Application of a simple mediation model in a regulatory setting

Brintellix
vortioxetine

DSBS Meeting
18 August 2016

Takeda

Lundbeck

Background: Vortioxetine Clinical Development

Vortioxetine/Brintellix is a worldwide, recently developed and approved antidepressant (MDD).

Pharmacological profile and animal data revealed potential for effect on cognition, well-known residual symptoms within MDD

Initial Profiling strategy:

Some cognitive tests and subjective rating scales were included as secondary parameters in MDD studies.

Specific Cognition strategy:

Two decicated studies in MDD patients with cognition as primary end point

Why Important ?

Labelling text gives a competitive advantage, since no other antidepressants have this

Particulary in US where labelling is required for promotion

Higher price in US

Strictly, not necessesary for promotion in EU, (but it helps)

Authorities are aware of this

Regulatory Challenges for Cognition within MDD

Cognition is part of the Depression diagnosis/disease

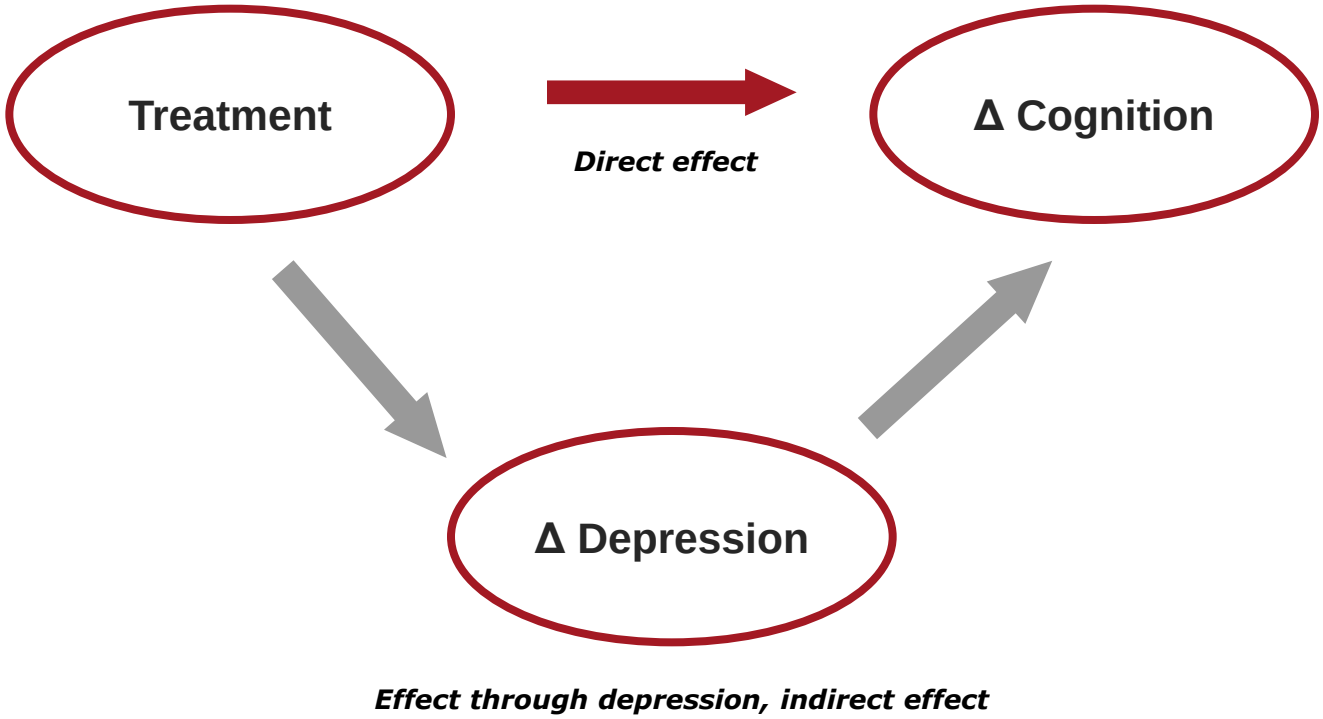
Pseudospecifity: any antidepressant will have effect

Not recognised as a target

Not recognised as unmet need , despite well-known residual symptoms

Consequently: No established endpoints

Mediation: Potential Treatment Effect Mediated by Effect on Depression



Cognition Development Program

- **ELDERLY (n>150 per group)**
  - Depression study exploring the effect of vortioxetine on cognitive performance (DSST, RAVLT) – included active reference

MDD Submission

Hypothesis generating

Variations: Type II/sNDA

- **FOCUS and CONNECT (n>200 per group)**
  - Designed to confirm effect of vortioxetine on cognitive dysfunction in adult MDD

2 pivotal studies with cognitive dysfunction as primary endpoint

- 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

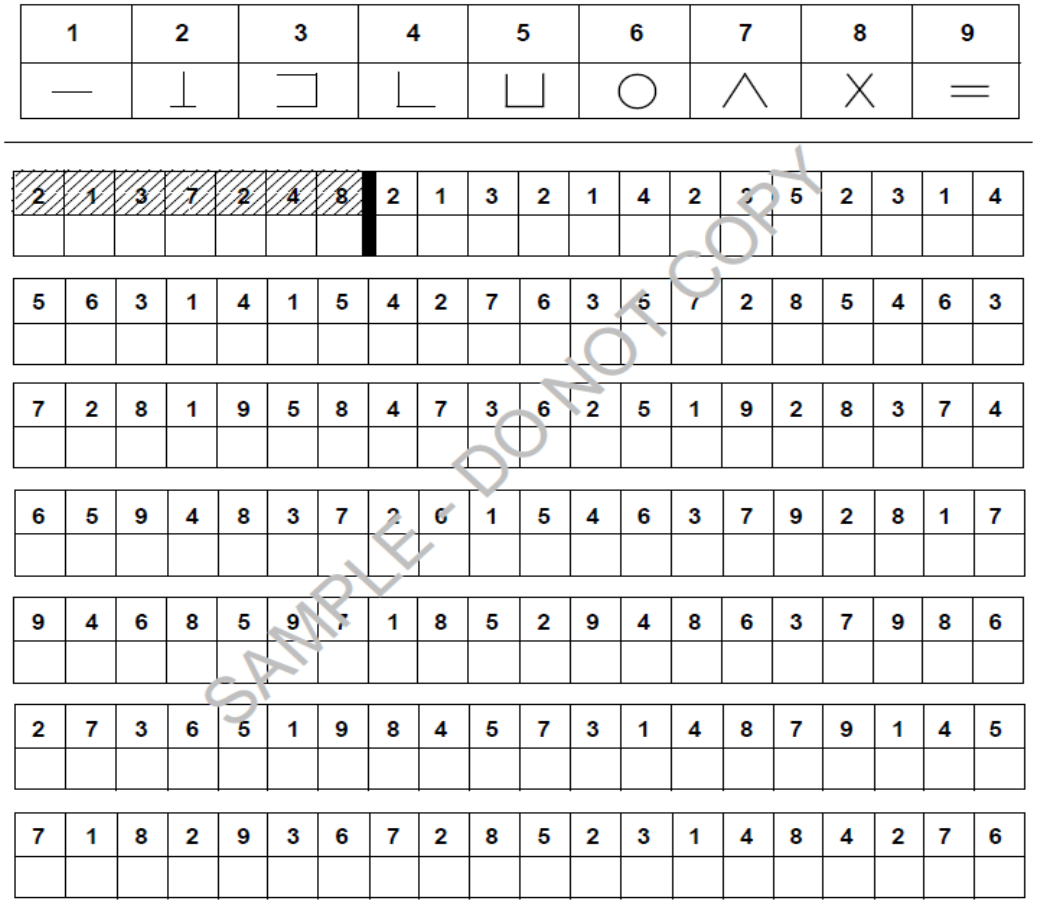
Supportive evidence

Depression Primary Endpoint: MADRS

- **MADRS: Montgomery-Åsberg Depression Rating Scale**
- **10 item clinician rated scale (0-6, max score of 60)**

