Targeting Cognitive Impairment in Major Depressive Disorder - Industry Perspective

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Disclosures

• I am an employee of H. Lundbeck A/S
• I am a shareholder in H. Lundbeck A/S
Brintellix® (vortioxetine)

- Discovered and patented by H. Lundbeck A/S and co-developed with Takeda Pharmaceutical Company Ltd. for the treatment of MDD
- Positive opinion for updating the SmPC with information on the effect of vortioxetine on certain aspects of cognitive function in MDD (European Commission Feb. 2015)
Background

Vortioxetine has a distinct mechanism of action

- Combined 5-HT receptor modulation and transporter inhibition
- Increased 5-HT, NA, DA, acetylcholine, histamine and glutamate neurotransmission, at least partly through inhibition of GABA interneurons
- Direct activity of vortioxetine at 5-HT receptors is essential for the pharmacodynamic profile of vortioxetine unlike SSRIs and SNRIs, which rely on SERT inhibition

Vortioxetine has differential effects in models of cognitive function

- Restores memory deficits due to low 5-HT or disrupted glutamatergic or cholinergic neurotransmission
- Activates cortical circuitries involved in cognitive processing (EEG)
- Restores memory deficits in old mice
- Induces dendritic branching in hippocampus
- Promotes expression of genes that regulate synaptic plasticity-related targets in frontal cortex and hippocampus
- Increases LTP in hippocampus (neuroplasticity) and increases pyramidal neuron firing in the rat mPFC

Vortioxetine modulates neural responses using fMRI during cognitive performance

- Across a circuit subserving working memory (N-Back task) in a direction opposite to the increases in BOLD-signal described in MDD
- In patients remitted from depression and healthy controls supporting direct effects on cognitive function unconfounded by syndromal depression

Approach

To demonstrate that

• vortioxetine’s effect occurs through improvement in cognitive dysfunction in addition to alleviation of depressive symptoms in MDD

• the improvement in cognitive dysfunction is specific to vortioxetine, and not just an additional outcome of an antidepressant effect achieved by other antidepressants
First Clinical Evidence

- Vortioxetine 5 mg/day improved cognitive performance as measured by the DSST and RAVLT tests\(^1\)
  - Cognition was a secondary endpoint
  - Key cognitive processes are involved in DSST and RAVLT e.g. executive function, working memory and attention
- Duloxetine (active reference) only improved cognitive performance in RAVLT and not in DSST
  - Confirms published data in both tests\(^2\)

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**Depressive symptoms**

![Graph showing HAM-D mean change from baseline over treatment weeks for Placebo (n=145), Vortioxetine 5 mg (n=155), and Duloxetine 60 mg (n=148).]

**Cognitive dysfunction\(^a\)**

![Graph showing standardised effect size vs placebo for Vortioxetine 5 mg and Duloxetine 60 mg across DSST, RAVLT acquisition, and delayed recall.]

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\(^a\)Compared to placebo

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DSST=Digit Symbol Substitution Test
RAVLT=Rey Auditory Verbal Learning Test

(Elderly: NCT00811252)
Approaches to Address Specificity

• To show significant separation on measures of cognitive function that is not seen with other antidepressants despite alleviation of depressive symptoms

• Applying mediation analysis to decompose correlations and assess the extent of an independent effect on cognitive performance that is not mediated solely through an improvement in depressive symptoms
Patient Population

- The patient has MDD, diagnosed according to DSM-IV-TR™ recurrent MDD
- The patient has a MADRS total score ≥ 26
- The patient has had the current MDE for ≥3 months
- The patient is aged ≥ 18 and ≤ 65 years

(FOCUS: NCT01422213; CONNECT:NCT01564862)
Study Design Considerations (Endpoints)

- Primary endpoint
- Sensitivity to change
- Standardised effect size

- Clinical relevance
- Specificity (influence of mood)
- Study burden

Cognitive function

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<tr>
<th>Objective</th>
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<td>Neuropsychological tests</td>
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Functionality

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Study Design Considerations (Test Selection Strategy)

**Executive Function**
- DSST (a measure of executive function, working memory, processing speed and visuospatial attention)
- Trail Making Test B (TMT-B) (a measure of executive control and cognitive flexibility/set-shifting)

**Speed of Processing**
- Groton Maze Learning Test (GMLT) (a measure of planning, spatial problem solving, visual learning and memory)
- Trail Making Test A (TMT-A) (a measure of attention, visual searching and mental processing speed)
- Stroop Color Naming Test (STROOP) (a measure of mental [attentional] vitality, cognitive flexibility/response inhibition [incongruent] and processing speed [congruent])

**Attention**
- One-Back Task (a measure of attention and working memory)
- Simple Reaction Time Task (SRT) (a measure of psychomotor function / Speed of Processing)

**Memory**
- RAVLT (a measure of verbal learning and memory, including proactive inhibition, retention, encoding versus retrieval, and subjective organization)
- Choice Reaction Time Task (CRT) (a measure of visual attention and vigilance)

(FOCUS: NCT01422213; CONNECT:NCT01564862)
DSST

- The Digit Symbol Substitution Test (DSST) is an objective neuropsychological test of executive function, working memory, processing speed and visuospatial attention
- Requires the integrity of a broad range of domains relevant for MDD
- Shares significant variance with cognitive test batteries as well as measures of functional capacity
- Used for more than 30 years with different age groups and found to be a predictor of outcome in patients with severe mental illness

➢ **DSST is an integrated measure incorporating multiple cognitive abilities**
Supportive Evidence

• The effect on DSST was supported by the significant effect on tests measuring other specific domains

DSST considered appropriate as primary endpoint and applied in the following study for replication


(FOCUS: NCT01422213)
The effect of vortioxetine on DSST performance is not mediated solely through an improvement in general depressive symptoms.

The effects on the subjective measure of cognitive function were found to a large degree to be attributable to the improvement in general depressive symptoms.


PDQ=Perceived Deficits Questionnaire
Objective measures of cognitive dysfunction are needed to disentangle the effect on cognitive dysfunction in the presence of mood symptoms.
The UPSA evaluates the abilities of an individual to perform everyday tasks that are considered necessary for independent functioning in the community.

Objective performance-based measures capture effects not addressed by depression scales, which are primarily designed to assess mood symptoms.

(CONNECT: NCT01564862, Mahableshwarkar et al. CINP. 2014)
Targeting Cognitive dysfunction in MDD

A perspective from the vortioxetine program

• Cognitive dysfunction is a distinct dimension of depression
• Studying the acute MDD population allows to evaluate the therapeutic effect in relation to both the mood and the cognitive components of depression
• Objective measures of cognitive function capture therapeutic effects not addressed by depression scales that primarily are designed to assess changes in mood symptoms
• Improvement on objective measures of cognitive function translates into improved functional capacity
• Patient’s perception, although relevant, is highly influenced by mood and is therefore less distinct
• Cognitive dysfunction in MDD can be specifically targeted by demonstrating effect on objective measures of cognitive function not achieved by other antidepressants