



Psychopharmacologic Drugs Advisory Committee Meeting

NDA 204447/S-006 Brintellix (vortioxetine):
Treatment of Cognitive Dysfunction in
Major Depressive Disorder

Tiffany R. Farchione, MD

Deputy Director, Division of Psychiatry Products

Discussion and Voting Questions

- **DISCUSSION:** Discuss whether the Digital Symbol Substitution Test (DSST) is an adequate measure of cognitive function in MDD?
- **DISCUSSION:** What, if any, additional data are needed pre- or post-approval to address outstanding issues? Please be clear whether you believe these data should be required prior to approval.
- **DISCUSSION:** Does a claim for an effect on cognitive function require showing of superiority to another antidepressant (or more than one) or is it sufficient to shown an effect vs placebo on cognitive function?
- **VOTE:** Has substantial evidence been presented by the applicant to support a claim of effectiveness for vortioxetine for treating cognitive dysfunction in MDD?

Regulatory History of Vortioxetine for the Treatment of Cognitive Dysfunction in MDD

Tiffany R Farchione, MD

Deputy Director

Division of Psychiatry Products

Center for Drug Evaluation and Research

Ideal Circumstances

- Sponsor requests a pre-IND meeting.
- We provide feedback on the development program.
- Sponsor incorporates that feedback into protocols.
- Early trial results look promising.
- Sponsor requests an End of Phase 2 meeting.
- We agree on endpoints and statistical plan for Phase 3.
- Two positive adequate and well-controlled trials.
- Drug gets approved.

Pseudospecificity: Early Feedback

- Sept 1, 2011: New IND with Study 14122A (FOCUS)
- Oct 17, 2011: May Proceed letter with non-hold clinical comments
 - *“Although cognitive symptoms are generally accepted as a component of MDD, they have not been adequately characterized. Furthermore, an adequate case has not been made to view them as a distinct clinical target for drug development.”*
 - Once cognitive dysfunction in this context has been well-characterized, will need an instrument that specifically assesses relevant symptoms
 - *“You have not made an adequate case to support the instruments you have selected for this program.”*

Consequences of Our Advice

- Applicant continued development program without additional input from the Division.
- Protocol for Study 202 (CONNECT) submitted on April 3, 2012.
- Reviewer comments communicated to the sponsor:
 - *“We would like to reiterate that the cognitive dysfunction associated with MDD is not yet recognized as a distinct clinical target for drug development. It is very likely that your proposed investigation would not support the claim you are seeking.”*

February 25, 2014 Guidance Meeting

- Goal: To obtain feedback from FDA on the adequacy of the vortioxetine clinical program to support a promotional claim on cognitive dysfunction in MDD.
- Division Comment: *“It will be necessary to gather adequate data to fully characterize such an entity, identify all relevant and clinically important cognitive domains, and establish valid and reliable instruments for objectively assessing the relevant domains.”*
- Division acknowledged that cognitive dysfunction in MDD was an evolving field and that a specific regulatory path to a claim based on the proposed Digit Symbol Substitution Test (DSST) scale had not yet been identified.

February 25, 2014 Guidance Meeting (con't.)

- Division described issues that would need to be addressed:
 - Relationship between changes measured on formal cognitive testing and meaningful clinical changes (i.e., need for functional co-primary measure)
 - Types of study designs that would be acceptable for assessing effects of antidepressants on cognition
 - Legitimacy of focusing on cognitive dysfunction when other residual symptoms may also be problematic
 - Acute phase vs. remitted state
 - Study duration
- Take home message: DPP still concerned that cognitive dysfunction is pseudospecific.

Evolving Views

- June, 2014: American Society of Clinical Psychopharmacology Annual Meeting
 - Workshop on Cognitive Dysfunction in MDD
- October, 2014: Massachusetts General Hospital Psychiatry Academy Workshop
 - Cognition in Depression: What Do We Know?
- February, 2015: Institute of Medicine
 - Enabling Discovery, Development, and Translation of Treatments for Cognitive Dysfunction in Depression
- Willing to consider applications seeking this claim.
- Issues related to study design and endpoints remain unresolved.

