ADPD 668

VAFIDEMSTAT SAFETY AND EFFICACY IN ALZHEIMER-RELATED AGITATION & AGGRESSION: PHASE II REIMAGINE-AD 6-MONTH DATA

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Introduction

Vafidemstat (ORY-2001) is a highly brain penetrant LSD1 inhibitor optimized for CNS indications with good selectivity, ADME and PK properties. Vafidemstat restores memory in SAMP8 Alzheimer's (AD) and in R6/1 Huntington (HD) disease mice models. Others have also shown that LSD1 inhibition restores working memory in schizophrenia (SCZ) and psychosis mice models. Vafidemstat also reduces significantly aggression and enhances sociability in rodent models. Vafidemstat's hypothesized impact on the CNS is mediated by overexpression of genes associated with neuronal plasticity and reduction of genes associated with neuro-inflammation, which is supported by animal studies to-date. In addition, supporting evidence in humans was reported in REIMAGINE, a single arm, open label Phase IIa basket trial conducted in ADHD, ASD and Borderline Personality Disorder patients, where a two month treatment with vafidemstat was efficacious in reducing agitation-aggression and improving the general status of study patients. In general, the prevalence of agitated-aggressive behavior increases as AD severity increases, reducing quality of life of patients and caregivers. This behavior is also the main reason for institutionalization. Current treatment options for agitated-aggressive AD patients include off-label antipsychotics; however, these drugs are associated to a higher risk of serious adverse effects. Therefore, new clinical options are needed to improve the management of behavioral disorders in AD patients. Vafidemstat has been shown to be safe in previous clinical trials.

Methods

REIMAGINE-AD (EudraCT Number: 2019-001436-54) is a single center, open-label, 1-arm study to evaluate the efficacy, safety and tolerability of vafidemstat in aggression in adult population with moderate-to-severe AD. Initially, the study was designed as a 13-week treatment study, but due to initial observations made by the PIs, it was decided to extend the treatment period up to 24 weeks. The Primary Objective is to investigate the efficacy of vafidemstat in aggression in AD population, while secondary objectives include the evaluation of the safety and tolerability of vafidemstat in AD population and to investigate other changes on behavior, cognition and caregiver burden. The scales used to measure agitation-aggression included the Cohen-Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory [NPI (4-item)] Agitation/Aggression subscale (NPI A/A subscale), as well as the Clinical Global Impression (CGI) focused on agitation and aggression. Other measures included measures of global patient well-being (NPI), cognition (MMSE) and caregiver burden (Zarit Caregiver Burden Interview , ZBI).

Table 1. Demographic features of the sample

nº of patients	12	
Sex	Male	5 (41.7%)
	Female	7 (58.3%)
Age	Mean	74.8
	Median	75.00
	Min /Max	64/84
Race	Caucasian	12 (100%)
Weight	Mean	68.1
	Median(kg)	66.0
	Min /Max	58.5/80.1
Height	Mean	157.5
	Median (cm)	159
	Min /Max	142/169
BMI	Mean	27.54
	Median	26.97
	Min / Max	33.6/22.3
Highest level of education	Some school	9 (75%)
	University degree	3 (25%)
MMSE	Mean	9.67
	Median	8
	Min/Max	1/19

Highlights

- Safe and well tolerated
- Significant Reduction of Agitation/Aggression after 6 months of treatment
- Significant improvement in caregiver-burden

