ORYZON

Pioneering personalized medicine in epigenetics

Corporate Presentation

2H 2024

ORY:SM / ORY.MC

Vafidemstat is safe and well tolerated drug

A very robust safety package; +430 treated subjects

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

Vafidemstat is a small molecule with oral bioavailability, with potent and selective inhibition of LSD1

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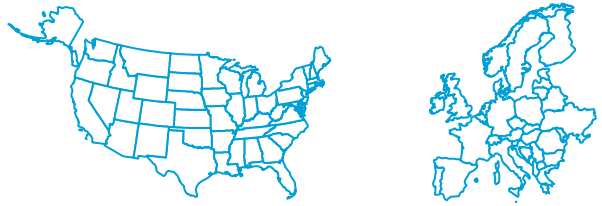
Two main catalysts in 2024

Program	Study	Preclinical Phase	Phase I		Phase II		Status	Expected Milestone(s)
			Phase Ia	Phase Ib	Phase IIa	Phase IIb		
CNS: Vafidemstat (ORY-2001) – CNS optimized LSD1 inhibitor								
Borderline personality disorder Agitation / Aggression & Overall Improvement	**PORTICO**						**Completed** Study has results	Top line data in January 2024 Final Data ECNP-2024 EoP2 FDA meeting in 2024 ★
Schizophrenia Negative Symptoms & Cognition	**EVOLUTION**						**Recruiting**	Timeline updates in 2024
Kabuki Syndrome	**HOPE**		**Phase Ib/II**				**IND in preparation**	IND in 2025

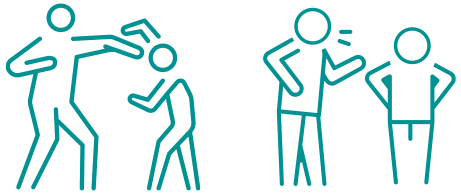
- Final Data of PORTICO in BPD were released at the European College of Neuropharmacology (ECNP) in Milano, on Sept 23rd, 2024
- PORTICO FDA end-of-Phase II meeting held on August 28th, 2024

Borderline personality disorder: an unmet medical need & vast commercial opportunity



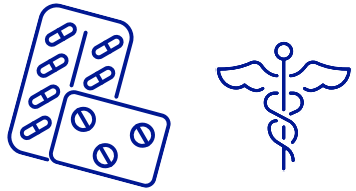
Prevalent & impairing disease

9 million in US & EU



Two main types of symptoms

Psychiatric symptoms
+
Agitation/Aggression
(including self-aggression)



No approved drugs yet

Patients on off-label anti-psychotics

Vafi improves these symptoms in:

- BPD patients
- PC models

Oryzon is leading the BPD field ahead of the competition

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

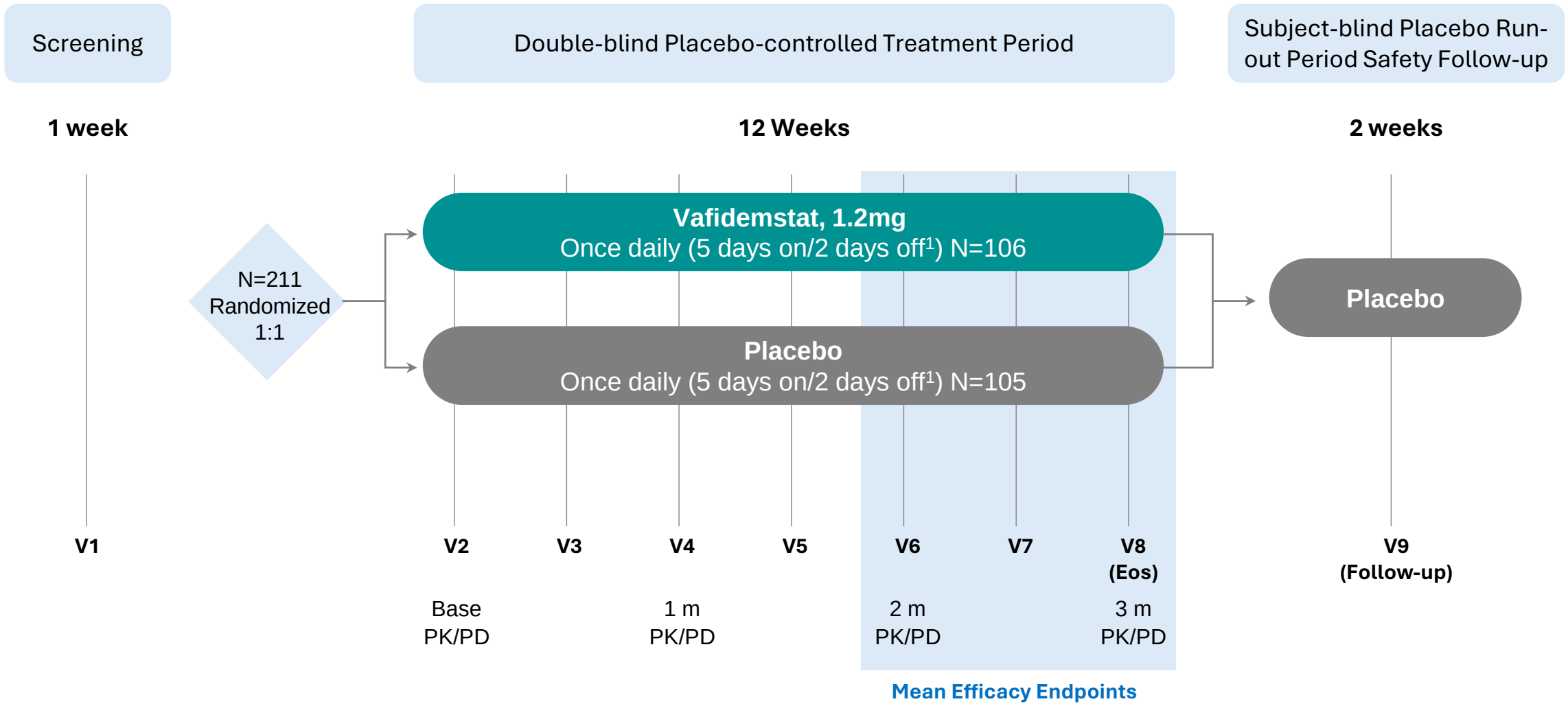
To evaluate the difference on the following measures, from baseline to weeks 8-12, as well as change over time, between the active treatment arm and the placebo arm:

- 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

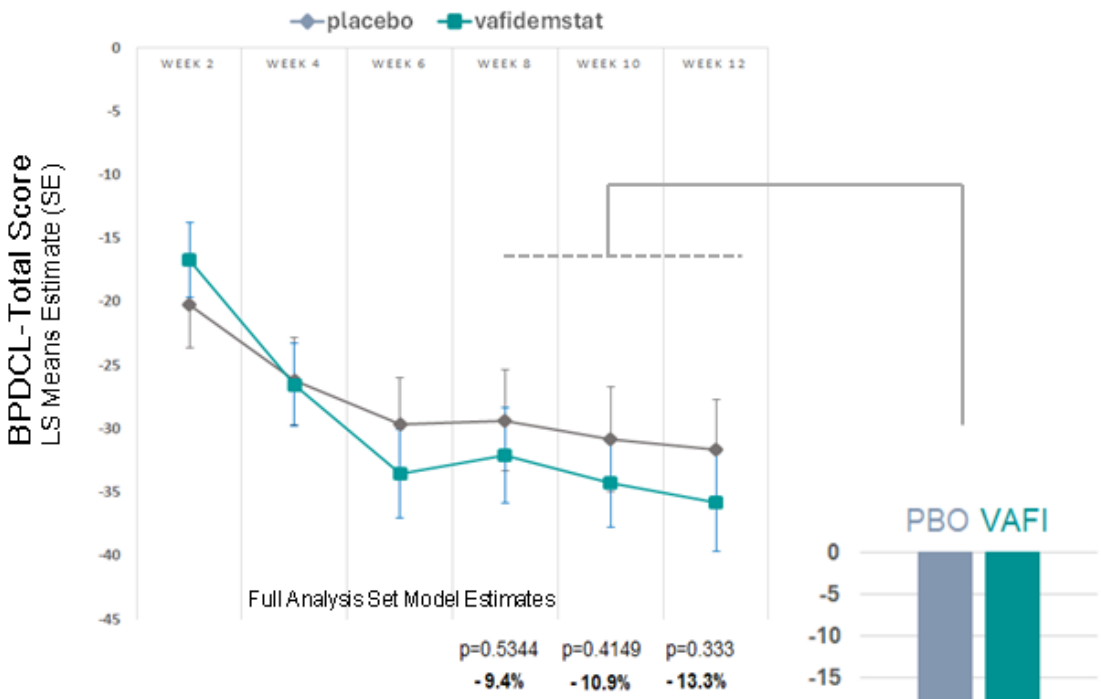
Final Results

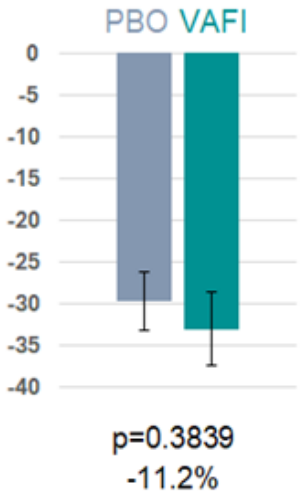
Phase 2b PORTICO study

Efficacy of vafidemstat in Borderline Personality Disorde

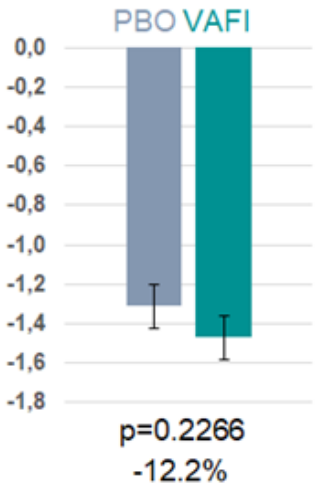
ECNP, Milan, Italy
September 23, 2024

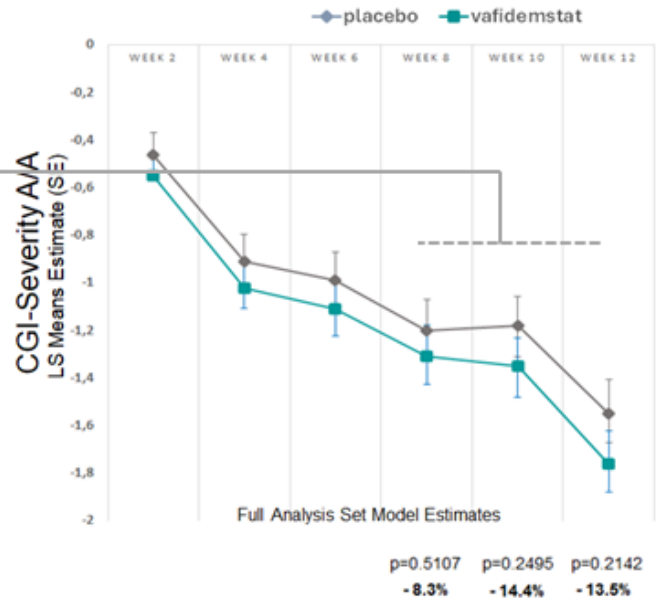
No statistical significance in the two primary endpoints: BPDCL and CGI-S A/A