February 18, 2015 Pre-sNDA Meeting

- *“...we believe that all antidepressants improve cognitive dysfunction in MDD to some degree, however, it is possible that some drugs have a greater effect at improving cognitive dysfunction than others. If you believe your drug is better at treating cognitive dysfunction in MDD, you will need to demonstrate that your drug is superior to other antidepressants (ideally drugs from more than one class) in treating this aspect of the disease while maintaining an effective antidepressant effect.”*
- Take home messages:
 - Unresolved issues will be considered in our review.
 - Advisory Committee meeting will be required.

Clinical Outcome Assessment Review of Digit Symbol Substitution Test (DSST): Vortioxetine for Cognitive Dysfunction in Major Depressive Disorder

Wen-Hung Chen, PhD

CDER, Clinical Outcome Assessment Staff

February 3, 2016

Human Cognition is a Multi-domain Construct

- Human cognition is a complex multi-domain construct that involves the total range of psychological processes.
- No single performance-based neuropsychological test is a pure measure of a specific cognitive domain, and no single performance-based neuropsychological test assesses the overall cognition construct.
- To assess the overall cognitive function, a battery of multiple cognitive tests is often used.

Primary and Secondary Study Endpoints

- Study 14122A (FOCUS):
 - Primary: A weighted composite z-score of DSST, Rey Auditory Verbal Learning Test (RAVLT)- acquisition/learning, and RAVLT- delayed recall/memory
 - Secondary endpoints: DSST, RAVLT acquisition/learning, RAVLT delayed recall/memory.
- Study 202 (CONNECT):
 - Primary: DSST
 - Secondary endpoints: Perceived Deficits Questionnaire (PDQ) attention/concentration and planning/organization combined subscore, and Clinical Global Impression - Improvement (CGI-I) score.

Other Endpoints

- Study 14122A (FOCUS):
 - Neuropsychological tests: Trail Making Test (TMT) -A and -B; Stroop Color Naming Test (Stroop); Simple Reaction Time Task (SRT); Choice Reaction Time Task (CRT);
 - Patient-reported outcome (PRO) assessment: Perceived Deficits Questionnaire (PDQ)
- Study 202 (CONNECT):
 - Neuropsychological tests: TMT A and B; Stroop; SRT; CRT; Groton Maze Learning Task (GMLT); One-Back Test;
 - PRO assessments: Cognitive and Physical Functioning Questionnaire (CPFQ), Working Limitation Questionnaire (WLQ);
 - Performance-based functional assessment: University of San Diego Performance-Based Skills Assessment (UPSA)

Digit Symbol Substitution Test (DSST)

- DSST is a neuropsychological test that belongs to a broader category of the performance-based outcome assessments (PerfO).
- The subject is given a piece of paper with nine symbols corresponding with nine digits.
- A series of 133 randomized digits are presented and the patient draws a symbol below each digit as indicated by the codes provided.
- The patient is asked to fill in as many corresponding symbols in 90 seconds, without skipping. The DSST number-correct score ranges from 0 (worst functioning) to 133 (best functioning).

Digit Symbol Substitution Test (DSST)*

Digit Symbol Substitution Test (DSST)

1	2	3	4	5	6	7	8	9
—	⊥	□	L	U	○	^	X	=

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

*Provided by Takeda for regulatory review purpose.

DSST: What does it measure in patients with MDD?

- There is no definite answer to what DSST actually measures in patients with MDD.
- In the literature, processing speed has been mentioned the most. Copy speed, visuomotor coordination, motivation, effort, and age also affect the performance on DSST.
- DSST has been shown to be associated other neuropsychological tests that assess attention, working memory, executive function, as most neuropsychological tests are inter-correlated or overlapping.

DSST: What does it measure in patients with MDD? (continued)

- Many alternative versions of DSST and with different patient populations have been used and described in the literature making generalizability of the findings difficult.
- These alternative versions contain symbols of varied familiarity resulting in different levels of difficulty.
- Different patient populations have different types or levels of cognitive dysfunction.
- Different findings regarding what DSST measures may be related to the use of different versions or with different populations.

DSST: How much change is required for clinically meaningful improvement in patients with MDD?

