Pioneering personalized medicine in epigenetics

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Final Results

Phase 2b PORTICO study

Efficacy of vafidemstat in Borderline Personality Disorde

ECNP, Milan, Italy
September 23, 2024

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Borderline Personality Disorder (BPD) - Multifactorial etiology

BPD etiology is multifactorial, but LSD1i effects are coherent with a potential therapeutic benefit.

- A growing body of data indicates that the glutamatergic system, particularly the *N*-methyl-D-aspartate (NMDA) subtype receptor, plays a major role in neuronal plasticity and other functions and may underlie the pathophysiology of multiple psychiatric disorders[1]
- Prefrontal glutamatergic emotion regulation is disturbed in cluster B (BPD) and C personality disorders[2]
- **LSD1 inhibition rescues/restores NMDA deficiencies in different preclinical models**

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[1] Grosjean B, Tsai GE. NMDA neurotransmission as a critical mediator of borderline personality disorder. J Psychiatry Neurosci. 2007 Mar;32(2):103-15. PMID: 17353939; PMCID: PMC1810584.

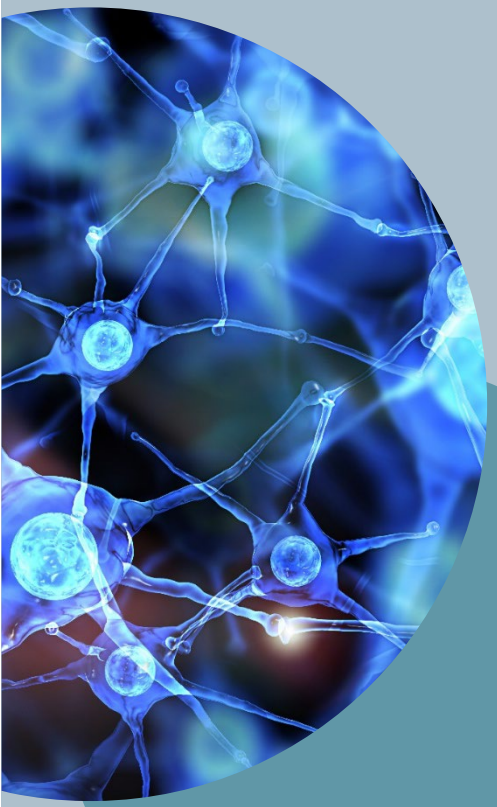
[2] Smesny S. et al., 2018 https://doi.org/10.1016/j.jad.2017.10.044)

LSD1 an epigenetic key enzyme in CNS

It plays a critical role in neuro-genesis and the regulation of cortical development

It localizes in-vivo to enhancers and promoters of confirmed CNS disease risk genes

It has been involved in neuro-developmental diseases



Vafidemstat is a highly selective LSD1 inhibitor with a new MoA, and whose pharmacology supports use in different mental diseases

Vafidemstat (aka ORY-2001) and other LSD1i induce expression of genes involved in neuronal plasticity, restoring neuronal morphology, branching and axonal navigation

Vafidemstat restores the response to stress by regulating genes involved in control of stress cues in the PFC-amygdala axis, as IEG, SRF, and others

LSD1i is able to rescue glutamatergic NMDA-R hypofunction in prefrontal cortex in different ASD and SCZ models

Vafidemstat improves sociability

Vafidemstat reduces aggression

Vafidemstat improves memory

Borderline Personality Disorder, Schizophrenia, Autism, ADHD, others

Vafidemstat is safe and well tolerated

10 clinical trials with vafidemstat in adult populations including 7 Phase 2 clinical trials in different neuro-degenerative and neuropsychiatric indications. As of April 2024, 423 subjects have been exposed to vafidemstat (87 subjects in a Phase 1 clinical trial and 336 in the Phase 2 trials) in Europe and the US. The vast majority have been exposed between 3 months to 1 year with some participants exposed up to 2 years

Brain Penetrant

An optimal
CSF: plasma
ratio of 0.9

Safe, No DDIs

Comparable SARs between
placebo and vafidemstat arms
in 6 Phase II trials:
1.0% vafidemstat vs 1.0% placebo

No side effects

No weight gain

No sedation / somnolence

No sexual dysfunction

No extrapyramidal signs

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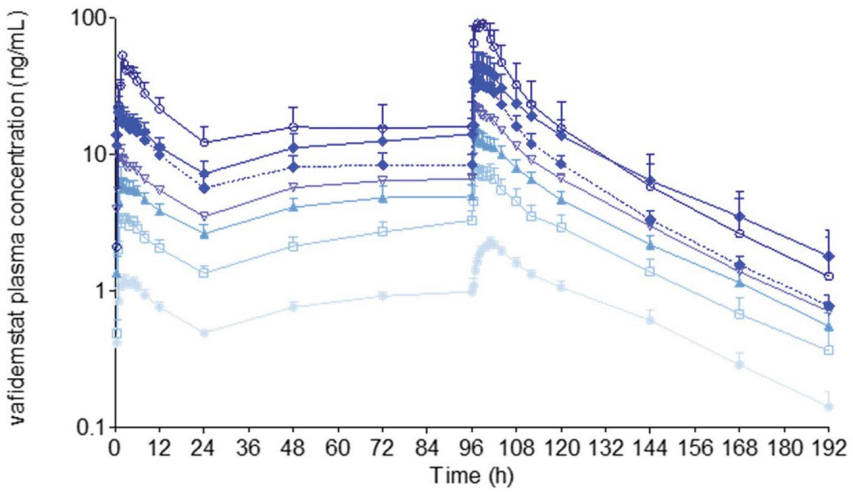
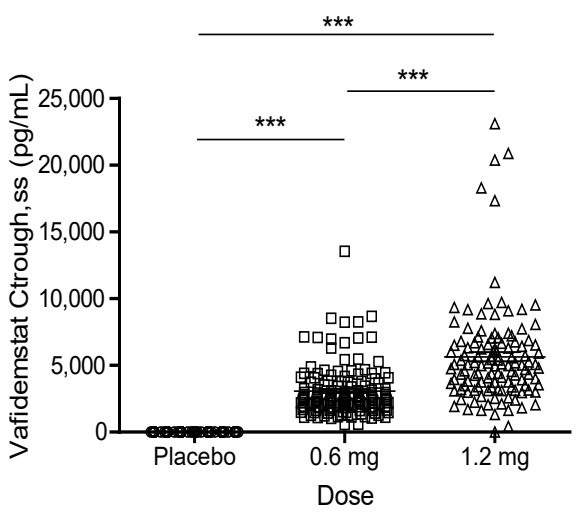
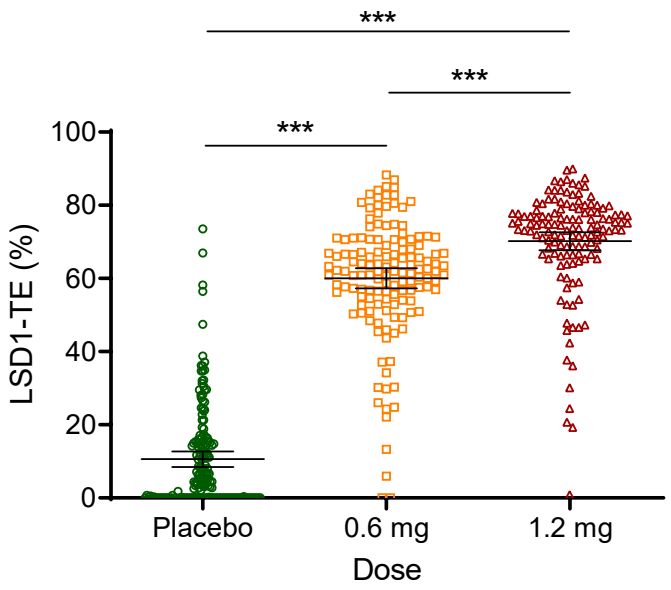
Vafidemstat: Excellent pharmacology & established RP2D from previous trials