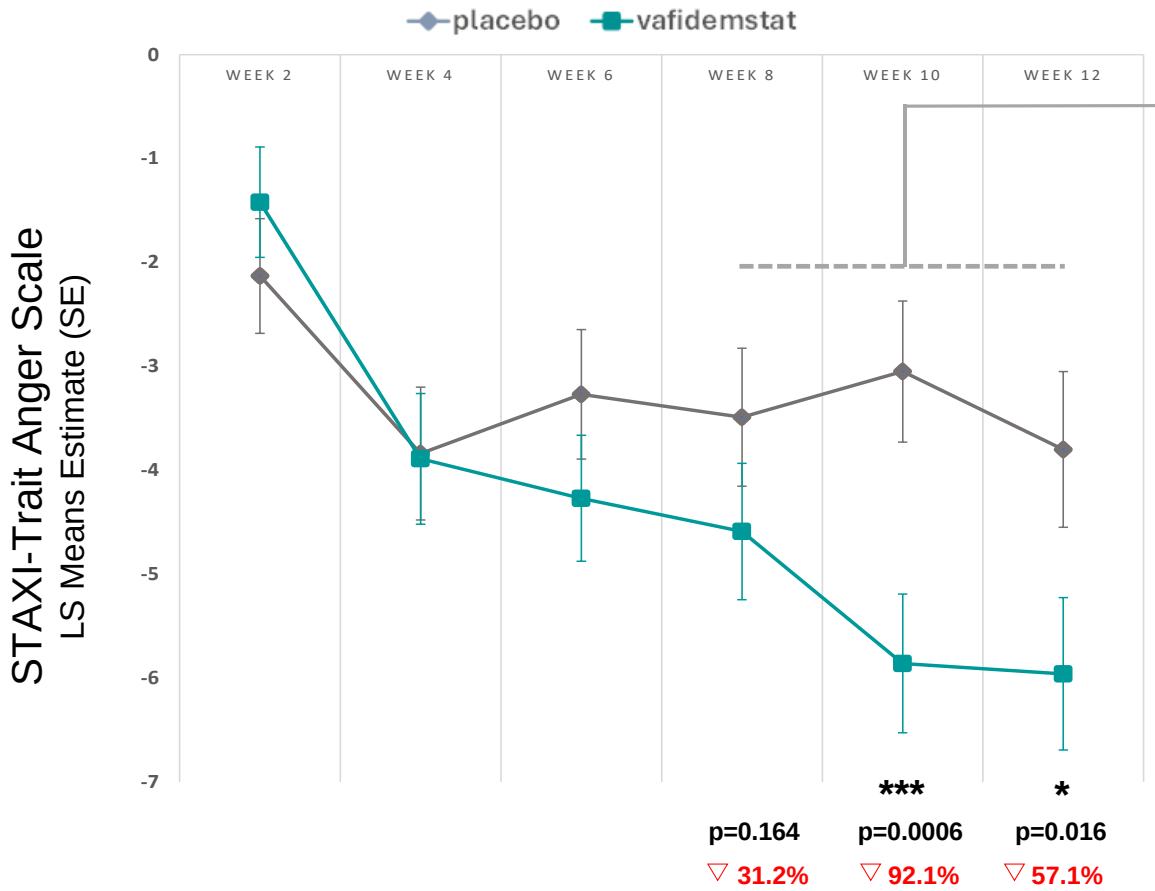
BPDCL-Total Score
Across weeks 8-12
LS Means Estimate (SE)

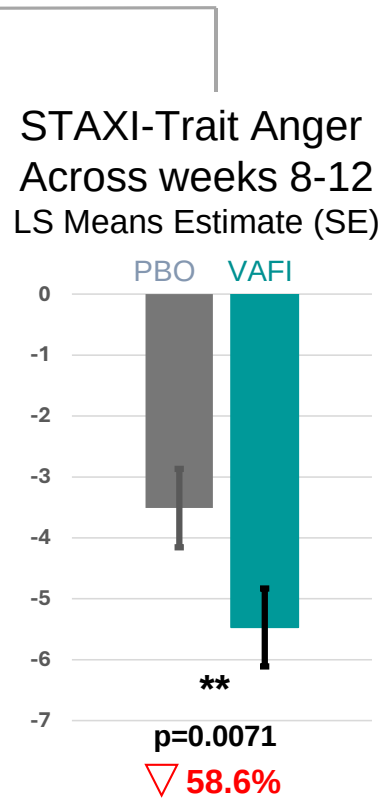




CGI-Severity A/A
Across weeks 8-12
LS Means Estimate (SE)