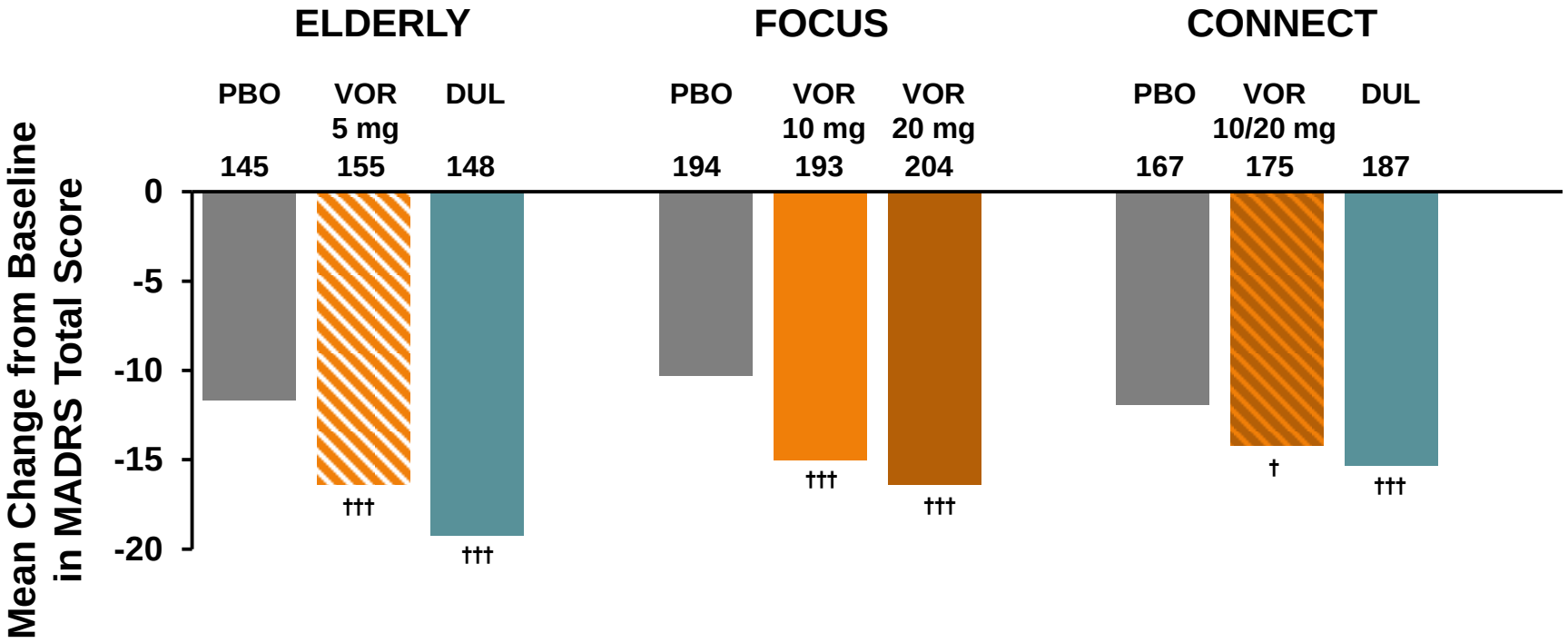
1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

Cognition Primary Endpoint: DSST: Digit Symbol Substitution Test



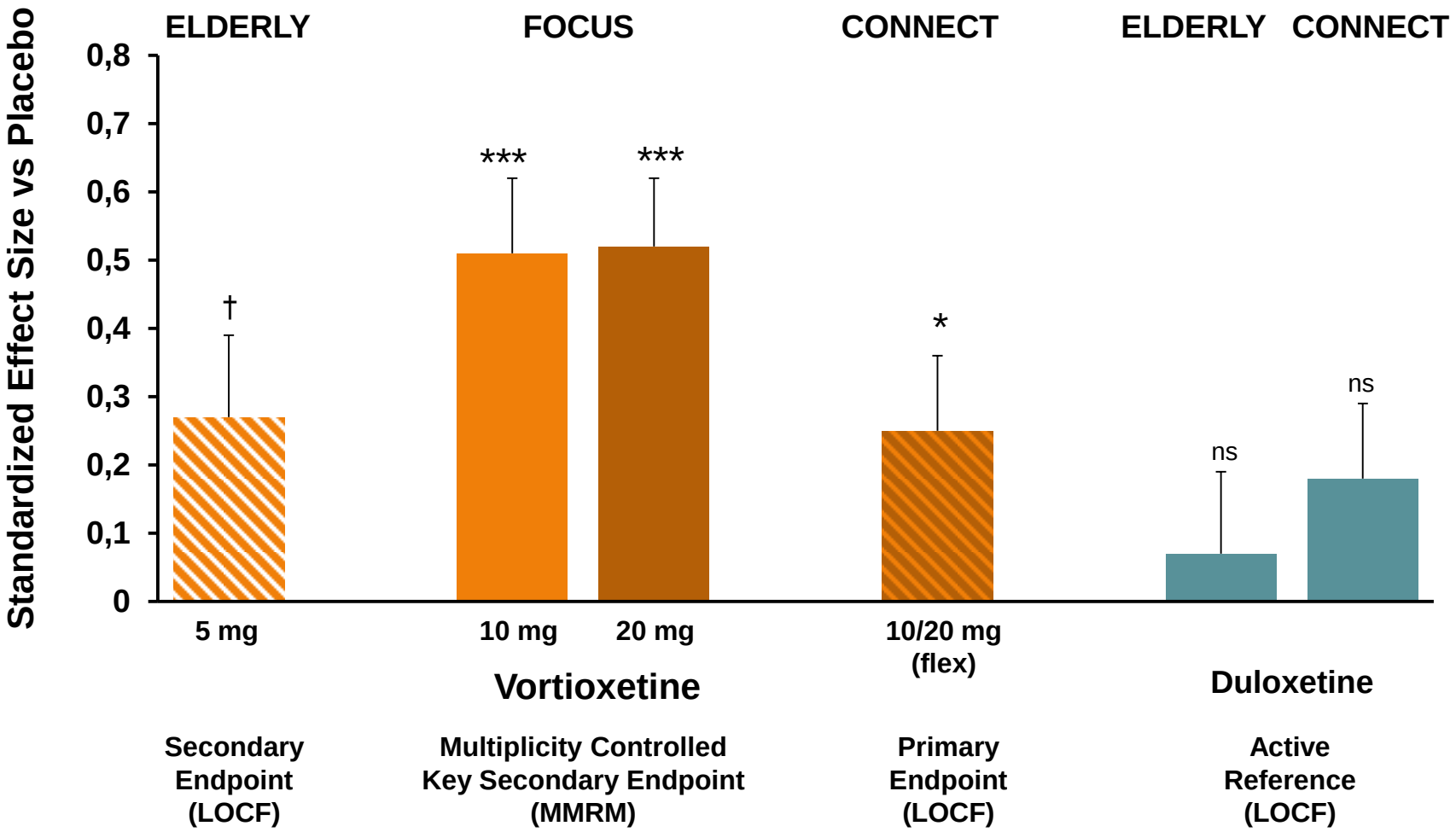
- **90/120sec administration time**

In All 3 Studies, Vortioxetine Improved Depressive Symptoms (MADRS)



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

Consistent Results Across Studies
Effect on DSST Cognitive Performance



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

Problems solved ?