- An empirically-based threshold for the change in DSST that represents meaningful improvement has not been established.
- Empirically-based thresholds are generally derived using anchor-based methods, which explore the associations between the targeted concept of the instrument in question and the concept measured by the anchors (e.g., other measures of related concepts or patient global assessments).

DSST: Whether the change can be translated into real world gain in patients with MDD?

- For regulatory purpose, it is critical to know whether the improvement in performance on DSST in patients with MDD can be directly translated into the improvement in real world function.
- A performance-based assessment of functional capacity, the University of San Diego Performance-Based Skills Assessment (UPSA), was included in Study 202 as one of other additional endpoints.

University of San Diego

Performance-Based Skills Assessment (UPSA)

- The UPSA involves role-play tasks that are administered as simulations of events that the person may encounter in the community. UPSA total score ranges from 0 to 100.

Example: Communication Skills - Telephone and letter

- Place the telephone in front of the subject and give the following instructions:

<p>We're going to use this telephone for the next tasks. Even though it's disconnected, show me everything you normally do when using a telephone.</p> <p>First, show me what number you would dial for help in case of an emergency.</p>	<p>Answer: (dial) 9-1-1</p>
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- Instruct the subject to do the following:

<p>Please call directory assistance and ask for the telephone number of David Johnson who lives in Midtown.</p>	<p>Answer: (dial) 4-1-1 (speak) David Johnson, Midtown</p>
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Summary

- There is no definitive answer to what DSST actually measures in patients with MDD.
- There is no empirically-based threshold for the change in DSST score that represents meaningful improvement in overall cognitive function or meaningful changes in everyday functioning for patients with MDD.

Clinical, Safety, and Efficacy Data

Aeva Gaymon-Doomes, MD

Medical Officer

Division of Psychiatry Products

Office of Drug Evaluation I

Office of New Drugs

Center for Drug Evaluation and Research

United States Food and Drug Administration

Cognitive Dysfunction in Major Depressive Disorder

- Core feature of MDD along with mood and behavior disturbances
- Occurs in about two-thirds of individuals with MDD
- May remain even when the mood symptoms are in remission
- No formal quantitative measures currently accepted for diagnostic purposes
- Ability to improve cognition may represent an unmet need

Vortioxetine

- Approved for the treatment of MDD in 2013
- Recommended dose is 20 mg; may be lower depending on tolerability or CYP metabolism
- Efficacy established in six short-term trials and one maintenance study
- Mechanism thought to be related to inhibition of 5-HT reuptake in the CNS
- Contribution of 5-HT₃ antagonism and 5-HT_{1A} agonism to antidepressant effect has not been established
 - Applicant hypothesizes that action at 5-HT₃ receptor is involved in vortioxetine's cognitive effects

Safety

- Vortioxetine is an approved product
- No new safety signals were identified
 - Most common adverse reactions in pre-marketing clinical trials: nausea, constipation, and vomiting
 - Labeled Warnings & Precautions: serotonin syndrome, abnormal bleeding, activation of mania/hypomania, angle closure glaucoma, hyponatremia, and a boxed warning for increased suicidal ideation and behavior in children, adolescents, and young adults

Study 12541A (ELDERLY)

- Randomized, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study
- Evaluated acute treatment of MDD in elderly patients
- Reviewed with original vortioxetine NDA