Oral, once a day





PK data supports once daily dosing in both adult and elder subjects



Full LSD1 occupancy at 1.2 mg/day

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PORTICO: Global Phase IIb double blind, randomized, placebo-controlled, adaptive 14-week, trial to evaluate the efficacy and safety of vafidemstat in an adult BPD population

N=211
Randomized
1:1

Vafidemstat, 1.2mg
Once daily (5 ON, 2 PBO), N=106

Placebo
Once daily, N=105

14-week trial

Endpoints

Primary (Multiple, Not Co-Primary):

Agitation/Aggression (CGI-S A/A) from baseline to weeks 8-12

Improvement in Borderline Personality Disorder Checklist (BPDCL) from baseline to weeks 8-12

Secondary (efficacy):

To evaluate the change over time on the CGI-S A/A

To evaluate the change over time on the BPDCL

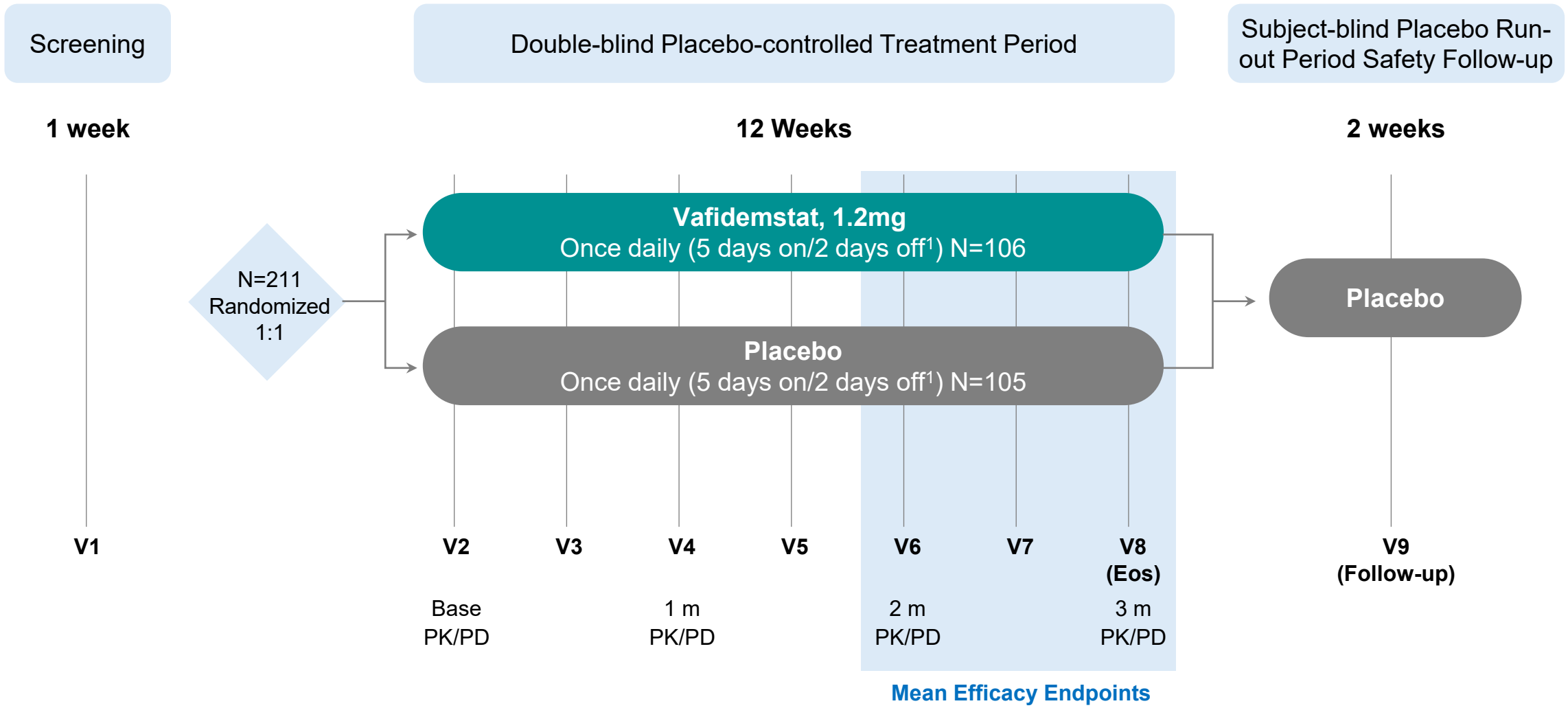
To evaluate the difference on the following measures, from baseline to weeks 8-12, as well as change over time, between the active treatment arm and the placebo arm:

- Borderline Evaluation of Severity over Time (BEST)
- State-Trait Anger Expression Inventory 2 (STAXI-2)
- State-Trait Anxiety Inventory (STAI)
- Beck Depression Inventory – II (BDI-II)

Considering there is no 'gold standard' measure of pharmacological improvement in BPD and because PORTICO was a Phase IIb trial, various measures of agitation/aggression and overall disease were included to help inform Phase III

In collaboration with the FDA, the PORTICO Statistical Analysis Plan was modified to incorporate and adopt all Agency recommendations in the final version of the study

PORTICO: Study design



1. During the 2 days off, patients took placebo capsules

DEMOGRAPHICS

PORTICO enrolled a representative real-world BPD population allowing common comorbidities and concomitant medications that are typically exclusionary in other BPD trials, as well as allowed subjects to receive psychotherapy during the trial