Both VOR and DUL have effect on MADRS but only VOR has effect on DSST:

Pseudospecifity Adressed ?!

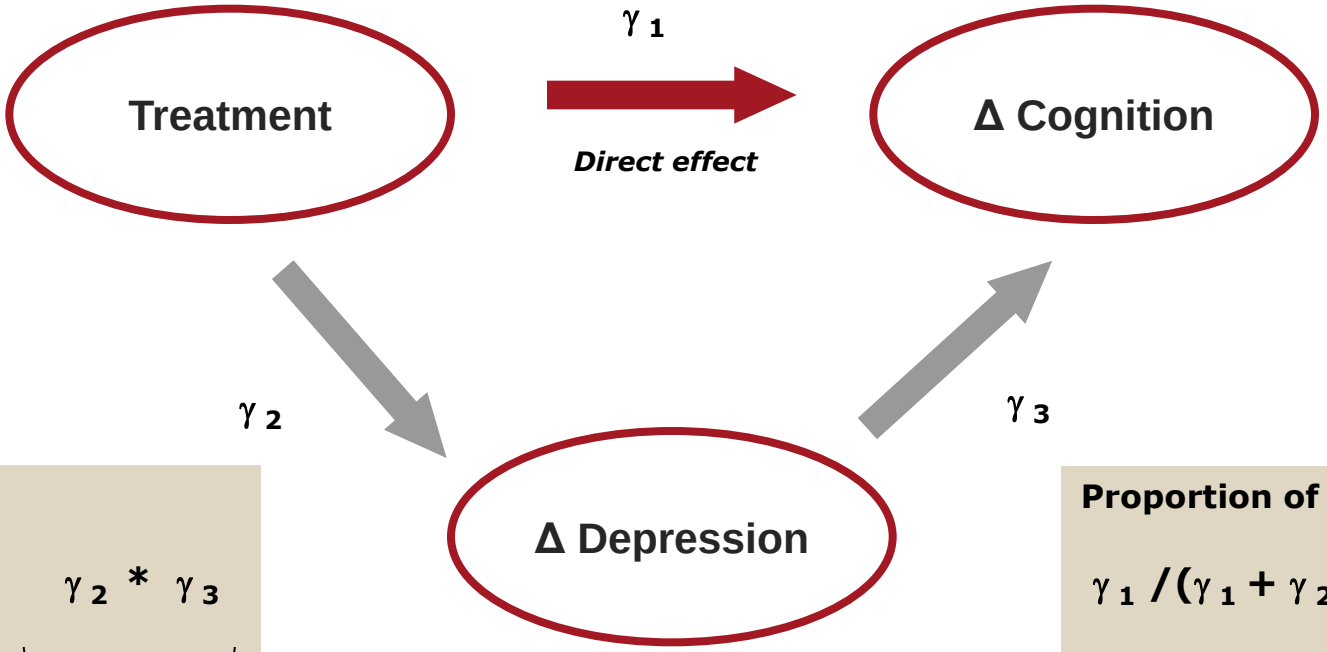
Not quite enough, support/quantify with Path Analysis :

”To evaluate the extent of the effect which is not driven by mood”

Not phrased as a confirmatory analyses

Cognition/MDD Path Analysis

Path analysis is used to separate the treatment effect (total effect) into a direct effect on cognition and an indirect effect on cognition mediated by an improvement in general depressive symptoms



Total effect

$\gamma = \gamma_1 + \gamma_2 * \gamma_3$

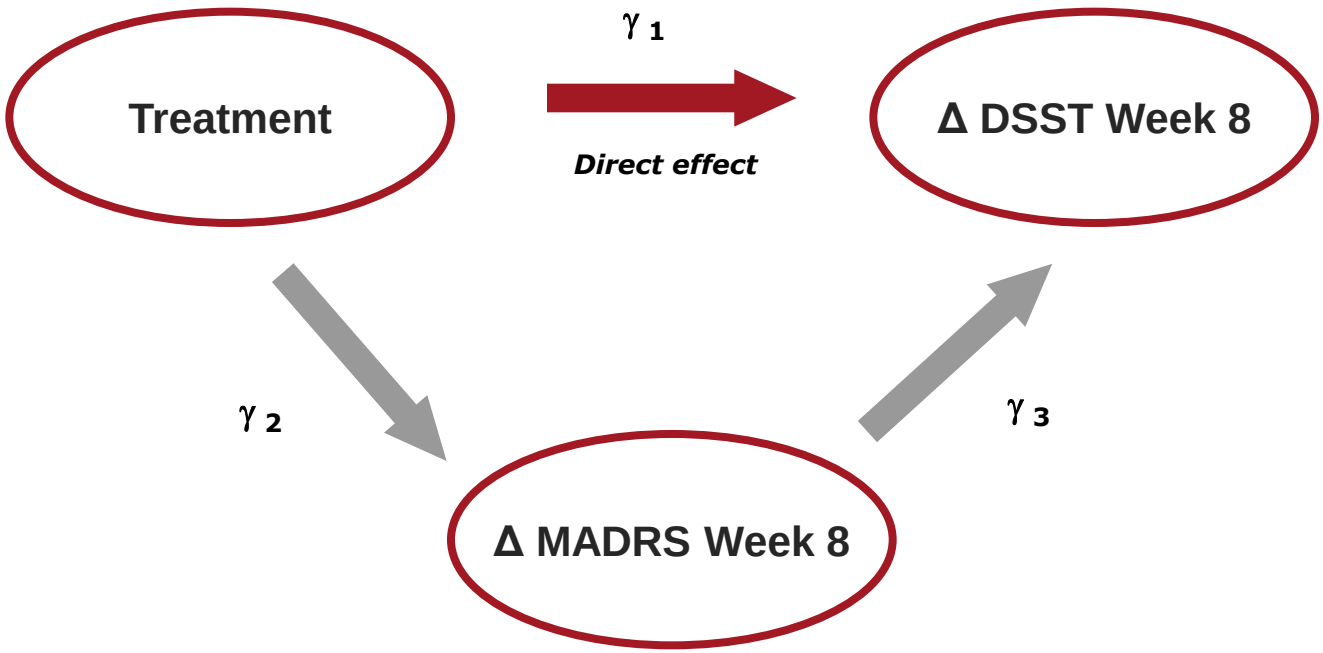
Direct effect *Indirect effect*

Proportion of direct effect

$\gamma_1 / (\gamma_1 + \gamma_2 * \gamma_3)$

Ditlevsen et al. The Mediation Proportion, A Structural Equation Approach for Estimating the Proportion of Exposure Effect on Outcome Explained by an Intermediate Variable. Epidemiology, 2005; 16.114-120