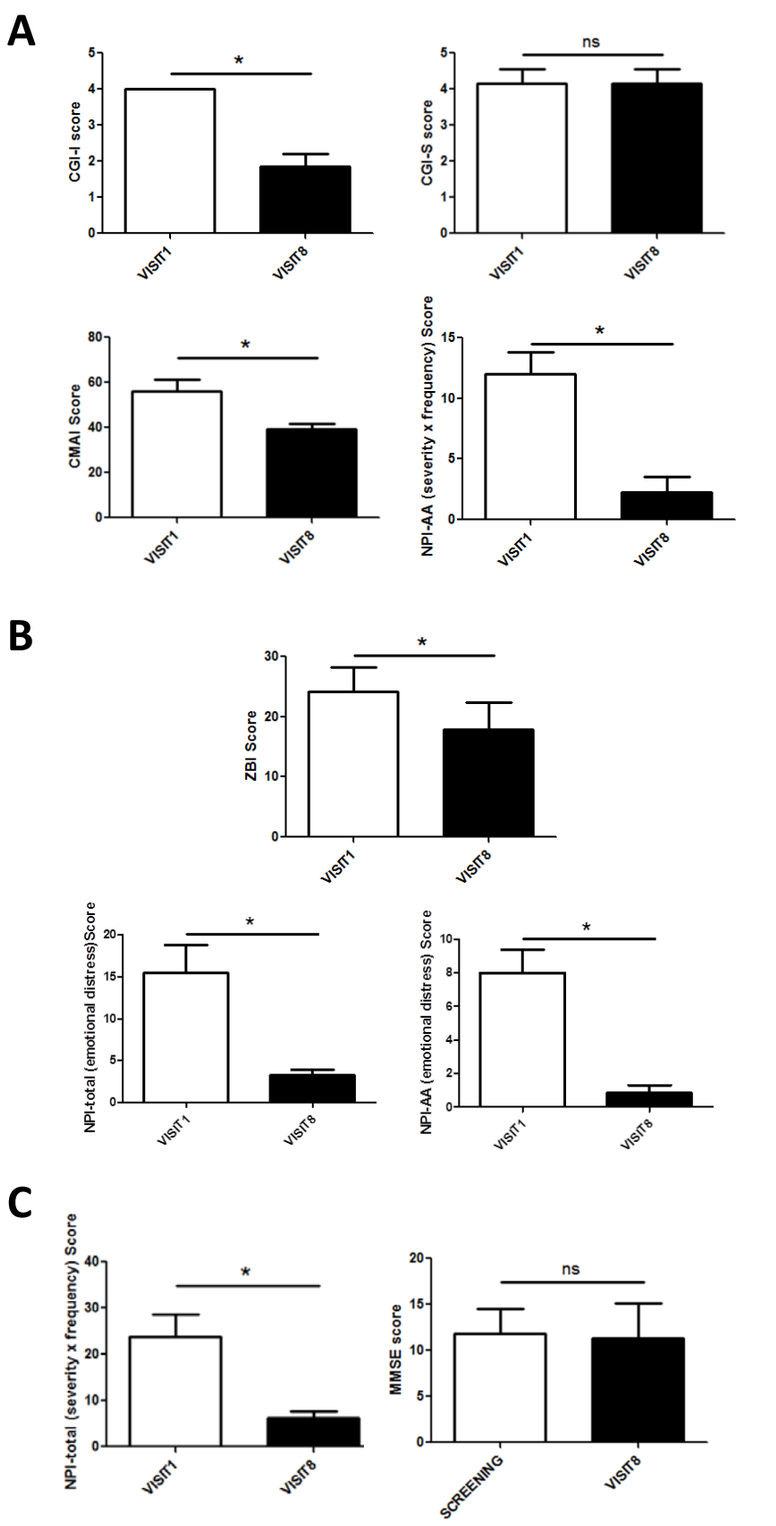

Figure 1. Efficacy evaluation of the clinical scales used to assess vafidemstat's effects on agitation and aggression (A), caregiver burden (B), or global patient performance, including memory/cognition (C). Data is analyzed comparing the variation observed after 6 months of vafidemstat treatment (visit 8) versus baseline status (visit 1 or screening) using one-tail repeated-measures Wilcoxon signed-rank test. Data presented in this poster is preliminary and it will not be final until database lock.