	Vafidemstat (n = 106)	Placebo (n = 104)
Psychotherapy at Baseline: No (n) / Yes (n)	84/22	82/22
Age (years, Mean (SD))	32.4 (10.68)	31.8 (10.89)
Female n (%)	78 (73.6)	79 (76.0%)
Male n (%)	28 (26.4%)	25 (24.0%)
Race, n (%) White	87 (82.1%)	86 (82.7%)
Black/African American	9 (8.5%)	7 (6.7%)
Other	10 (9.4%)	11 (10.6%)
Height Mean (SD)	167.4 (9.09)	168.4 (10.36)
Weight Mean (SD)	73.0 (15.91)	75.8 (16.05)
BMI Mean (SD)	26.0 (4.89)	26.6 (4.48)

(Data based on safety population)

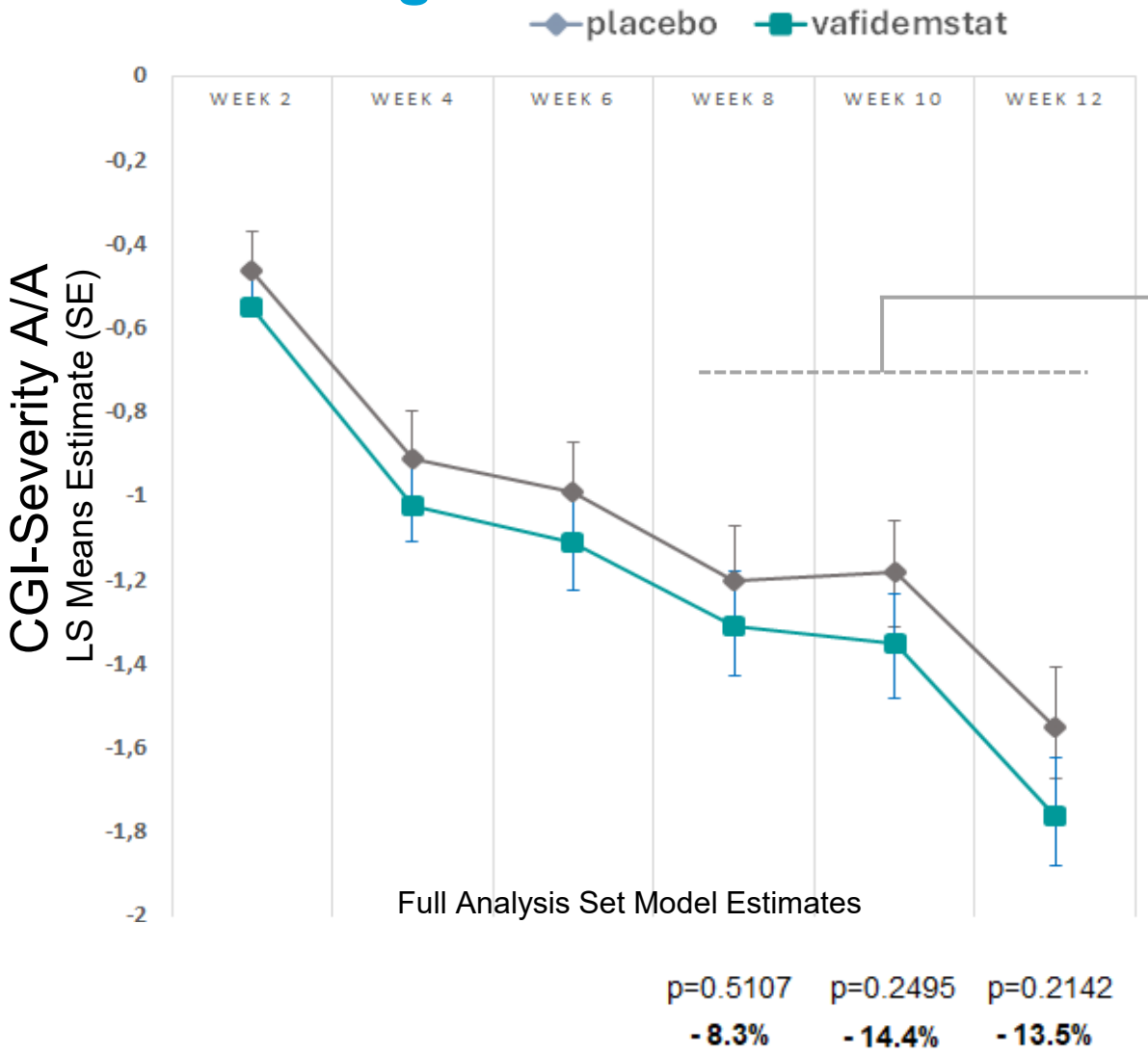
BASELINE CHARACTERISTICS

There were no statistically significant group differences across endpoints at baseline

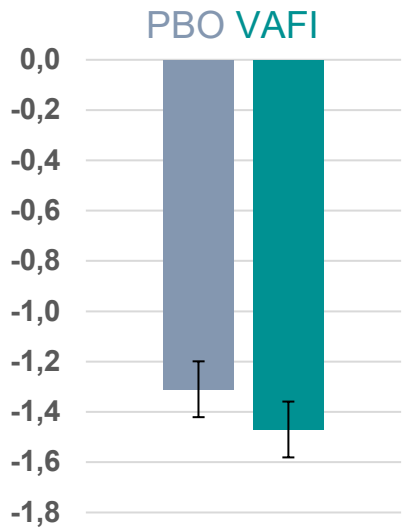
	Vafidemstat (n = 106)	Placebo (n = 104)
AAPI-CR Total	74.1 (22.51)	78.0 (22.30)
BPDCL Total	141.7 (36.96)	144.6 (34.08)
CGI-Severity A/A	4.8 (0.82)	4.7 (0.82)
BEST Total	39.9 (10.06)	39.6 (10.02)
STAXI-2 Trait Anger	27.5 (6.73)	27.0 (6.47)
STAXI-2 State Anger	23.5 (8.98)	23.3 (9.36)
Beck Depression Inventory-II	24.7 (14.58)	26.3 (13.67)
STAI State Anxiety	50.6 (11.69)	50.4 (11.32)
STAI Trait Anxiety	59.0 (11.23)	59.3 (10.51)

(Data based on safety population)

Improvement in agitation/aggression measured by CGI-S A/A. Yet, no statistical significance