Cognition/MDD Path Analysis



Postulated model: Not taking time e.g. aspects or other mediators into account

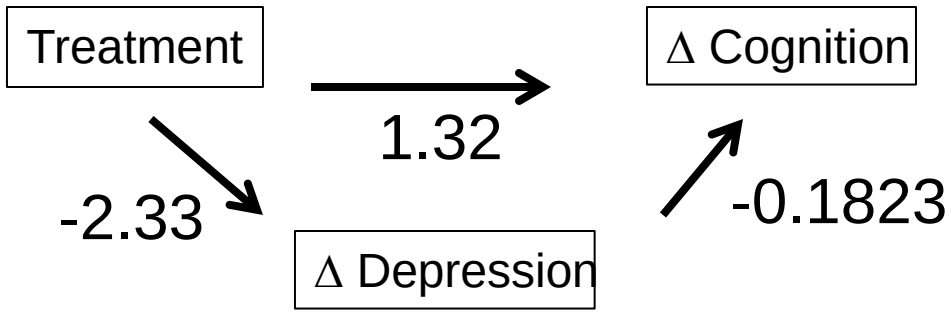
Path Analysis: ANCOVA Models

M1: $\Delta\_DSST = \gamma_1 * Treatment + \gamma_3 * (\Delta MADRS) + B\_DSST + SITE$

M2: $\Delta\_MADRS = \gamma_2 * Treatment + B\_MADRS + SITE$

M0: $\Delta\_DSST = \gamma_{TOT} * Treatment + B\_DSST + SITE$

Path Analysis Example for DSST: CONNECT (202) Vortioextine



Total effect: 1.32 + (-2.33*-0.1823) = 1.74

Direct Effect: 1.32 (76%)

Indirect effect= 2.33*0.1823 = 0.42 (24%)

Path Analysis Precision of proportions CONNECT (202)

Ditlevsen, Keiding et al. The Mediation Proportion, A Structural Equation Approach for Estimating the Proportion of Exposure Effect on Outcome Explained by an Intermediate Variable. Epidemiology, 2005; 16.114-120 , **Appendix A:**

$$\frac{\gamma_2\gamma_3}{\gamma_1+\gamma_2\gamma_3} = \text{The Mediation Proportion.}$$

The standard error of the mediation proportion can be calculated by the δ-method in the following way:

Let the covariance of (γ_i, γ_j) be denoted by $\sigma_{ij}; i, j, = 1, 2, 3$, where σ_{ii} are denoted $\sigma_i^2, i = 1, 2, 3$. The variance of the mediation proportion will approximately be

$$\frac{\gamma_2^2\gamma_3^2\sigma_1^2+\gamma_1^2\gamma_3^2\sigma_2^2+\gamma_1^2\gamma_2^2\sigma_3^2-2\gamma_1\gamma_2\gamma_3^2\sigma_{12}-2\gamma_1\gamma_2^2\gamma_3\sigma_{13}+2\gamma_1^2\gamma_2\gamma_3\sigma_{23}}{(\gamma_1+\gamma_2\gamma_3)^4}$$

Confidence Intervals for Proportions: CONNECT Study

Vortioxetine: Total effect: 1.32 + (-2.33*-0.1823) = 1.74

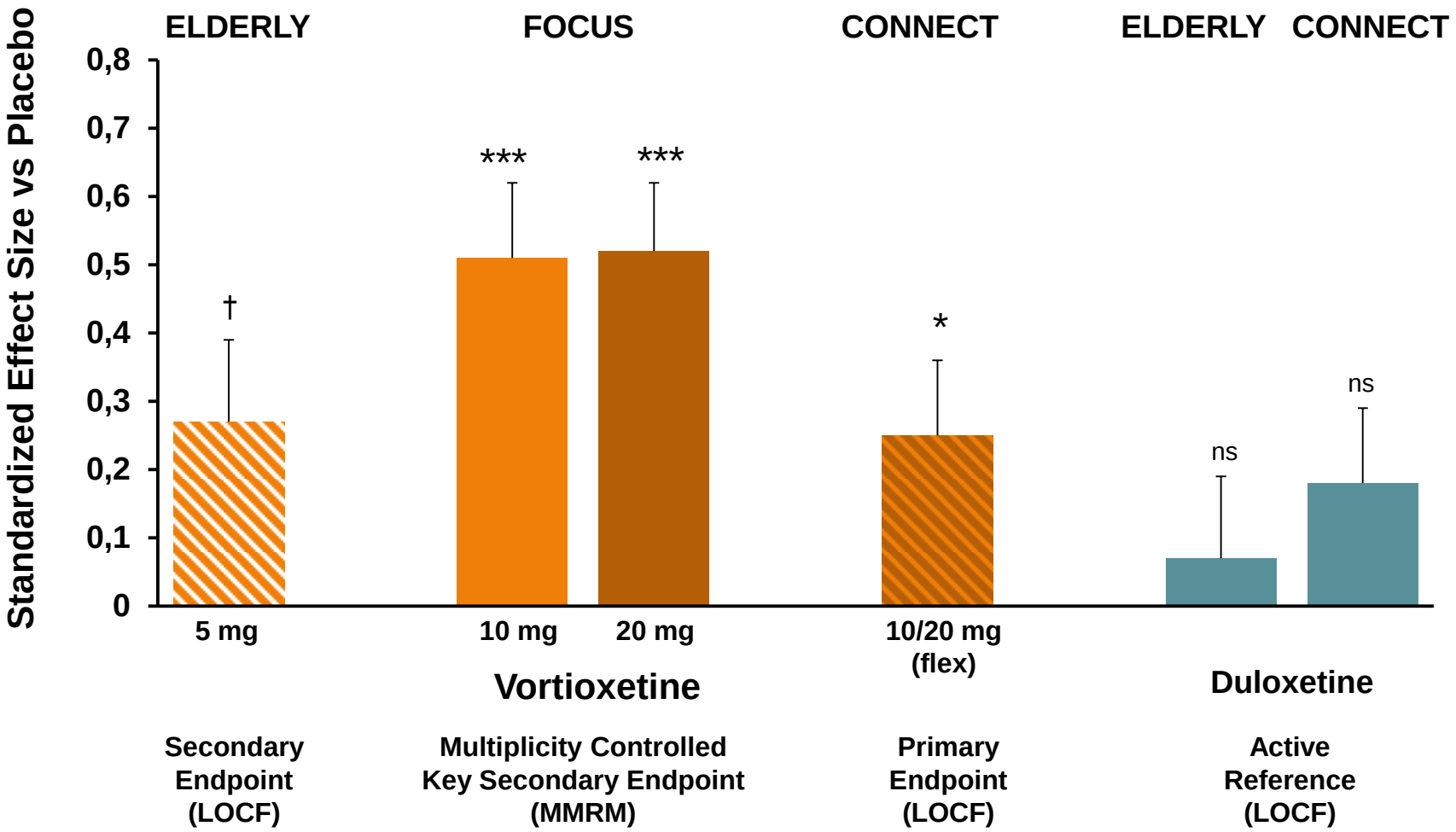
Direct Effect: 1.32, 76% [49 ; 102]

Duloxetine: Total effect: 1.21

Direct Effect: 0.58, 48% [-16 ; 113]