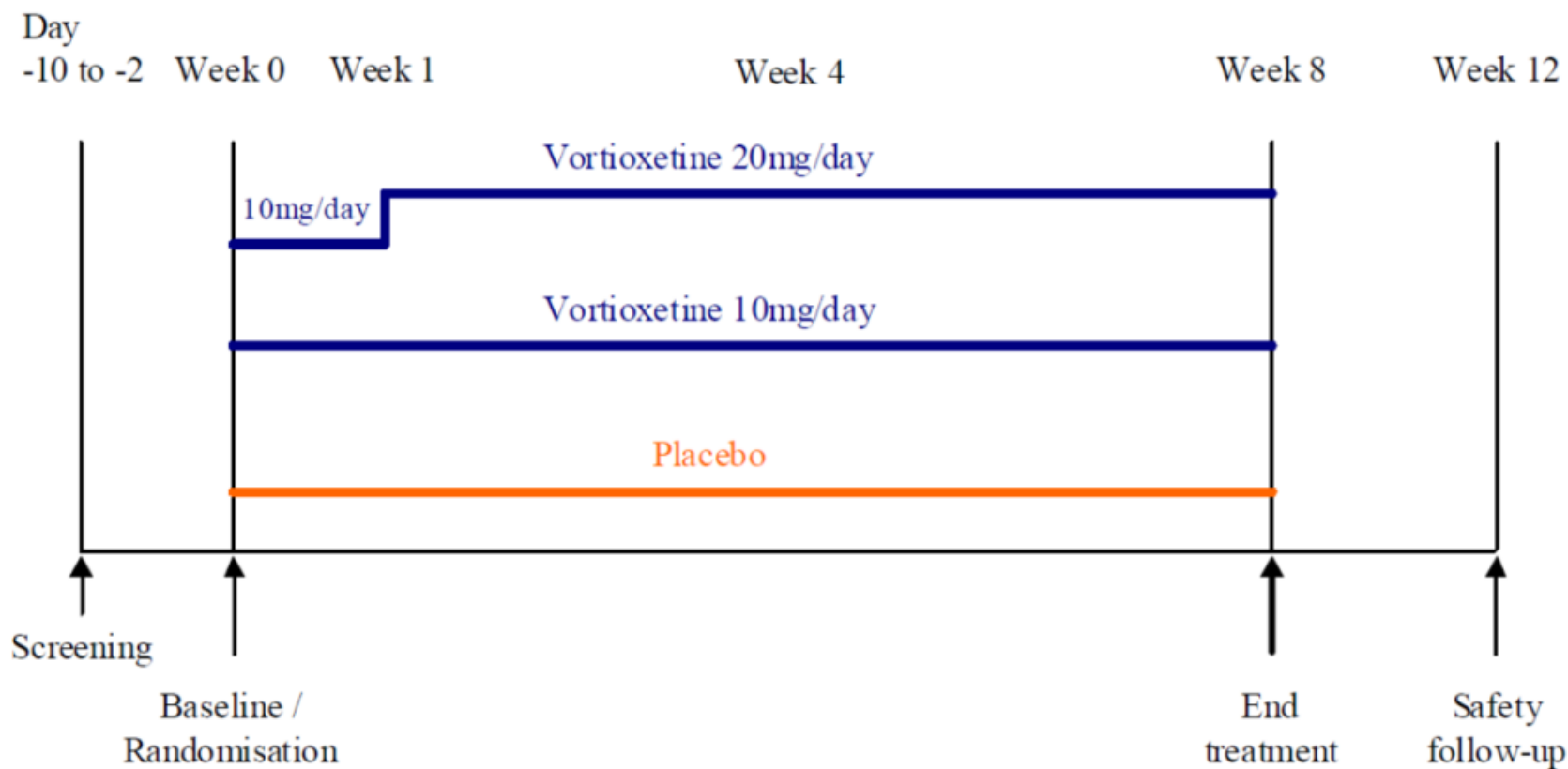
Relevance of ELDERLY Study to Cognitive Dysfunction Development Program

- Digit Symbol Substitution Test (DSST) was included as one of many secondary endpoints
 - After 8 weeks, change from baseline in DSST greater in patients taking vortioxetine 5mg compared to placebo (least squares mean treatment difference = 2.79, nominal $p = 0.0225$)
 - Duloxetine 60 mg treatment arm was also numerically better than placebo (least squares mean treatment difference = 0.77, $p = 0.53$), but the effect was numerically smaller than the effect of vortioxetine
- Exploratory analysis of DSST results encouraged the applicant to pursue new claim

Study 14122A (FOCUS)

- 8-week randomized, double-blind, parallel-group, placebo- controlled, fixed-dose study
- First of two studies specifically designed to assess the effect of vortioxetine on cognitive dysfunction in adult patients with MDD
- 602 patients
 - Placebo (n=198), vortioxetine 10 mg/day (n = 197), and vortioxetine 20 mg/day (n = 207)
 - MADRS \geq 26 and current episode \geq 3 months
 - Required DSST (number correct) $<$ 70, RAVLT (learning) $<$ 42 and RAVLT (memory) $<$ 14 at baseline