CGI-Severity A/A
Across weeks 8-12
LS Means Estimate (SE)



p=0.2266
-12.2%

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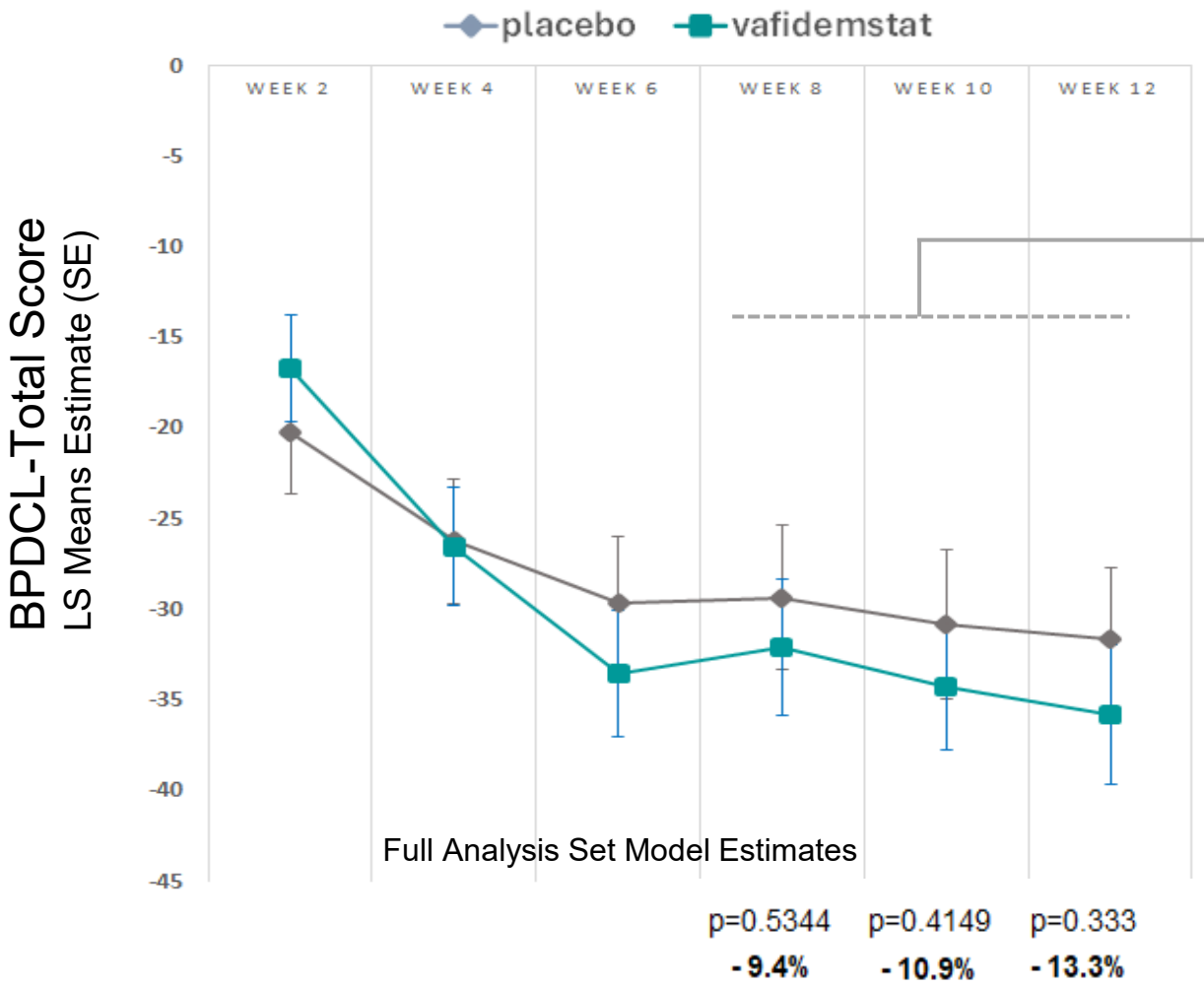
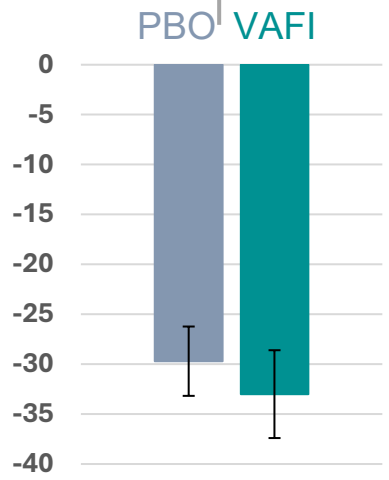
Overall disease improvement measured by the BPDCL scale. Yet, no statistical significance



BPDCL-Total Score
Across weeks 8-12
LS Means Estimate (SE)