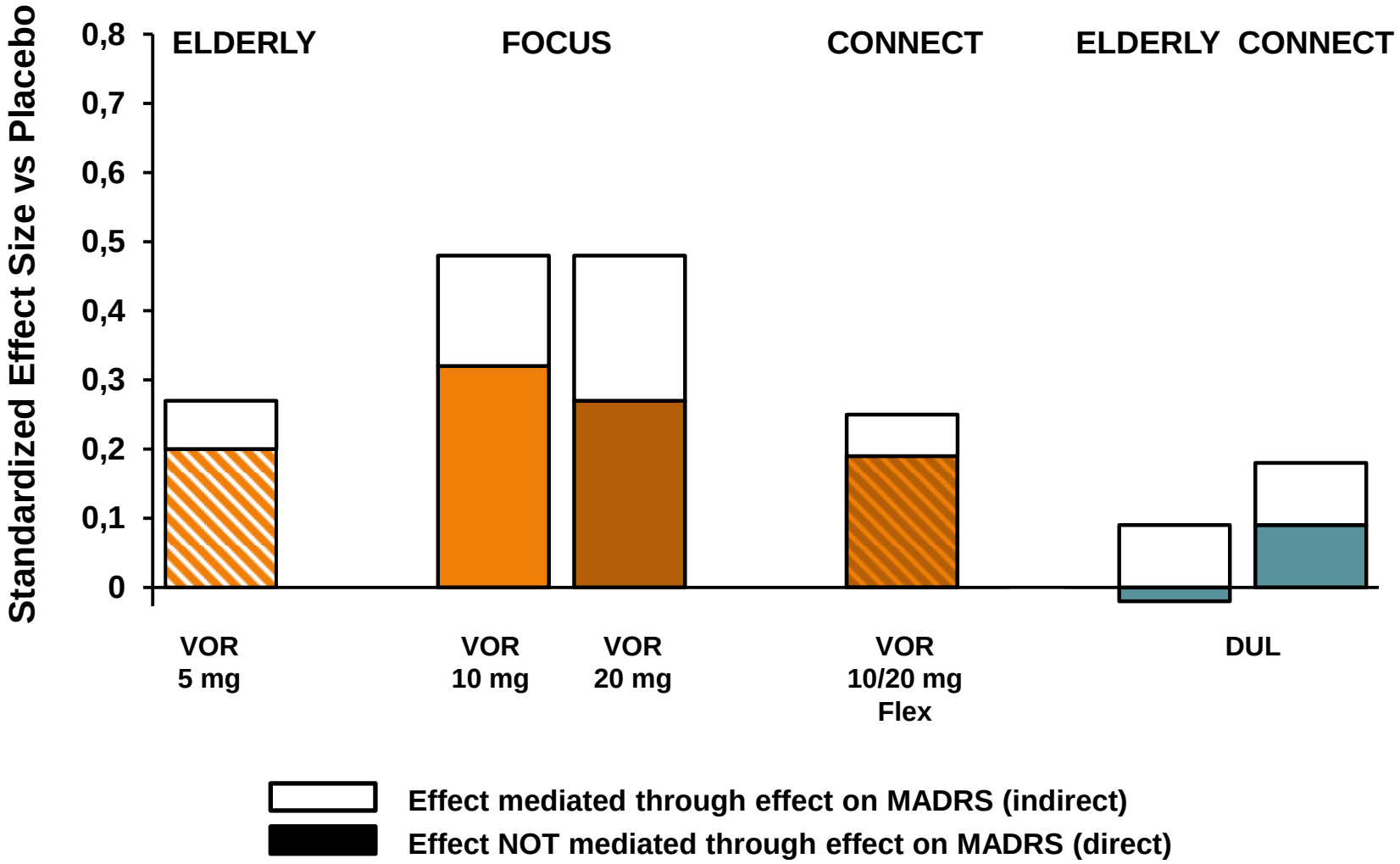
Very wide CI's even with n>200 per group

Consistent Results Across Studies
Effect on DSST Cognitive Performance



*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



Attempt 1: Part of EU Filing for Depression

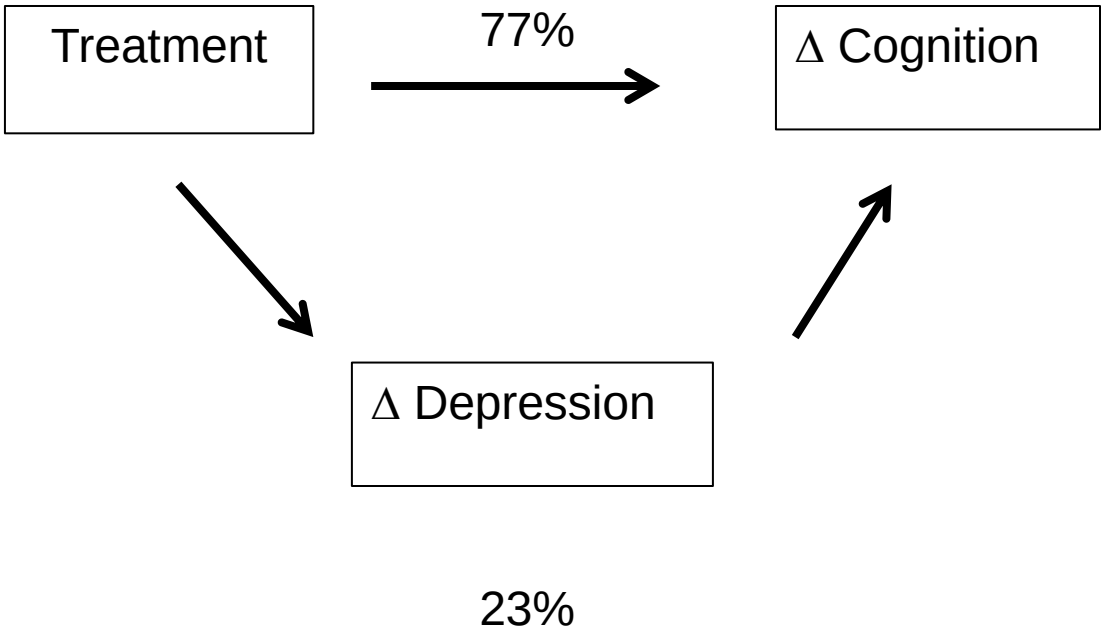
Filing for MDD, but also applying for label text on cognition

Only cognition data from one study: ELDERLY

Path Analysis included

Methodology only described briefly using references

Path Analysis Example for DSST: ELDERLY



EMA Day 150 Question: Path Analysis

Q169:

b. *“The robustness and the precision of the post-hoc path analyses to assess the direct and indirect effects of Lu AA21004 on DSST, RAVLT, and CPFQ are unclear. Details of these analyses should be provided. In particular, it should be clarified how the model for the path analyses were selected and whether the results depend on the choice of the model. Secondly, confidence intervals for the proportions of the explained effects should be provided to assess the precision of these estimates”*