Study Design Schematic (FOCUS)



Source: Applicant's Clinical Study Report

Primary Endpoint (FOCUS)

- Primary endpoint: change from Baseline to Week 8 in a composite cognitive measure based on DSST and RAVLT

$$\text{Composite Z Score} = 0.5 * Z_{DSST}(\text{number correct}) + 0.25 * Z_{RAVLT}(\text{learning}) + 0.25 * Z_{RAVLT}(\text{memory}),$$

Illustration: $Z_{DSST}(\text{number correct})$ Score calculated as *patient's change from baseline - mean of the changes of all patients* / *standard deviation of the changes of all patients in trial*

- FDA Comments:
 - Clinical relevance uncertain
 - Independence assumption required for statistical analysis

Prespecified Secondary Endpoints

- **DSST**

1. LS mean differences from placebo at Week 8 were 4.20 points (number of correct symbols) in favor of vortioxetine 10 mg/day ($p < 0.0001$) and 4.26 points in favor of vortioxetine 20 mg/day ($p < 0.0001$)

- **RAVLT**

2. Learning scores were not significantly different ($p > 0.025$) from placebo for either vortioxetine group
3. **Testing hierarchy stopped with failure on learning score**; however, improvement in RAVLT memory scores was nominally better in each vortioxetine groups ($p < 0.05$) than in the placebo group

Additional Secondary Endpoints: Neuropsychological Tests

Test	Cognitive Domains
Trail Making Test A, B (TMT-A, B)	Attention, speed of processing (TMT-A), Executive Function, cognitive flexibility (TMT-B)
Stroop	Speed of processing (Stroop congruent) Executive function, response inhibition (Stroop incongruent)
Choice Reaction Time Task (CRT), Simple Reaction Time Task (SRT)	Attention (CRT), Psychomotor speed (SRT)
One-back Task* *(Study 202 only)	Attention, working memory
Groton Maze Learning Task (GMLT)	Executive function, learning

Neuropsychological Tests (con't.)

Difference from Placebo at Week 8

	vortioxetine 10 mg/day			vortioxetine 20 mg/day		
	LS mean	95% CI	effect size	LS mean	95% CI	effect size
Δ TMT-A	-3.76*	-6.45; -1.08	0.29	-3.80*	-6.46; -1.14	0.29
Δ TMT-B	-7.57*	-12.9; -2.20	0.29	-9.01*	-14.3; -3.70	0.35
Δ Stroop congruent	-4.00*	-6.50; -1.49	0.33	-4.45*	-6.93; -1.97	0.37
Δ Stroop incongruent	-6.75*	-10.8; -2.74	0.35	-6.52*	-10.5; -2.54	0.34
Δ SRT	-0.046*	-0.07; -0.02	0.41	-0.03*	-0.05; -0.01	0.26
Δ CRT	-0.032*	-0.05; -0.01	0.38	-0.01	-0.03; -0.01	0.10

* nominal p-value <0.05

A negative value represents advantage compared to placebo.