p=0.3839
-11.2%

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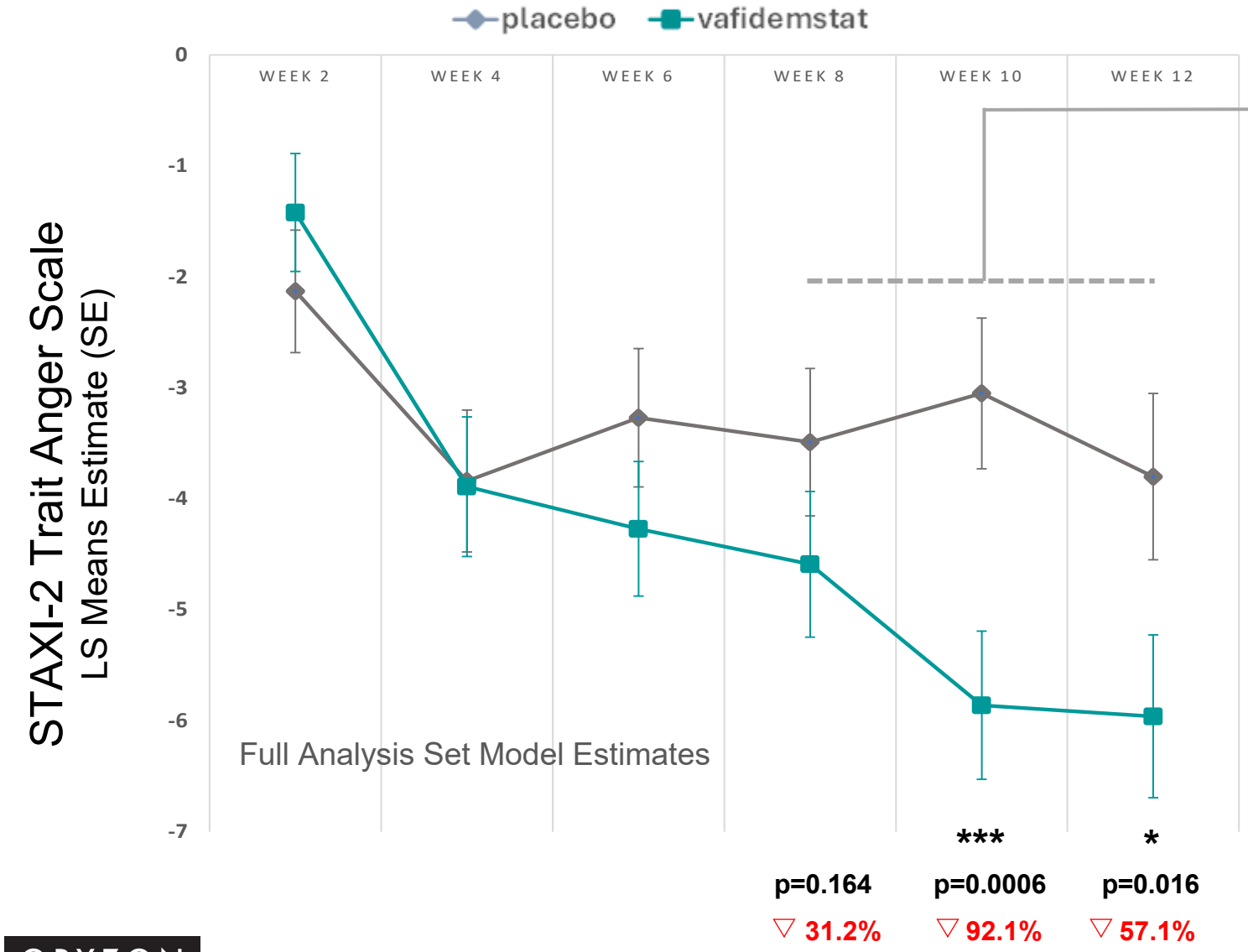
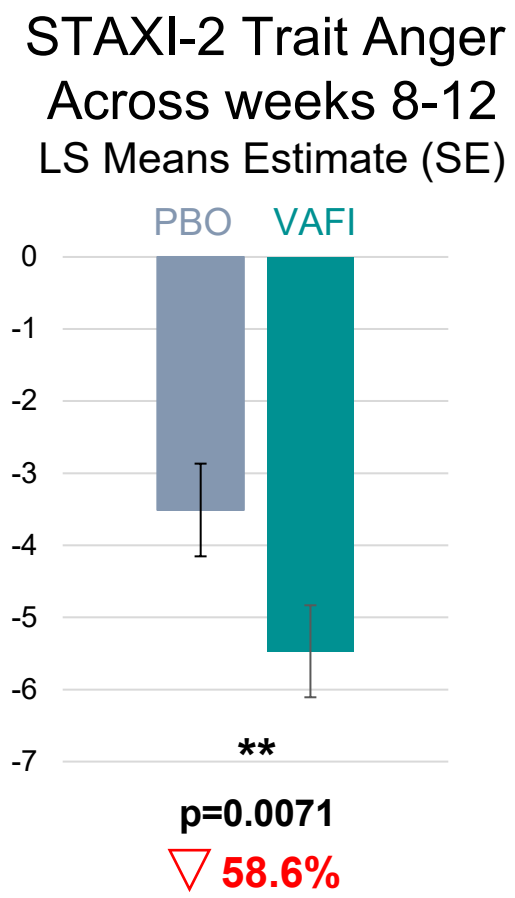
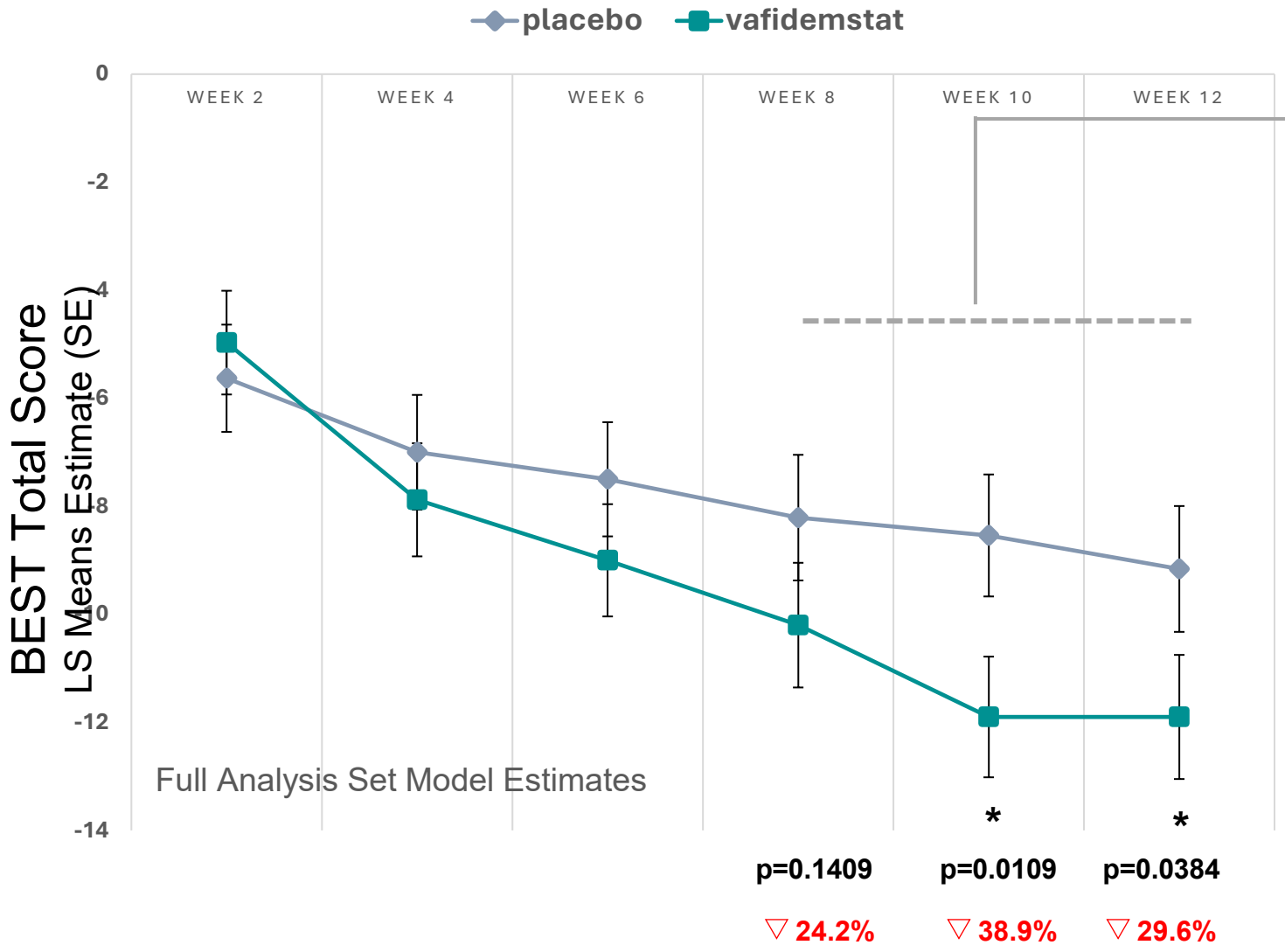
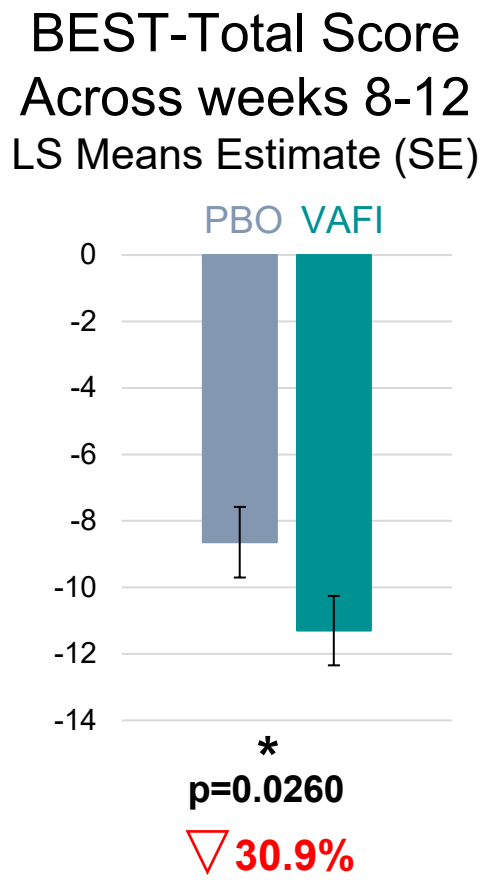
Nominal statistical significance in secondary endpoint: improvement in STAXI-2 Trait Anger across weeks 8-12