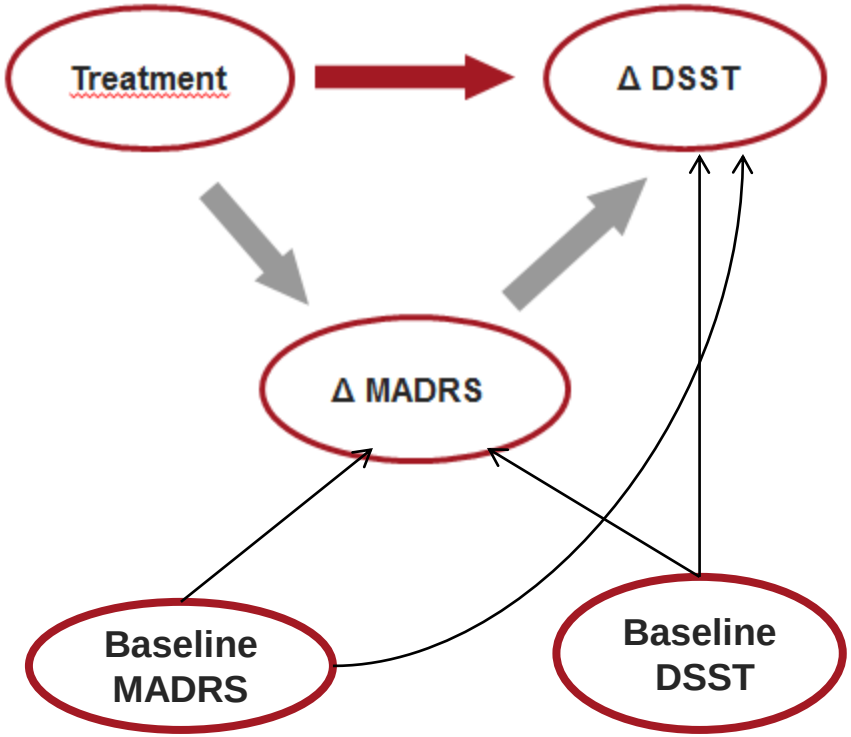
Other Comments:

Negative Estimates, boundary issues
Significance of Direct Effects
Other mediators

EMA Day 150 Question: Sponsor Answer

- Detailed methodology description with formulas etc.
- Explaining Negative Estimates: Prerequisits for mediation
- Confidence Intervals provided
- Sensitivity analyses:
  - Baselines in each model
  - Site in/out
  - MADRS item 1, clean depression measure
  - Excluding MADRS Item 6, reduce cognition part
  - MADRS total instead of cfb.
- No major impact of sensitivity!

Cognition/MDD Path Analysis
Inclusion of Baselines



Both Baselines in both ANCOVA models

EMA Day 150 Question: Response to Sponsor Reply

Concerning the path analysis, the additional information and the sensitivity analyses that were provided are somewhat reassuring on the robustness of the results of this analysis. Nevertheless, the path analysis is considered a post-hoc exploratory analysis without independent replication. Compared with duloxetine, a markedly higher direct effect of Lu AA21004 was observed only for one of the three parameters of the neuropsychological tests DSST and RAVLT, which does not consistently support the claim of a different profile of Lu AA21004 (Furthermore, the validity of the path analysis is somewhat challenged by the path analysis for DSST using total MADRS as a mediator where a negative direct effect on cognitive symptoms was found for duloxetine (Table 116), which appears not reasonable.)

EU process

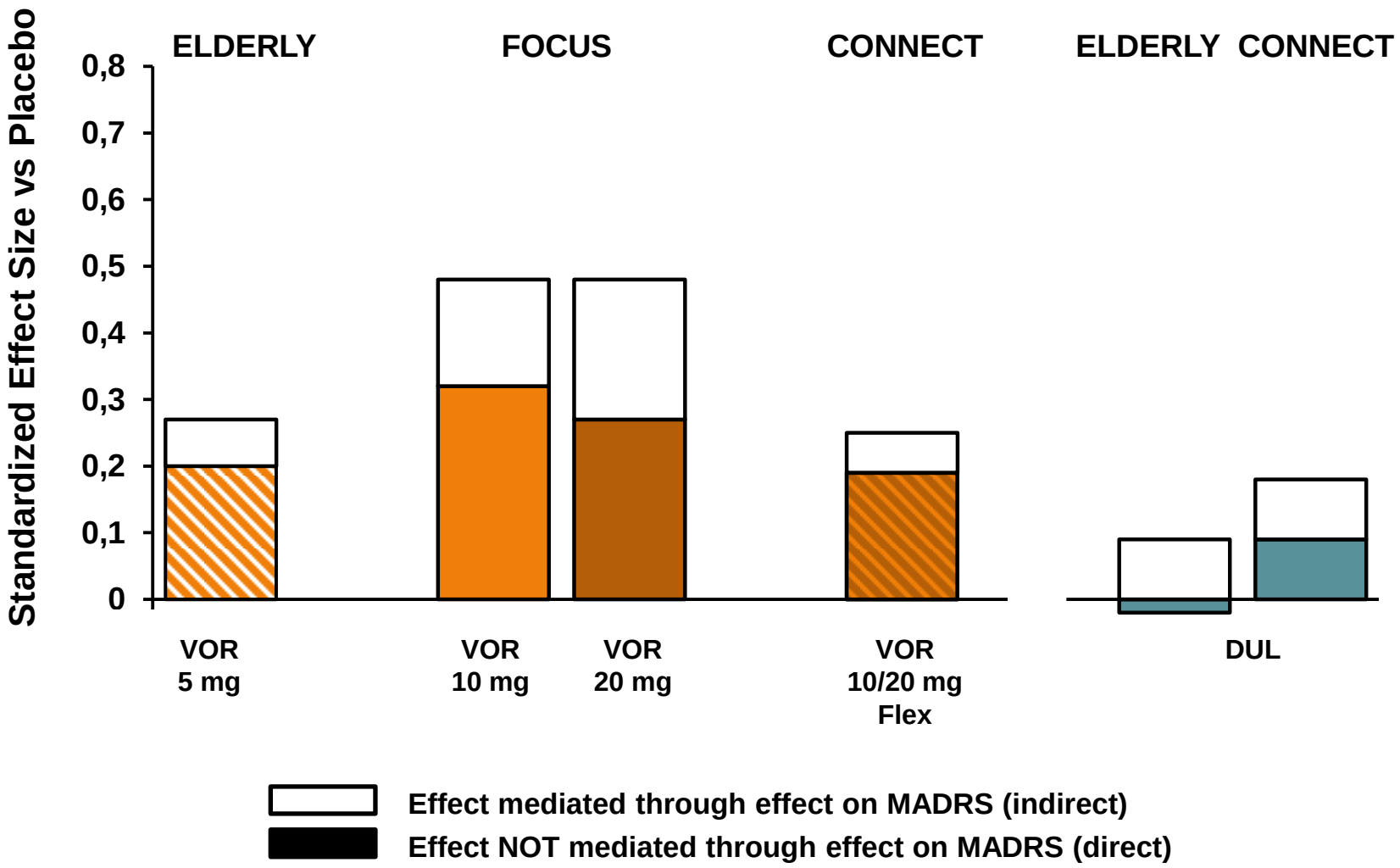
Attempt 1:

Reasons (Fair):	No primary analysis, focus on MDD No replication, only one study Only study in Elderly Only data on 5 mg
Process:	Mutual Recognition process, with two Rapporteurs Rapporteur and co-rapporteur has to agree Statisitical Review sometimes by consultants Elements of randomness to assessment

