Safety And Efficacy Data From Sateen Trial In Multiple Sclerosis

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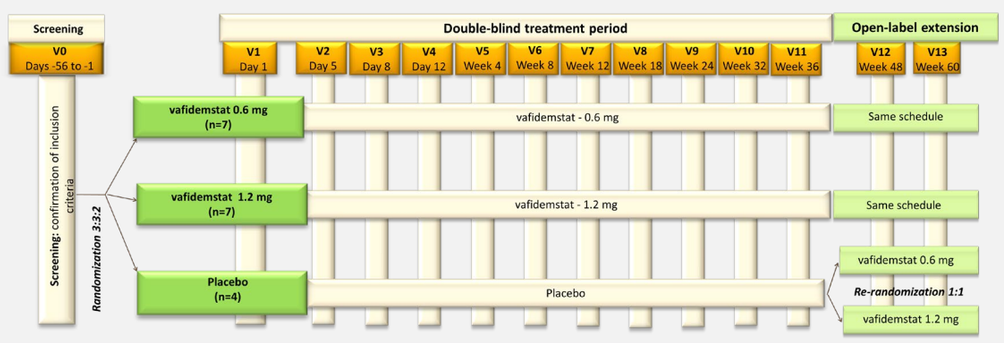
HIGHLIGHTS

- Long-term vafidemstat treatment was **safe and well tolerated with drugs exposures up to 2 years**
- **Anti-inflammatory activity** was observed in vafidemstat-treated patients
- SATEEN was a pilot, small scale trial **not powered to get conclusive efficacy data**

BACKGROUND Vafidemstat is a highly brain penetrant LSD1 inhibitor that has been shown to reduce neuroinflammation and promote remyelination in multiple sclerosis (MS) preclinical models. Vafidemstat has shown safety and clinical activity in different neurological disorders.

METHODS SATEEN (EudraCT: 2017-002838-23) was a Phase II randomized, double-blind, placebo-controlled, parallel group, dose-finding trial that evaluated the safety and tolerability of two vafidemstat doses (0.6 mg or 1.2 mg, randomization ratio 2:3:3) in relapse-remitting MS (RRMS) or secondary progressive MS (SPMS) subjects. The study design is depicted in Figure 1. As per inclusion criteria, study participants were adult subjects with at least one relapse or one T1 Gadolinium-enhancing lesion within the previous 12 months or one new or enlarging T2 lesion within the previous 18 months on magnetic resonance imaging (MRI). Data analyses occurred after 9 and 15 months of treatment, with an additional open-label extension in SPMS patients. Effect of vafidemstat on preliminary efficacy was measured through brain tissue damage and inflammation by MRI, optical coherence tomography (OCT), inflammatory biomarkers and clinical measures such as Expanded Disability Status Scale (EDSS).