Nominal statistical significance in secondary endpoint: improvement in BEST across weeks 8-12





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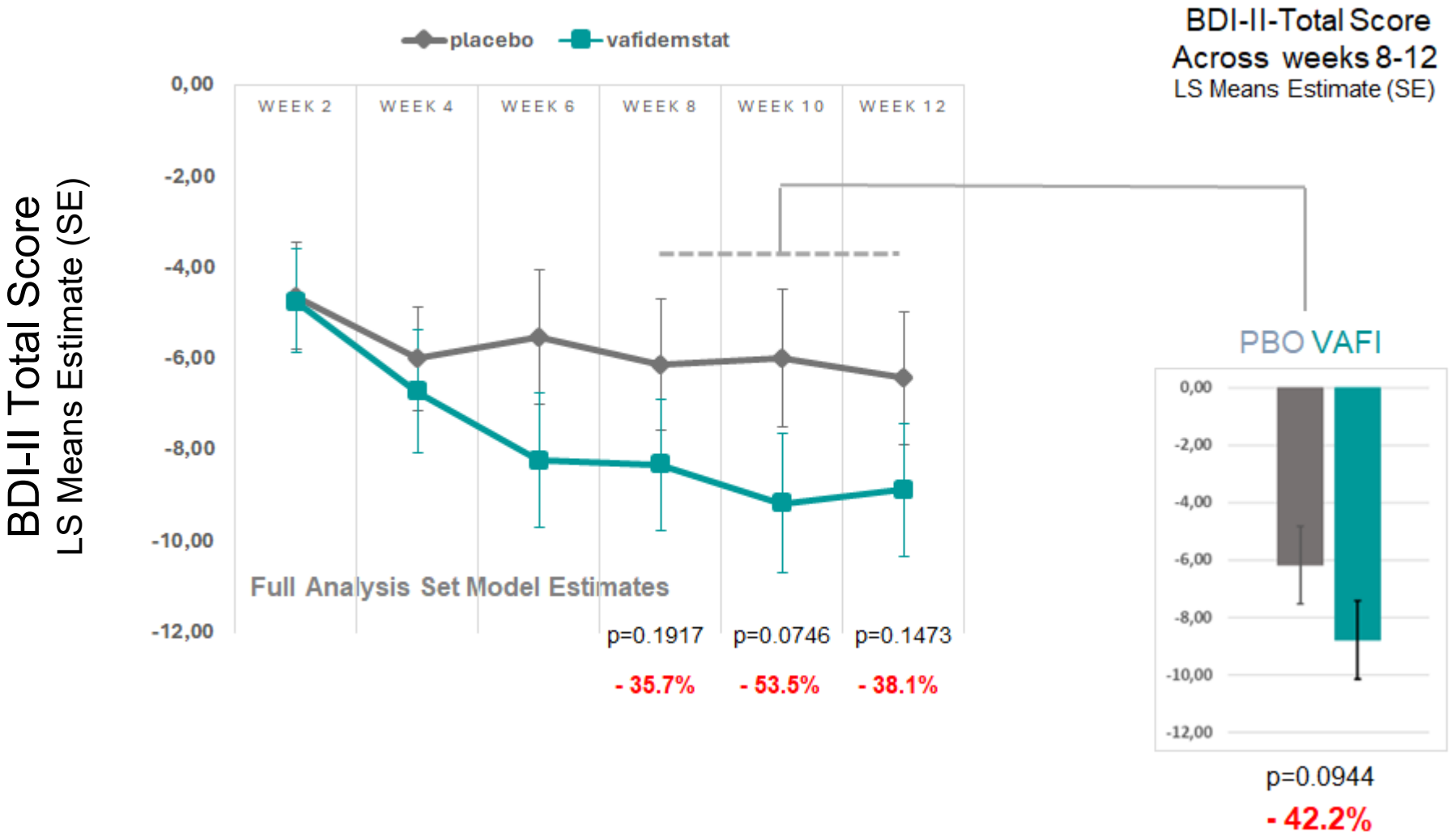
A trend in secondary endpoint: improvement in depression by BDI-II Total Score by weeks 8-12