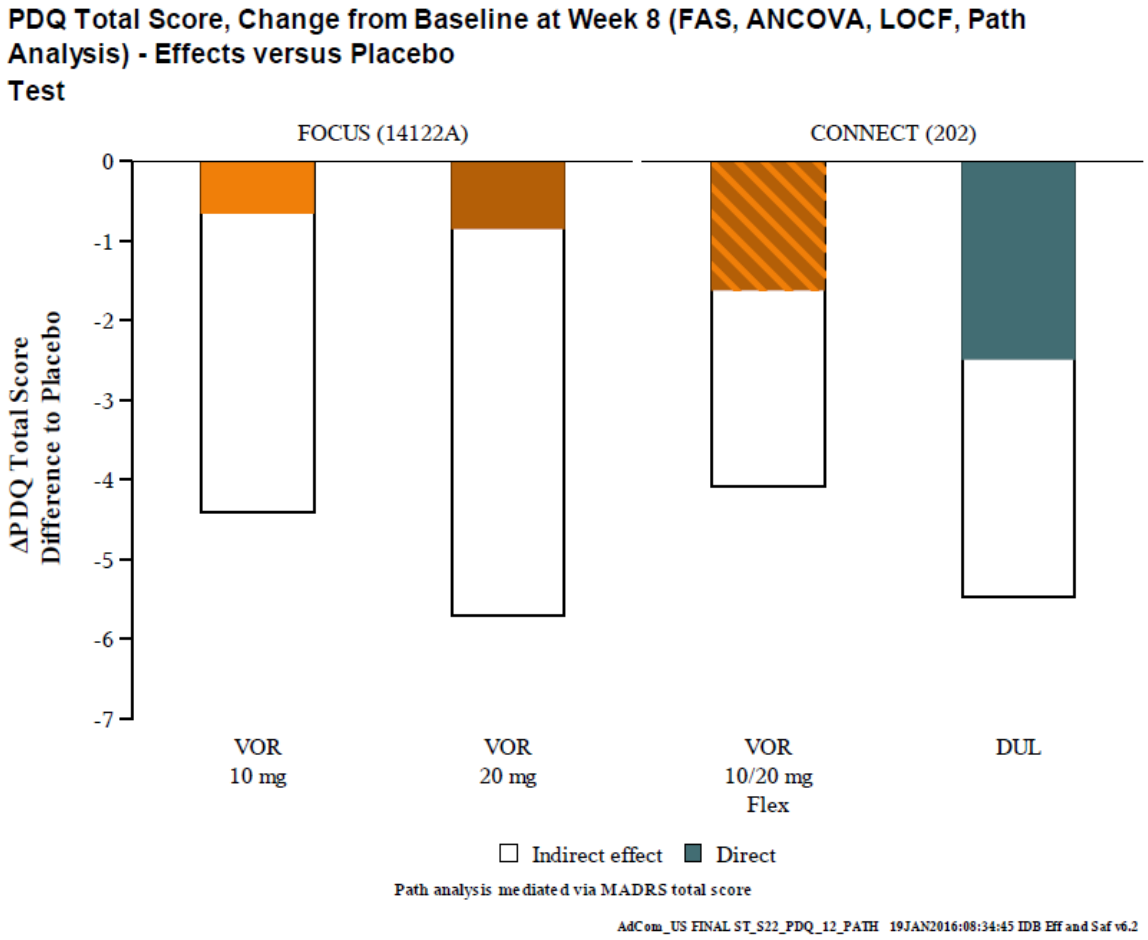
EU process: Type II Variation

Attempt 2: MDD approved
Type II Variation Application Submitted
Improved package
2 large dedicated Cognition Studies
Additional Neuropsychological tests
Subjective Assessments of Cognition
High doses

Effect of Vortioxetine on DSST Performance is Largely a Mood-independent Effect



Effect of Vortioxetine on Subjective Cognitive Scale :PDQ



Subjective Cognition too correlated with Depression

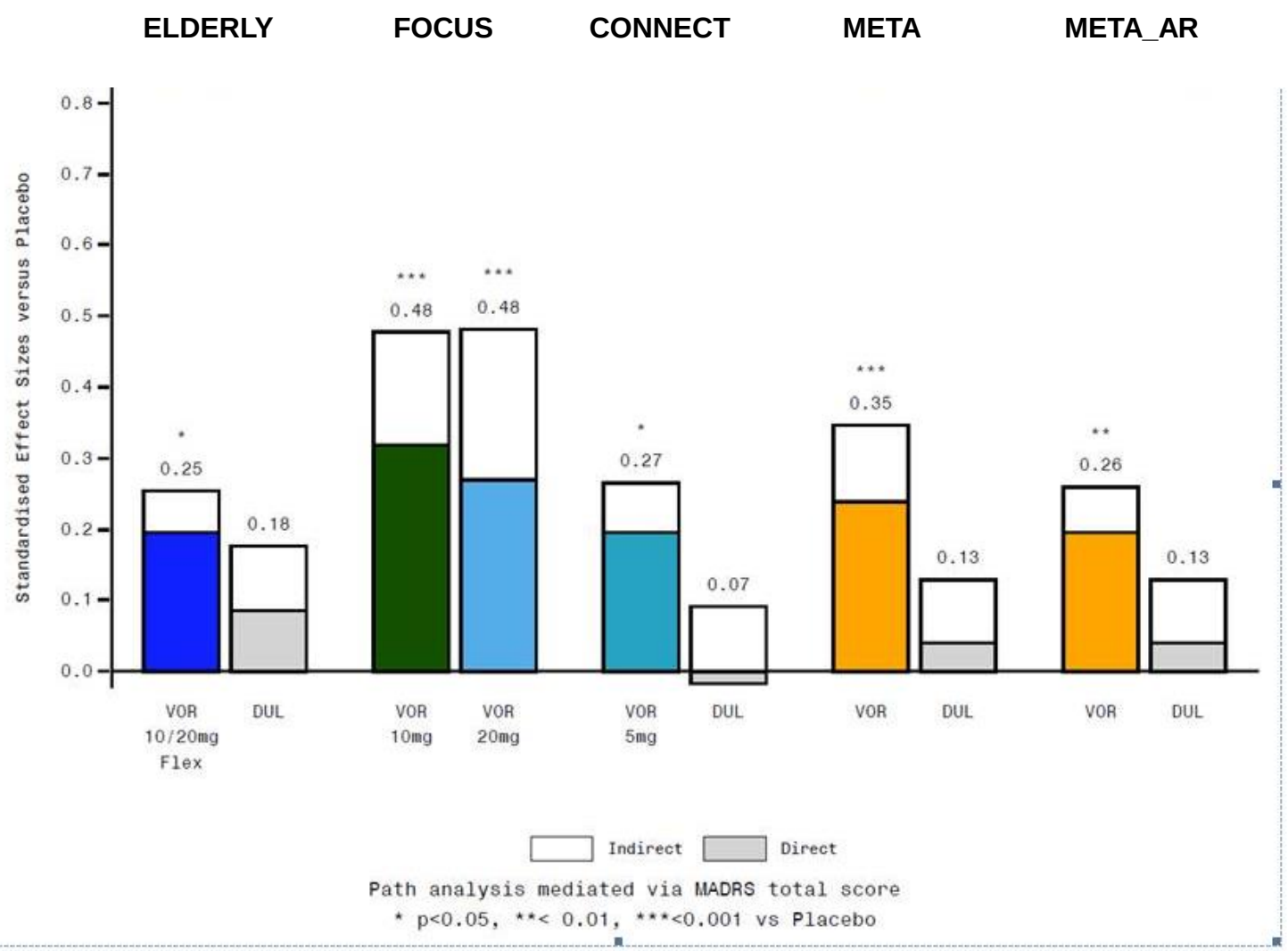
EMA Type II Variation comment

11. In section 5.1., the statement that that improvements of PDQ and CPFQ for duloxetine were mainly driven by the effect on overall depressive symptoms appears to be based on path analyses. However, the validity of the results of path analyses depends on the validity of the assumptions of the underlying models. Therefore, unless it can be convincingly shown that the results of the path analysis are robust, the results of the path analyses are considered explorative and statements based on these analyses should not be included in the SmPC.