Figure 1: Study design



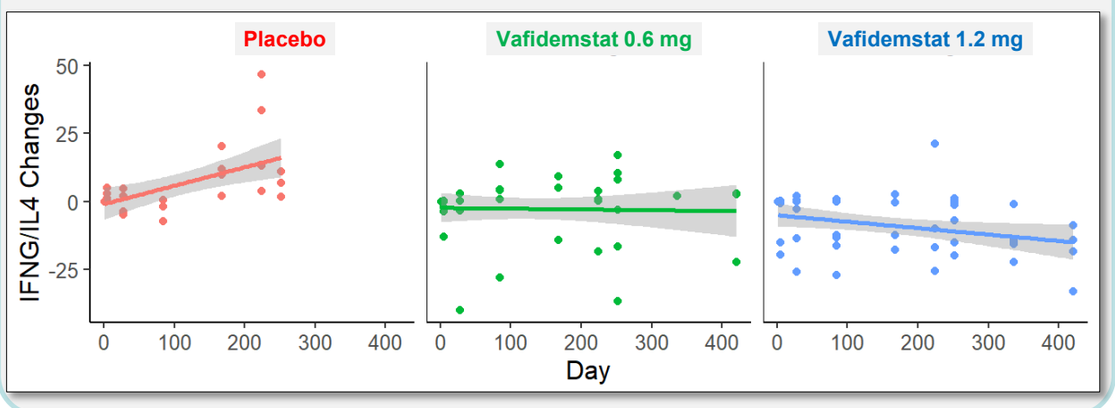
RESULTS SATEEN trial enrolled 18 MS patients (median age 49 years; 72% female; 67% RRMS), with a mean study permanence of 408 ± 156 days (**Table 1**). ***Safety and tolerability:*** No serious adverse events (SAE) were reported. Out of the 55 adverse events (AE) reported in the full population, only 13 in 7 patients were assessed as potentially related to treatment, 4 of which (including the only one considered severe during the trial) in 2 placebo patients (**Table 2**). Biochemistry and hematological parameters, as well as vital signs, ECG, and physical examinations did not show any clinically relevant differences between study arms. Despite the known impact of LSD1 inhibition on the hematologic compartment, only one patient at each dose level showed mild transient cytopenia. ***Pharmacodynamics and efficacy:*** This was a pilot, small scale trial not powered to get conclusive efficacy data. Accordingly, there were no statistically significant differences between groups in MRI, OCT or EDSS evaluations. Relapse or disease progression was recorded in 4 patients (22.2%). However, selected patients treated with vafidemstat showed improvement in one or more clinical readouts. In addition, promising signs of pharmacodynamic anti-inflammatory activity were reported in most of the vafidemstat-treated patients compared to placebo. Particularly, serum Th1/Th2 cytokine ratios were modulated with vafidemstat treatment, reaching statistical significance in 3 instances, including a clear dose-dependent decrease of the IFNγ/IL-4 ratio (**Figure 2**).

Table 1: Patient demographics

nº of patients = 18		
Type of MS	RR-MS	12 (66.7%)
	SP-MS	6 (33.3%)
Sex	Male	5 (27.8%)
	Female	13 (72.2%)
Age	Median	49.4
	Min / Max	28 / 62
Race	Caucasian	18 (100%)
Weight (kg)	Median	65.1
	Min / Max	48.0 / 95.0
Height (cm)	Median	164.0
	Min / Max	149.0 / 176.0
BMI	Median	25.0
	Min / Max	17.6 / 33.8

Figure 2: Pharmacodynamics and Efficacy. Vafidemstat treatment decreases IFNγ/IL-4 ratios in a dose-dependent and statistically significant manner.

Change from visit 11 to baseline is presented in %, as determined by Quanterix Simoa® immunoassays; dots: individual values, line: mean, grey area: 95% confidence interval



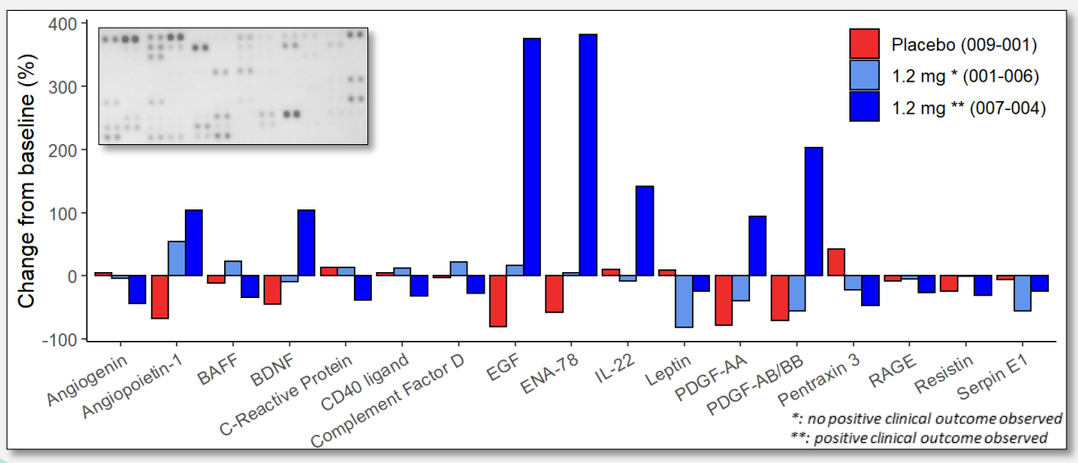
Additionally, protein array analysis (Human XL Cytokine Array Kit, R&D Systems, Inc.) of plasma samples revealed that vafidemstat promotes changes in the expression of several soluble markers described to play relevant roles in MS pathogenesis, such as BDNF1 or EGF2, among others, and that, at the same vafidemstat dose, the differences were overall markedly larger when a positive clinical outcome was observed in the studied patient (**Figure 3**). Similarly, in the same patients, plasma chemokine levels assessed by specific immunoassays (IP-10, MCP-1, RANTES) were also overall decreased upon vafidemstat treatment compared to placebo (not shown).