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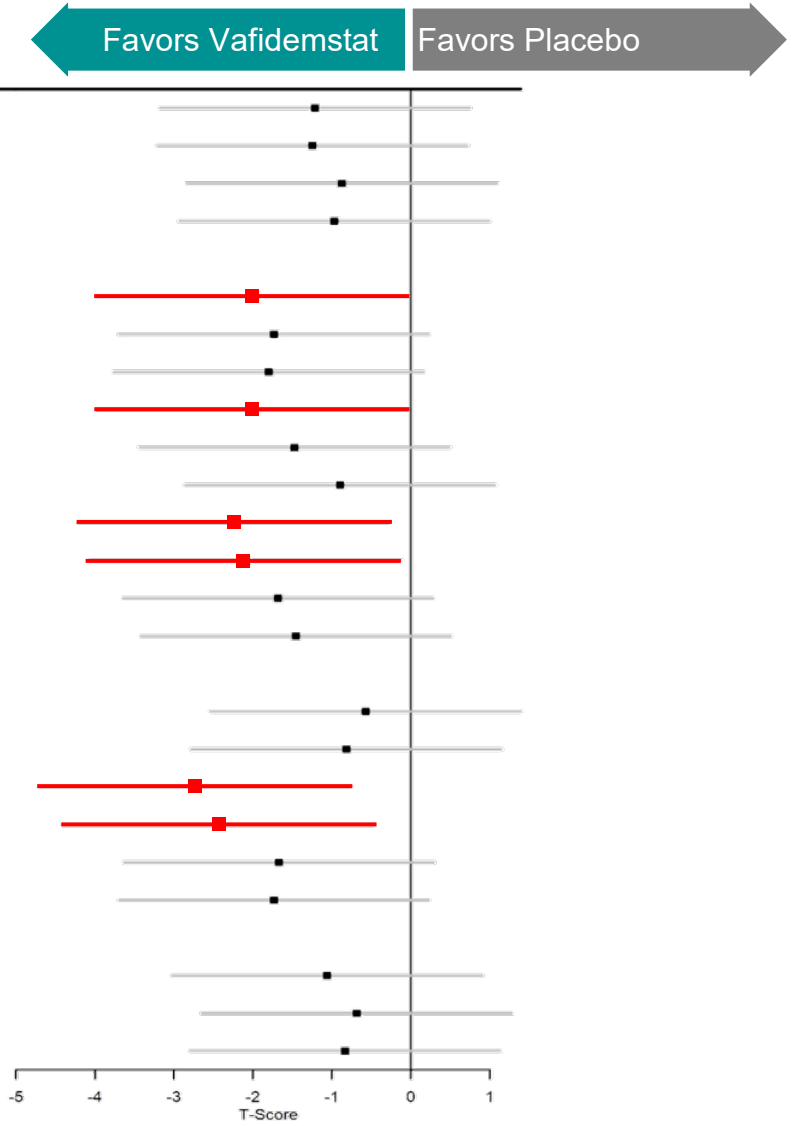
PORTICO: all primary and secondary efficacy endpoints consistently favored vafidemstat

Full Analysis Set

Parameter	Analysis Type	Cohen's D	P-value	Difference	CI	T-Score
CGI - Severity	Average Mean	-0.1672	0.2266	-0.16	(-0.42,0.10)	-1.21
	Week 12 Mean	-0.1718	0.2142	-0.21	(-0.54,0.12)	-1.25
BPDCL - Total Score	Average Mean	-0.1202	0.3839	-3.44	(-11.22,4.34)	-0.87
	Week 12 Mean	-0.1336	0.3333	-4.21	(-12.78,4.36)	-0.97
BEST						
Thoughts and Feelings Score	Average Mean	-0.2733	0.0488	-1.50	(-2.98,-0.01)	-1.98
	Week 12 Mean	-0.2386	0.0851	-1.44	(-3.09,0.20)	-1.73
Behaviors Negative Score	Average Mean	-0.2479	0.0736	-0.55	(-1.16,0.05)	-1.80
	Week 12 Mean	-0.2768	0.0462	-0.66	(-1.31,-0.01)	-2.01
Behaviors Positive Score*	Average Mean	-0.2030	0.1424	-0.50	(0.17,-1.16)	-1.47
	Week 12 Mean	-0.1234	0.3715	-0.37	(0.45,-1.19)	-0.90
Total Score	Average Mean	-0.3093	0.0260	-2.67	(-5.02,-0.32)	-2.25
	Week 12 Mean	-0.2875	0.0384	-2.71	(-5.27,-0.15)	-2.09
BDI - Total Score	Average Mean	-0.2316	0.0944	-2.61	(-5.68,0.45)	-1.68
	Week 12 Mean	-0.2005	0.1473	-2.45	(-5.78,0.87)	-1.46
STAXI						
State Anger Scale Raw Score	Average Mean	-0.0787	0.5684	-0.57	(-2.53,1.39)	-0.57
	Week 12 Mean	-0.1124	0.4157	-0.84	(-2.88,1.20)	-0.82
Trait Anger Scale Raw Score	Average Mean	-0.3755	0.0071	-2.02	(-3.49,-0.56)	-2.73
	Week 12 Mean	-0.3359	0.0158	-2.17	(-3.92,-0.41)	-2.44
Anger Expression Index Raw Score	Average Mean	-0.2300	0.0966	-2.62	(-5.72,0.48)	-1.67
	Week 12 Mean	-0.2385	0.0851	-3.05	(-6.53,0.43)	-1.73
STAI						
State Anxiety Raw Score	Average Mean	-0.1461	0.2901	-1.54	(-4.41,1.33)	-1.06
	Week 12 Mean	-0.0943	0.4942	-1.20	(-4.64,2.25)	-0.69
Trait Anxiety Raw Score**	Week 12 Mean	-0.1148	0.4057	-1.05	(-3.54,1.44)	-0.83



* P-values are uncorrected for multiplicity

PORTICO: Cumulative Global Statistical Test (GST) using the pre-specified hierarchy is consistent with a global treatment effect favoring vafidemstat

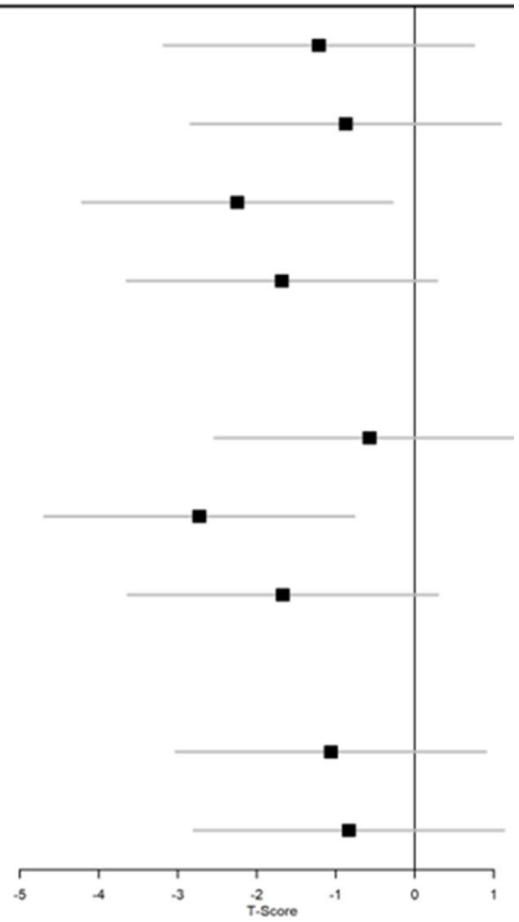
BPD is a multisymptomatic disease with psychiatric, behavioral, and functional outcomes.