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





Agitation and aggression of patients, as measured by the secondary endpoint STAXI-2 Trait Anger scale, showed a substantial, statistically significant, and clinically meaningful reduction in the vafidemstat arm compared to placebo, with a p-value of 0.0071 across Weeks 8–12 (previously p = 0.0259). The relative reduction in the vafidemstat-treated group over the placebo group reached a maximum of 92.1% at Week 10, with an average reduction of 58.6% across Weeks 8–12 (previously 80.8% and 46.7%, respectively).

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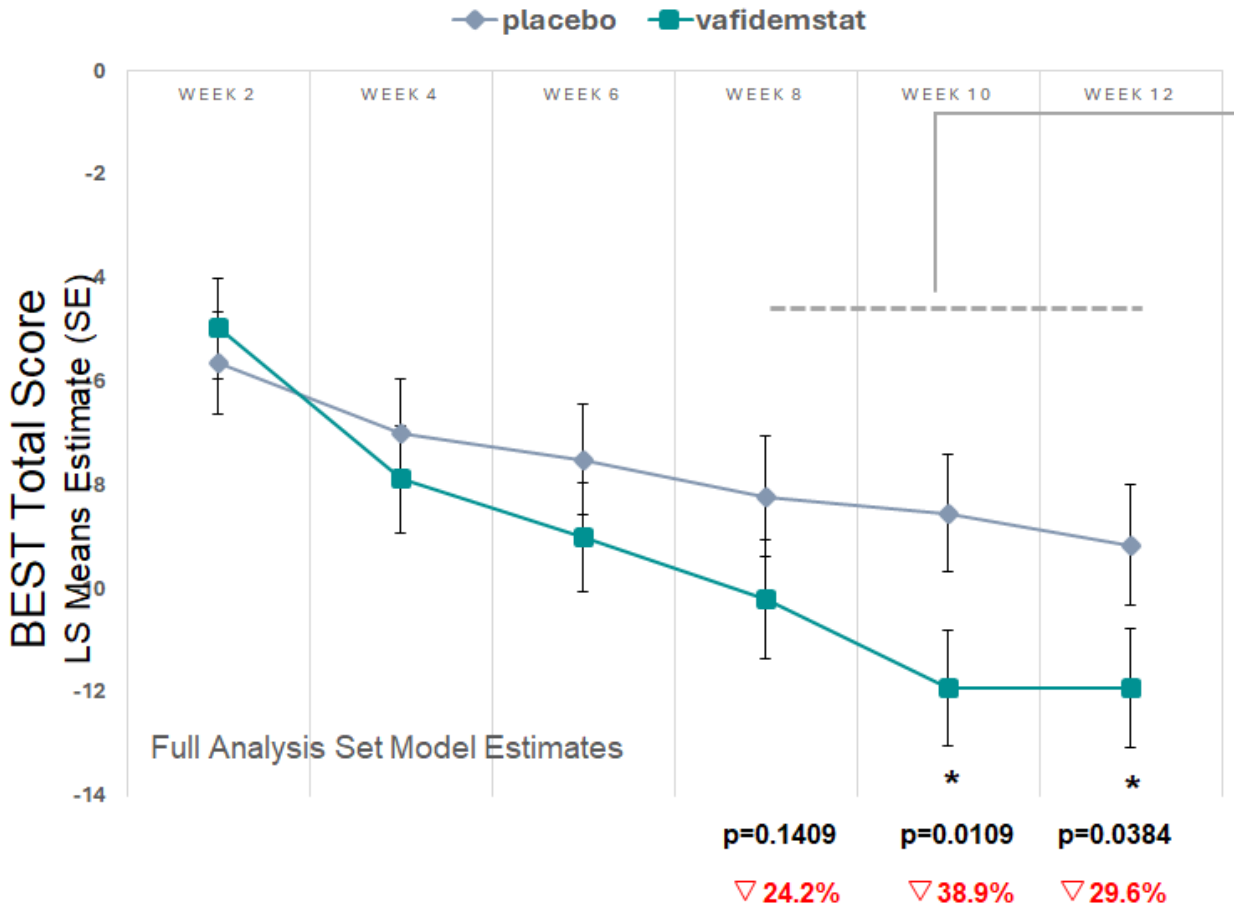
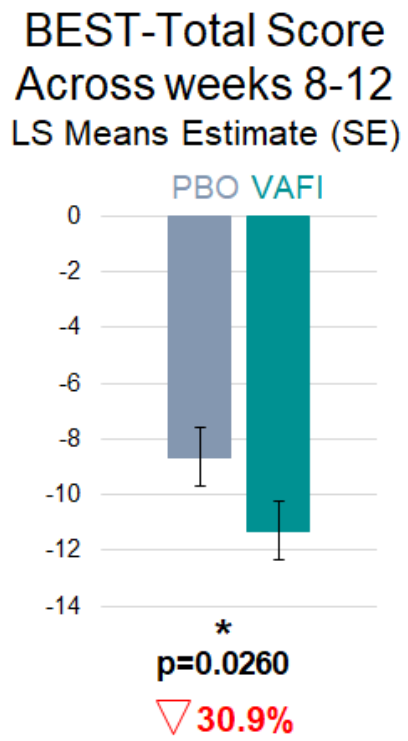
Nominal statistical significance in secondary endpoint: improvement in BEST across weeks 8-12