Adapted from applicant's background document

Additional Secondary Endpoints—Self-Report

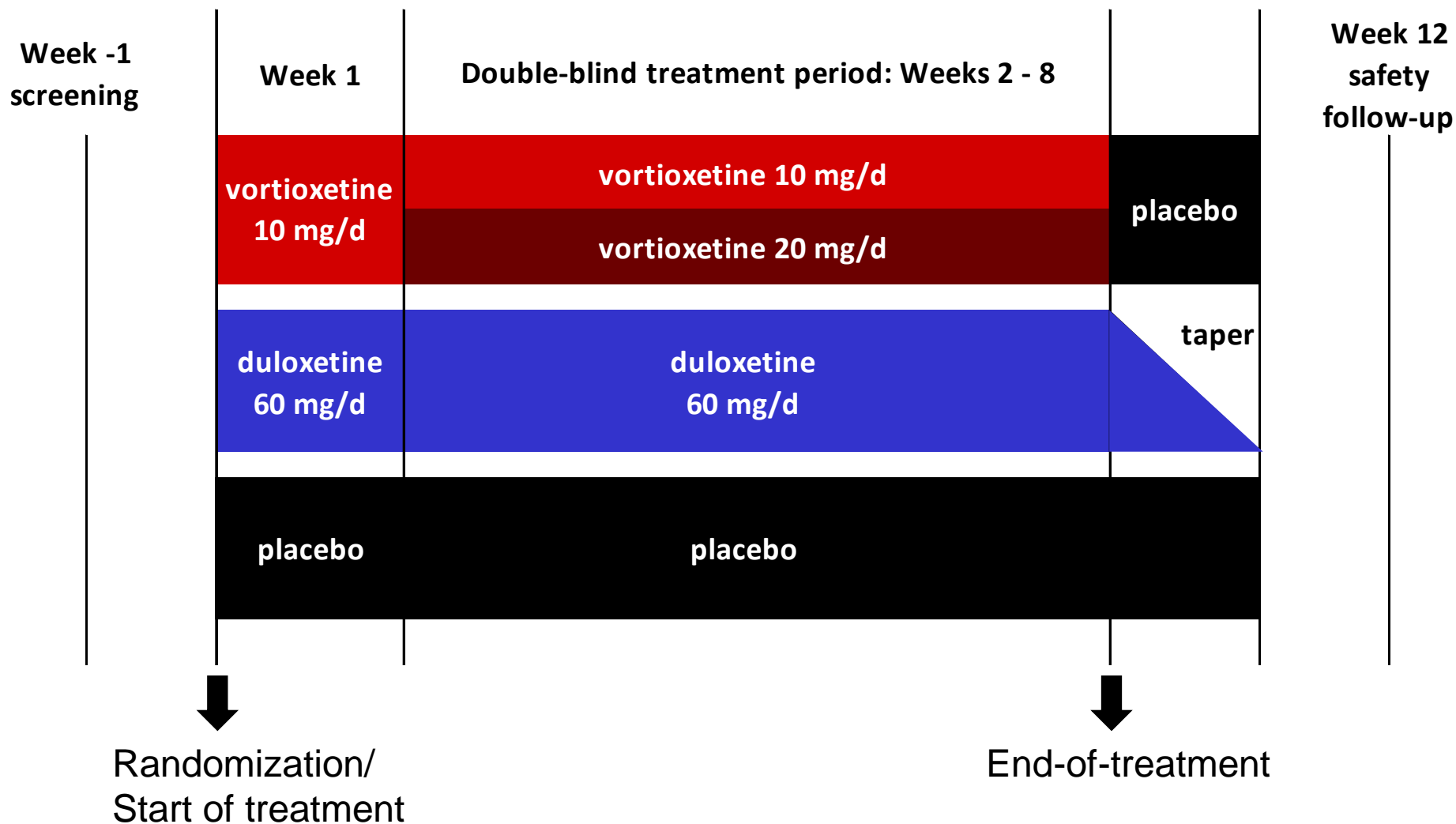
Perceived Deficits Questionnaire (PDQ): Self-reported Cognitive Symptoms

	vortioxetine 10 mg/d vs. placebo		vortioxetine 20 mg/d vs. placebo	
	LS mean difference	nominal p-value	LS mean difference	nominal p-value
Total Score	-4.40	0.001	-5.71	0.001
Attention/concentration and planning/organization combined subscore	-2.55	0.001	-3.79	0.001

Study 202 (CONNECT)

- Multicenter, randomized, double-blind, placebo- and active-controlled (duloxetine 60 mg/day), parallel-group flexible dose study
- Vortioxetine 10 mg/day or 20 mg/day
- 602 patients
 - Vortioxetine flexible doses 10 or 20 mg/day (n = 198), duloxetine 60 mg/day (n = 210), or placebo (n = 194)
 - Montgomery-Asberg Depression Rating Scale (MADRS) ≥ 26 and current episode ≥ 3 months
 - Subjective self-reported cognitive dysfunction
 - DSST (number correct) < 70 at baseline

Study Design Schematic (CONNECT)



Primary Endpoint (CONNECT)

- Change from baseline to Week 8 in **DSST** (number correct), vortioxetine vs. placebo
- LS mean difference vs. placebo was 1.75 points in favor of vortioxetine ($p = 0.019$)
 - LS mean difference between the duloxetine (active comparator) and placebo groups was 1.21 points (nominal $p = 0.099$)