GST is designed to address whether a treatment is efficacious across different aspects of a condition. GST efficiently summarizes a treatment's merit when the medical question is complex.

When a treatment improves all target outcomes, the GST often has a higher power than tests of single outcomes or other multiple-test procedures. As such, GST incorporates the impact of consistent directional change across multiple key target outcomes, even when individual outcomes may not show statistically significant improvement on their own.

Full Analysis Set

Parameter	Cohen's D	GST P-value	Difference	CI	T-Score	P-value
CGI - Severity	-0.1672		-0.16	(-0.42,0.10)	-1.21	0.2266
BPDCL - Total Score	-0.1202	0.2134	-3.44	(-11.22,4.34)	-0.87	0.3839
BEST - Total Score	-0.3093	0.0811	-2.67	(-5.02,-0.32)	-2.25	0.0260
BDI - Total Score	-0.2316	0.0661	-2.61	(-5.68,0.45)	-1.68	0.0944
STAXI						
State Anger Scale Raw Score	-0.0787	0.0853	-0.57	(-2.53,1.39)	-0.57	0.5684
Trait Anger Scale Raw Score	-0.3755	0.0397	-2.02	(-3.49,-0.56)	-2.73	0.0071
Anger Expression Index Raw Score	-0.2300	0.0362	-2.62	(-5.72,0.48)	-1.67	0.0966
STAI						
State Anxiety Raw Score	-0.1461	0.0403	-1.54	(-4.41,1.33)	-1.06	0.2901
Trait Anxiety Raw Score**	-0.1148	0.0503	-1.05	(-3.54,1.44)	-0.83	0.4057



GST p-value shows a statistical significance particularly when considering global improvement in the severity of the disease and in agitation/aggression (p= 0.0362)

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PORTICO safety: vafidemstat was safe and well tolerated

- Treatment Emergent Adverse Events (TEAEs) were slightly lower for those receiving vafidemstat
- Treatment-Related TEAEs were similar between groups
- TEAEs leading to Study Discontinuation, Study Drug Withdrawal or Study Drug Interruption were low overall: 5 on vafidemstat and 3 on placebo
- TEAEs by Severity were consistent between groups, with slightly more Mild and Moderate TEAEs for those receiving placebo
- Severe TEAEs were low, 5 on vafidemstat and 4 on placebo
- The majority of TEAEs Recovered/Resolved by the end of the trial
- There were no deaths in PORTICO, and the only TEAE with sequelae was on placebo

	Placebo (N=104) n (%), e	Vafidemstat (N=106) n (%), e
Treatment Emergent AEs (TEAEs)	68 (65.4%), 214	61 (57.5%), 192
Treatment-Related TEAEs	33 (31.7%), 68	36 (34.0%), 91
TEAEs Leading to Study Discontinuation	1 (1.0%), 1	5 (4.7%), 8
TEAEs Leading to Study Drug Withdrawal	1 (1.0%), 1	5 (4.7%), 8
TEAEs Leading to Study Drug Interruption	3 (2.9%), 4	5 (4.7%), 7
TEAEs by Severity	68 (65.4%), 214	61 (57.5%), 192
Mild	60 (57.7%), 157	51 (48.1%), 128
Moderate	35 (33.7%), 52	29 (27.4%), 57
Severe	4 (3.8%), 5	5 (4.7%), 7
TEAEs by Outcome	68 (65.4%), 214	61 (57.5%), 192
Recovered/Resolved	66 (63.5%), 174	56 (52.8%), 165
Not Recovered/Not Resolved	17 (16.3%), 29	14 (13.2%), 18
Recovering/Resolving	9 (8.7%), 10	8 (7.5%), 9
Recovered/Resolved With Sequelae	1 (1.0%), 1	0 (0.0%), 0
Death	0 (0.0%), 0	0 (0.0%), 0
Unknown	0 (0.0%), 0	0 (0.0%), 0

(Data based on safety population)

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PORTICO safety: vafidemstat-treated patients showed a reduced inclination towards self-harm

Treatment-Emergent Adverse Events by Preferred Term Occurring in > 5% of Subjects

	Placebo (N=104) N (%), e	Vafidemstat (N=106) N (%), e
TEAEs by Preferred Term	68 (65.4%), 214	61 (57.5%), 192
Headache	17 (16.3%), 18	13 (12.3%), 16
Nasopharyngitis	18 (17.3%), 22	9 (8.5%), 11
Tension Headache	6 (5.8%), 17	5 (4.7%), 11
Platelet Count Decreased	1 (1.0%), 1	8 (7.5%), 8*
Nausea	2 (1.9%), 2	6 (5.7%), 6
Intentional Self-Injury	6 (5.8%), 10	1 (0.9%), 2

(Data based on safety population)

Serious Adverse Events

- There was 1 serious AE, a kidney infection, in a vafidemstat treated subject
- Case was independently judged by the PI as 'Unlikely Related' to treatment (started before treatment)
  - Subject's dose was not changed, the condition 'Recovered/Resolved' within 7 days, and the subject completed the trial

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* *7 cases of numerical, clinically insignificant, and transient platelet (PLT) reductions & 1 transient and rapidly self-resolved thrombocytopenia (TP) grade 1*

PORTICO: final summary

- Primary endpoints not met by FAS. Yet, a trend by PPA in CGI-S A/A was detected
- Four important pre-specified secondary endpoints reached nominal statistical significance by FAS, with clinically meaningful value reductions compared to placebo
  - Improvement in Agitation/Aggression, with overall improvement over the results of placebo of 59%
  - Overall improvement in BPD disease severity, with overall improvement over the results of the placebo arm of 31%
- Reduction in agitation/ aggression and overall BPD disease severity consistent with Phase IIa REIMAGINE trial results
- Results across ALL primary and secondary efficacy endpoints favored vafidemstat over placebo.
- Global Statistical Test (GST-p values) significant and consistent with a global treatment effect favoring vafidemstat.
- Vafidemstat was safe and well tolerated.
- No deaths/suicides. Suicidal ideation was low.
- Lower intentional self-harm events in treated patients.

Primary Endpoints (p-values)		**FAS**
BPDCL Total	Avg w 8-12	0.38
CGI-Severity A/A	Avg w 8-12	0.22
Secondary Endpoints (p-values)		
BEST Total	Avg w 8-12	0.026
STAXI-2 Trait Anger	Avg w 8-12	0.007
BEST Total	By w 12	0.038
STAXI-2 Trait Anger	By w 12	0.016

Thank you!

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