Various Negotiations and reiterations of arguments

Suggested meta-analysis approach (From Rapporteur)

Meta-Analyses



EMA Type II Variation Label Text

Meta-analysis gave significant direct effects (also verus DUL): Well received !

Text in EPAR:

Vortioxetine had a statistically significant effect versus placebo on the Digit Symbol Substitution Test (DSST), ranging from $\Delta = 1.75$ ($p = 0.019$) to 4.26 ($p < 0.0001$) in the 2 studies in adults and $\Delta = 2.79$ ($p = 0.023$) in the study in the elderly. In the meta-analyses (ANCOVA, LOCF) of the mean change from baseline in DSST number of correct symbols in all 3 studies, vortioxetine separated from placebo ($p<0.05$) with a standardised effect size of 0.35. When adjusting for the change in MADRS the total score in the meta-analysis of the same studies showed that vortioxetine separated from placebo ($p<0.05$) with a standardised effect size of 0.24.

EU process

Attempt 2:

US process (ongoing)

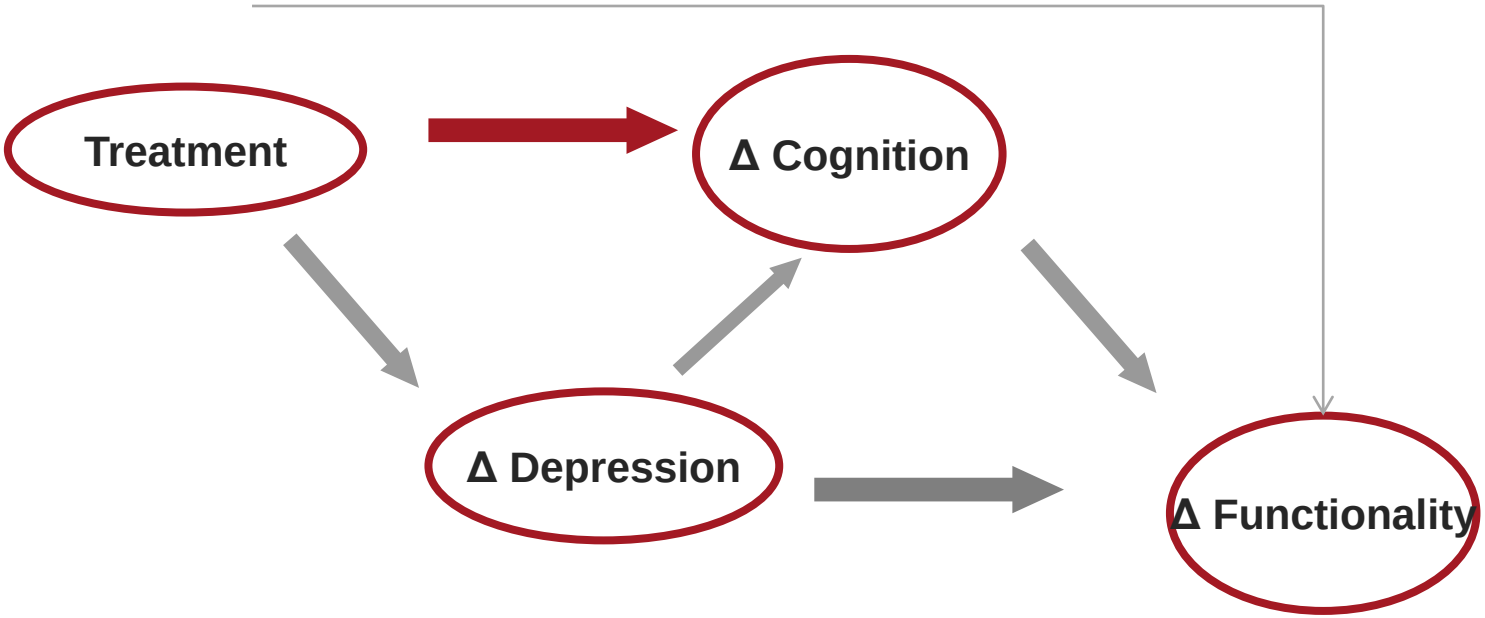
Filing Strategy similar to EU
Similar reservations to Path Analysis, (but also to meta-analyses)

After EU Cognition approval: sNDA with associated AdCom (PDAC) meeting,

AdCom: Positive vote, but negative opinion

Mediation/Path Analysis was expected to be a major issue at AdCom (preparations), but no questions were raised

US Application: Demand on Functionality



Does the effect on Cognition translate into Improved functionality ?

Experiences and conclusions

- The term ‘Path Analysis’ seems to tricker a lot reactions
  Some times easier to stick to ‘Mediation’ analyses
- Authorities willing to discuss and listen to arguments
- The Mediation Analysis played a central role in the approval together with weight of evidence from research and non-clinical data
- Still some way to go though before a mediation analyses could e.g. be primary not to mention more advanced structural equations models
- Postulated Causalities in the path diagrams are difficult to prove and method hard to communicate….

Primary Analysis….

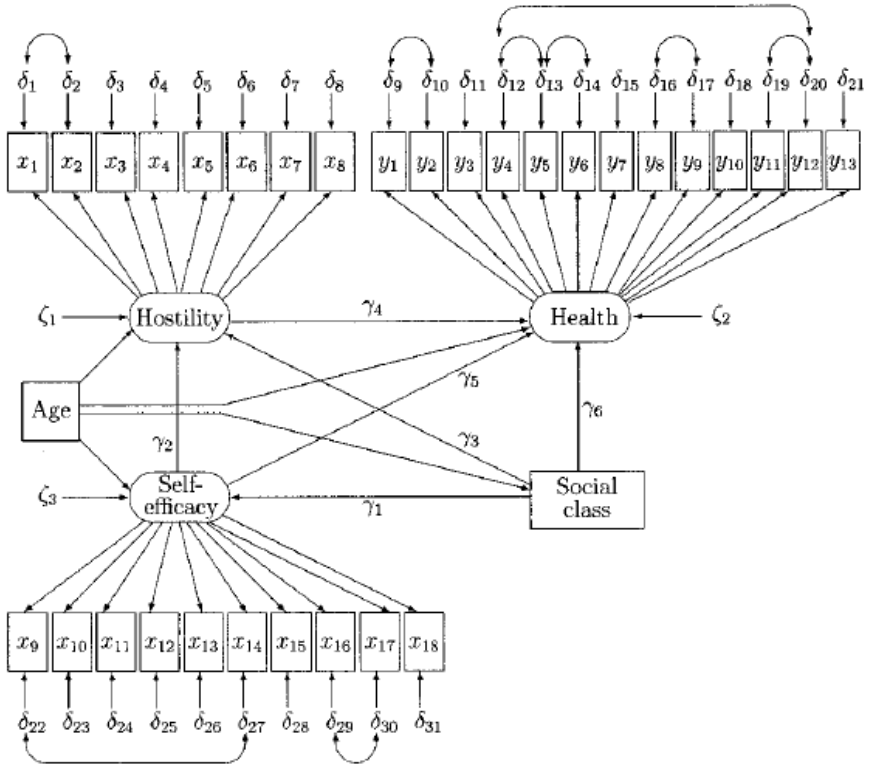


FIGURE 4. Structural equation model for relations between symptom load, social class, cynical hostility, and self-efficacy. The arrows connecting the error terms of the indicator variables are explained in Appendix B (available in the electronic version of this article).

Ditlevsen et al.