Prespecified Secondary Endpoints (CONNECT)

- Vortioxetine vs. placebo
 - Change from baseline in **PDQ** attention/concentration and planning/organization combined subscore, $p < 0.01$
 - **CGI-I** score, $p < 0.05$

Other Secondary Endpoints (CONNECT)

- Cognitive tasks
 - Trail Making Test A and B, Stroop congruent and incongruent, Groton Maze Learning Task, Simple Reaction Time Task, Choice Reaction Time Task, and One-Back Task
 - In vortioxetine vs. placebo, only Trail Making Test B was better than placebo (nominal $p < 0.001$)
 - No comparisons reached nominal significance for duloxetine vs. placebo

Other Secondary Endpoints (CONNECT)

- Self-report cognition
 - PDQ total score
 - Vortioxetine vs. placebo: LS Mean difference = -4.2, nominal $p < 0.01$
 - Duloxetine vs. placebo: LS Mean difference = -5.5, nominal $p < 0.001$
 - PDQ attn/conc and plan/org combined subscore
 - Duloxetine vs. placebo: LS Mean difference = -3.0, nominal $p < 0.001$
 - Cognitive and Physical Functioning Questionnaire (CPFQ), change from baseline in total score, all patients
 - Vortioxetine vs. placebo: LS Mean difference = -1.2, $p = \text{NS}$
 - Duloxetine vs. placebo: LS Mean difference = -1.7, nominal $p < 0.05$
 - CPFQ, change from baseline in total score, only patients with baseline score ≥ 25
 - Vortioxetine vs. placebo: LS Mean difference = -1.7, nominal $p < 0.05$
 - Duloxetine vs. placebo: LS Mean difference = -1.8, nominal $p < 0.05$

Other Secondary Endpoints (CONNECT, con't.)

- UCSD Performance-Based Skills Assessment (UPSA)
 - Measure of functional capacity
 - Vortioxetine vs. placebo, LS Mean difference = 2.94, nominal $p < 0.001$
 - Duloxetine vs. placebo, LS Mean difference = 0.38, $p = \text{NS}$
- Working Limitation Questionnaire (WLQ)
 - Patient-Reported Work Limitations
 - Includes subscales for rating time, physical, mental-interpersonal, and output demands
 - Vortioxetine vs. placebo, time demands subscale, LS Mean difference = -8.13, nominal $p < 0.05$
 - No other comparisons reached nominal significance

Comparison of DSST Results Across Studies

Treatment	N	Baseline	Change from Baseline	Difference from Placebo	
		Mean (SD ¹)	LS ² Mean(SE ³)	LS Mean (SE)	95% CI ⁴
Study 14122A (FOCUS)					
Placebo	194	42.4 (13.8)	4.83 (0.63)	-	-
Vortioxetine 10 mg	193	42.0 (12.6)	9.03 (0.63)	4.20 (0.87)	(2.50, 5.90)
Vortioxetine 20 mg	204	41.6 (12.7)	9.09 (0.61)	4.26 (0.86)	(2.57, 5.94)
Study 202 (CONNECT)					
Placebo	167	43.0 (12.3)	2.85 (0.54)	-	-
Vortioxetine (10-20 mg)	175	42.1 (11.9)	4.60 (0.53)	1.75 (0.74)	(0.28, 3.21)
Duloxetine 60 mg	187	42.8 (12.2)	4.06 (0.51)	1.21 (0.73)	(-0.23, 2.65)

¹Standard Deviation, ²Least Squares, ³Standard Error, ⁴Confidence Interval

(Extracted from: Clinical Study Report 14122A and Clinical Study Report 202)

Summary

- Positive results for vortioxetine on DSST in ELDERLY (exploratory), CONNECT and FOCUS studies
- Greater magnitude of DSST change observed in FOCUS
- Observed improvement on DSST at Week 8 was better in the vortioxetine group than in the duloxetine group in CONNECT
- CONNECT also included functional measures and, although they were not prespecified, the results seem to suggest superiority of vortioxetine at nominal significance level of 0.05