The overall measure of BPD severity measured by the secondary endpoint Borderline Evaluation of Severity (BEST), also showed an improvement compared to TLD, with a p-value of 0.0260 across Weeks 8–12 (previously p = 0.0423). The maximal relative reduction in the vafidemstat-treated group over the placebo group reached 38.9% at Week 10, with an average reduction of 30.9% across Weeks 8–12 (previously 29.9%).

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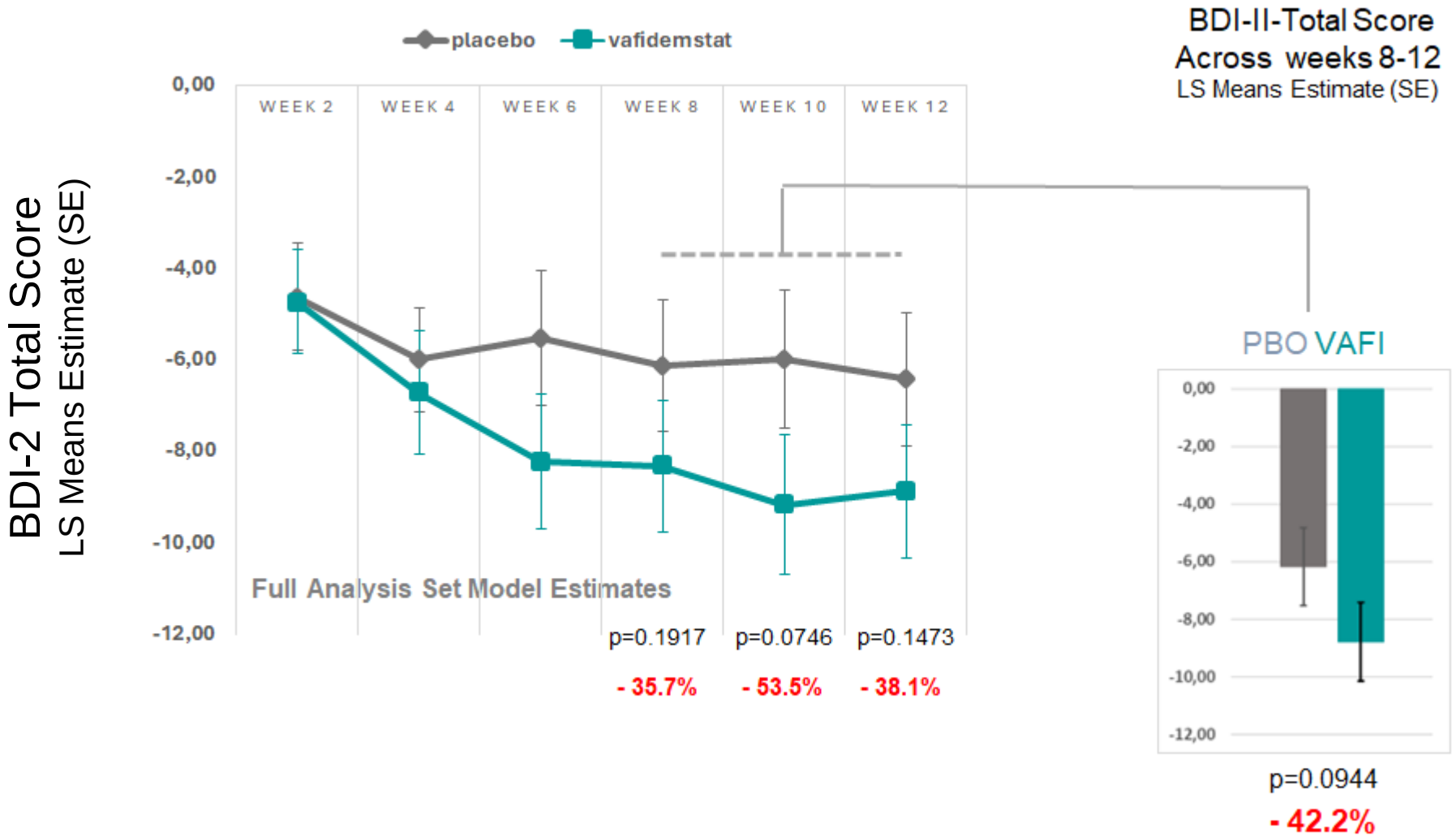
A trend in secondary endpoint: improvement in depression by BDI-2 Total Score by weeks 8-12