Table 2: Safety. Vafidemstat was safe and well tolerated upon long-term treatment in MS patients, with no significant differences in AE frequency between treatment arms.

No. of patients (%) events	Total (N=18)	Placebo (n=4)	Vafidemstat 0.6 mg (n=7)	Vafidemstat 1.2 mg (n=7)
Total AEs	**16 (88.9%) 55**	**3 (75%) 17**	**6 (85.7%) 17**	**7 (100%) 21**
Drug-related AEs	**7 (38.9%) 13**	**2 (50%) 4**	**2 (28.6%) 5**	**3 (42.9%) 4**
Gastrointestinal Disorders:	**5 (27.78%) 6**	**2 (50.00%) 3**	**2 (28.57%) 2**	**1 (14.29%) 1**
Abdominal Discomfort	1 (5.56%) 1	1 (25.00%) 1	-	-
Abdominal Pain	1 (5.56%) 1	1 (25.00%) 1	-	-
Abdominal Pain Upper	1 (5.56%) 1	-	1 (14.29%) 1	-
Constipation	1 (5.56%) 1	-	1 (14.29%) 1	-
Diarrhoea	1 (5.56%) 1	1 (25.00%) 1	-	-
Nausea	1 (5.56%) 1	-	-	1 (14.29%) 1
General Disorders:	**1 (5.56%) 1**	-	-	**1 (14.29%) 1**
Chills	1 (5.56%) 1	-	-	1 (14.29%) 1
Infections And Infestations:	**1 (5.56%) 1**	-	-	**1 (14.29%) 1**
Infectious Mononucleosis	1 (5.56%) 1	-	-	1 (14.29%) 1
Investigations:	**1 (5.56%) 1**	1 (25.00%) 1	-	-
Blood creatine phosphokinase increased	1 (5.56%) 1	1 (25.00%) 1	-	-
Musculoskeletal and connective tissue disorders:	**1 (5.56%) 1**	-	-	**1 (14.29%) 1**
Musculoskeletal discomfort	1 (5.56%) 1	-	-	1 (14.29%) 1
Nervous system disorders:	**1 (5.56%) 2**	-	**1 (14.29%) 2**	-
Tension headache	1 (5.56%) 1	-	1 (14.29%) 1	-
Somnolence	1 (5.56%) 1	-	1 (14.29%) 1	-
Skin and subcutaneous tissue disorders:	**1 (5.56%) 1**	-	**1 (14.29%) 1**	-
Alopecia	1 (5.56%) 1	-	1 (14.29%) 1	-

Figure 3: Pharmacodynamics and Efficacy. Vafidemstat modulates expression of soluble inflammatory markers involved in MS pathogenesis.

Change from visit 11 and baseline is shown in % in three different patients. Out of the 105 assessed markers, only those with the largest differences in expression upon vafidemstat treatment are presented



CONCLUSION The SATEEN trial supports the safety of vafidemstat long-term treatment and its pharmacodynamic effects on the immune-modulatory activity in MS, although larger trials are needed to confirm the clinical benefit.

DISCLOSURES

BRA has received honoraria for consulting services from Wellspect and Novartis. JEMR has participated as principal investigator in pharmaceutical company-sponsored clinical trials by Novartis, Roche, Merck-Serono, Actelion, Celgene, Oryzon Genomics, and Medday, carried out in Hospital del Mar, IMIM, Barcelona; speaking fees for consulting services and lectures from Novartis, Sanofi and Biogen Idec; and travel funding from Biogen Idec and Sanofi.

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