vice Chair, Department of Psychiatry, Massachusetts General Hospital Executive Director, Clinical Trials Network and Institute</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Louis Mini, MD</td>
<td>Vice President, Global Medical Head, CNS Medical Affairs Takeda Pharmaceuticals International, Inc.</td>
</tr>
</tbody>
</table>
Conclusions

Louis Mini, MD
Vice President, Global Medical Head, CNS Medical Affairs
Takeda Pharmaceuticals International, Inc.
Advance the Understanding

- Today, cognitive dysfunction is a gap in MDD treatment
- Need to communicate new clinical research data
- Need to more fully treat patients
Evidence of Vortioxetine Benefit

- Pharmacologic profile
- Nonclinical studies
- Clinical fMRI data
- Prospective, placebo-controlled clinical trials
Vortioxetine Cognition Studies in MDD

- First clinical program focused specifically on addressing this unmet need in MDD
  - No guidance on clinical research, an evolving concept
  - Founded on strong scientific rationale and principles
  - Expert input
- The primary endpoint was met in both pivotal trials
Conclusions

- Vortioxetine is indicated for the treatment of Major Depressive Disorder
- In two large, adequate and well-controlled studies, vortioxetine was effective in treating cognitive dysfunction in acute MDD as assessed by the DSST
- These data are clinically meaningful
- The study results are consistent and advance the understanding of the clinical profile of vortioxetine
- It is important to appropriately inform clinicians of this data in the Clinical Studies section of the US label
Additional Slides Shown
FOCUS
DSST, Change from Baseline (FAS, LOCF) Distribution – Absolute

Placebo

VOR 10 mg

VOR 20 mg

Change in DSST

Proportion of Patients (%)
Response Rate at Week 8 (FAS, LOCF)

Absolute Points Improvement

**FOCUS**

- **≥1 Point**
  - PBO: 60%
  - VOR 10: 80%
  - VOR 20: 80%
  - NNT: 6

- **≥3 Points**
  - PBO: 40%
  - VOR 10: 80%
  - VOR 20: 80%
  - NNT: 6

- **≥5 Points**
  - PBO: 20%
  - VOR 10: 80%
  - VOR 20: 80%
  - NNT: 5

**CONNECT**

- **≥1 Point**
  - PBO: 40%
  - VOR 10/20: 80%
  - NNT: 9

- **≥3 Points**
  - PBO: 20%
  - VOR 10/20: 80%
  - NNT: 9

- **≥5 Points**
  - PBO: 10%
  - VOR 10/20: 80%
  - NNT: 13

Nominal p-values: †p<0.05; ††p<0.01; †††p<0.001 vs placebo.
## Overview of Subgroups

### Baseline Subgroup

<table>
<thead>
<tr>
<th>Baseline Subgroup</th>
<th>N</th>
<th>ELDERSLY</th>
<th>N</th>
<th>FOCUS</th>
<th>N</th>
<th>CONNECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>152</td>
<td></td>
<td>193</td>
<td></td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>NA</td>
<td></td>
<td>114</td>
<td></td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Age ≥50</td>
<td>152</td>
<td></td>
<td>79</td>
<td></td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>49</td>
<td></td>
<td>61</td>
<td></td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>103</td>
<td></td>
<td>74</td>
<td></td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>56</td>
<td></td>
<td>35</td>
<td></td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Non-US</td>
<td>96</td>
<td></td>
<td>38</td>
<td></td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>DSST ≤ Mean</td>
<td>75</td>
<td></td>
<td>97</td>
<td></td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>DSST &gt; Mean</td>
<td>77</td>
<td></td>
<td>110</td>
<td></td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>MADRS &lt;30</td>
<td>64</td>
<td></td>
<td>96</td>
<td></td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>MADRS ≥30</td>
<td>88</td>
<td></td>
<td>94</td>
<td></td>
<td>112</td>
<td></td>
</tr>
</tbody>
</table>

**VOR 5**  **VOR 10**  **VOR 20**  **VOR 10/20**

**Change from Baseline**

- **Favors Placebo**
- **Favors Treatment**

---

**AS-148**

DSST, Week 8 (LOCF, ANCOVA)

Standardized Effect vs. Placebo

ELDERLY FOCUS CONNECT

-1 0 1
Objective 1: Cognitive Impairment at Baseline

**FOCUS**

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>VOR 10</th>
<th>VOR 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>124</td>
<td>125</td>
<td>130</td>
</tr>
<tr>
<td>NO</td>
<td>70</td>
<td>68</td>
<td>74</td>
</tr>
</tbody>
</table>

**CONNECT**

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>VOR 10/20</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>101</td>
<td>119</td>
</tr>
<tr>
<td>NO</td>
<td>66</td>
<td>56</td>
</tr>
</tbody>
</table>

1SD or Below on 2 or More Tests (DSST, CRT, TMT-A, TMT-B)
Error bars indicate SE.
DSST, Week 8 (FAS, ANCOVA, LOCF)
Objective 1 Cognitive Impairment at Baseline

**FOCUS**

- **YES**
  - PBO: 124
  - VOR 10: 125
  - VOR 20: 130

- **NO**
  - PBO: 70
  - VOR 10: 68
  - VOR 20: 74

**CONNECT**

- **YES**
  - PBO: 101
  - VOR 10: 119
  - VOR 20: 120

- **NO**
  - PBO: 66
  - VOR 10: 56
  - VOR 20: 67

1SD or Below on 2 or More Tests (DSST, CRT, TMT-A, TMT-B)
Error bars indicate SE.