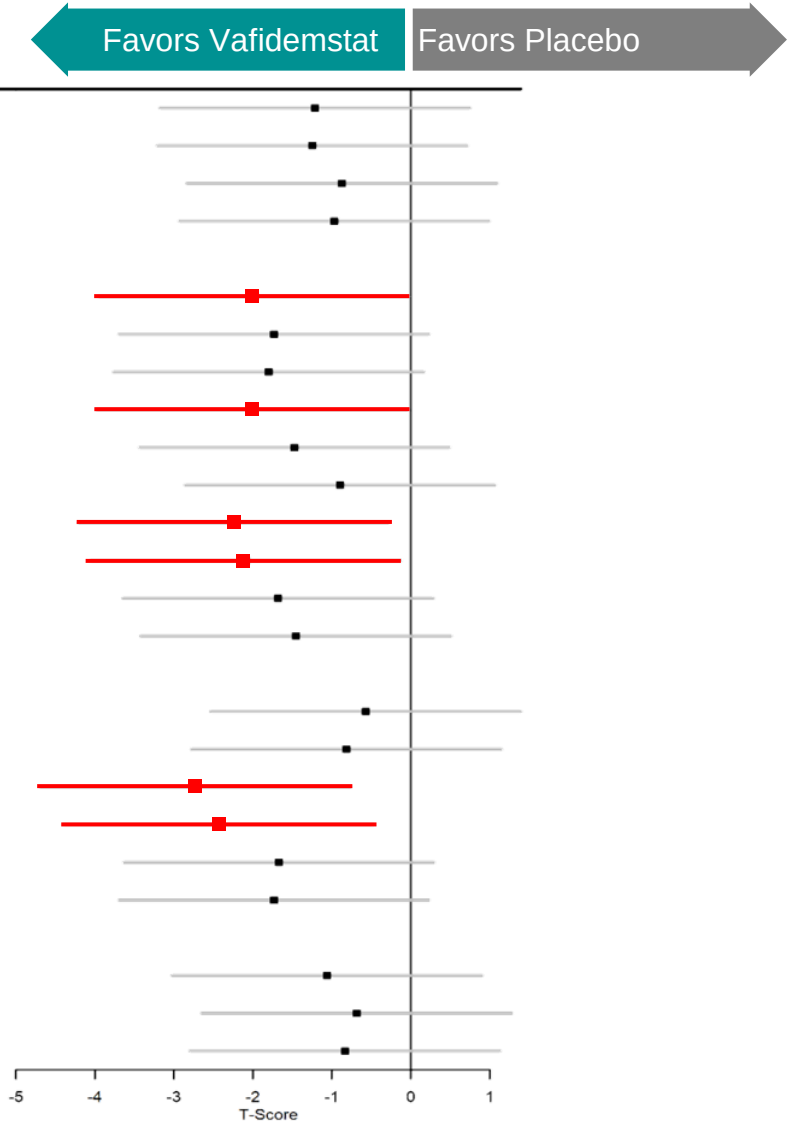


Interestingly, a trend of improvement in depression measured by the BDI-II Total Score by Weeks 8–12 was detected (p= 0.0944), with an average reduction over the placebo group of 42.2% across Weeks 8–12 (previously 0.1699)

PORTICO: all primary and secondary efficacy endpoints consistently favored vafidemstat over placebo

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

Global statistical test (GST) 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.

The final analysis confirmed now a global treatment effect favoring vafidemstat by the Global Statistical Test (GST), with the GST p-value showing a statistical significance, particularly when considering global improvement in the severity of the disease and in agitation/aggression (p = 0.0362, previously a strong trend).

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

Topline 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

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

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PORTICO:

Final Summary

PORTICO's efficacy and safety results support further clinical development

Oryzon requested an End-of-Phase II meeting with the FDA to discuss plans for a registrational BPD Phase III trial

FDA: End-of-Phase II Meeting

Objective: To obtain agreement on study design, safety, and efficacy endpoints for the registrational Phase III study (PORTICO-2)

EOP2 meeting briefing package:

- Summaries of previous investigations
- Information of Phase 2 trial PORTICO
- Synopsis of protocol of PORTICO-2 Phase III study
- Other info

FDA End-of-Phase II Meeting minutes: summary

- FDA's feedback supports the initiation of the Phase III trial
- Agitation-Aggression in Borderline Personality Disorder (BPD) acknowledged as a possible therapeutic indication
- The FDA agrees that Oryzon may pursue a Phase III study using STAXI-2 Trait anger as a primary efficacy endpoint measure, but the company will have to provide additional information to demonstrate that STAXI-2 Trait anger is a clinically meaningful endpoint in this indication (i.e through a Qualitative Research of the scale in BPD patients)
- Secondary endpoints will include both patient-rated and clinician-rated scales, as CGI-S A/A to assess agitation/aggression, and BEST and CGI-S to assess overall BPD improvement

FDA End-of-Phase II Meeting minutes: summary

- A Qualitative Research Study will be conducted with a subset of PORTICO-2 patients to provide further validation of the proposed endpoints. The Qualitative Study protocol will be submitted prior to its initiation for FDA review and feedback
- Oryzon plans to also provide the psychometric properties and performance for the selected primary and key secondary endpoints for FDA review prior to the initiation of the Phase III study
- The estimated total sample size for the PORTICO-2 Phase III study is 350 patients (randomized 1:1 vafidemstat or control), with a trial duration of 18 weeks in total
- Subject to FDA review of the final data, the PORTICO-2 Phase III study has the potential to be one of the two registrational trials required by the FDA

FDA End-of-Phase II Meeting: conclusions

- Based on the positive feedback received, ORYZON will now move forward with preparing a full PORTICO-2 Phase III trial protocol to be submitted to the FDA for study approval
- The company will also engage with European regulatory agencies following standard practice before initiation of the PORTICO-2 Phase III trial