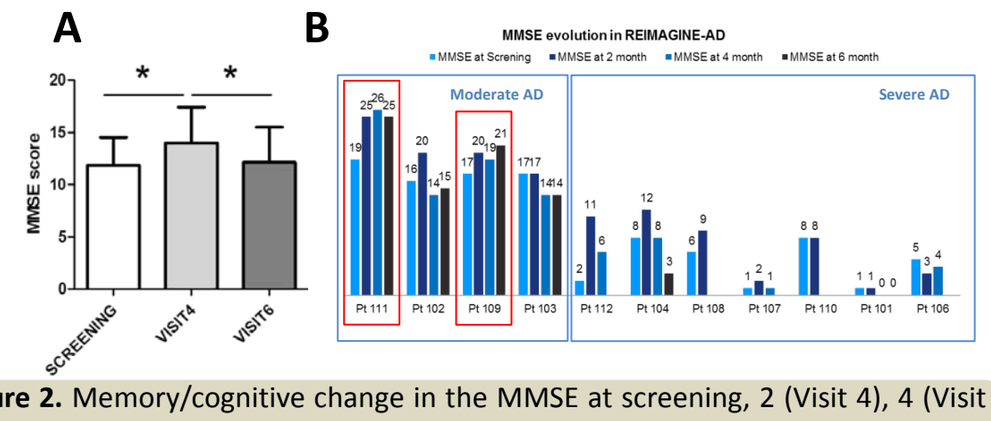

Figure 2. Memory/cognitive change in the MMSE at screening, 2 (Visit 4), 4 (Visit 6) and 6 (Visit 8) months after vafidemstat treatment in REIMAGINE-AD patients. A) shows statistical differences between screening, V4 and V6 visits assessed by one tail paired t-test study ($p \leq 0.05$) (data for V8 is shown in Figure 1C), while B) shows individual patient change over time. Treatment in red-box patients has been extended up to 12 months,

Results

A total of 12 patients were enrolled (Table 1). One patient withdrew consent during the first two months of treatment. After two months, subjects were offered to continue in the study and 9 and 7 patients completed the 4 and 6 months study visits, respectively. The study population included 58% females and 42% males. Median age was 75 years. Seven (58%) patients had severe AD and four (42%) patients moderate AD (median MMSE values of 5 and 17, respectively).

Safety data support the safety and tolerability of long-term vafidemstat treatment in this patient population, which is aligned with the safety data obtained in the parallel running randomized, double-blind placebo controlled AD disease trial (ETHERAL trial). AEs observed in REIMAGINE-AD are presented in Table 2. Only mild thrombocytopenia and neutropenia was observed in one patient who withdrew consent during the first two months of treatment.

As regards efficacy outcomes, treatment with vafidemstat produced the following statistically significant findings when comparing patients treated for 6 months (Visit 8) with respect to baseline (Visit 1):

- Regarding agitation-aggression measurements, improvement in CGI-I as well as a reduction in the CMAI scale, and in the NPI Agitation/Aggression subscale (Fig 1A).
- A global improvement on the caregiver burden as measured by ZBI and both of the NPI related emotional distress scores (Fig 1B).
- A global improvement on the total NPI (Fig 1C).

As expected given the short-term nature of this study, no statistically significant effects were noted on a cognitive screener, the MMSE, after 6 month of treatment (Fig 1C). A more granular evaluation of the MMSE results revealed a statistical improvement in the MMSE across the 11 patients after 2 months of treatment (Fig. 2A). That is 7 patients improved, 3 remained stable and 1 subject's MMSE score worsened (Fig 2B). This improvement was not maintained at months 4 and 6. However, two out of four moderate AD patients consistently scored significantly better at months 4 and 6 (Fig 2B). The treatment in these two patients has been extended to 12 months to further investigate this observation. Finally, it is also worth noting that behavioral improvements were taking longer to become evident in the AD versus the psychiatric populations studied in the original REIMAGINE study.

Table 2. Safety evaluation of the REIMAGINE-AD patients

Study-drug related TEAEs (ADRs) by SOC and PT (n=12)	
Number of Patients (%) Event Count	
Blood and lymphatic system disorders	**2 (16.66 %) 3**
Leukopenia	1 (8.33) 1
Neutropenia	1 (8.33) 1
Thrombocytopenia	1 (8.33) 1
Investigations	**1 (8.3%) 1**
Blood creatine phosphokinase increase	1 (8.33) 1
Musculoskeletal/connective tissue disorders	**1 (8.33%) 1**
Inflamation lef doll	1 (8.33) 1
Nervous system disorders	**1 (8.33%) 1**
Myoclonus	1 (8.33) 1
Psychiatric disorders	**1 (8.33%) 1**
Insomnia	1 (8.33) 1

A patient with more than one finding in a specific category was only counted once. Percentages based on total no. of patients (n=12)

Conclusions

Vafidemstat appears safe and well tolerated in this elderly moderate-to-severe AD population. These findings are aligned with preliminary safety data from ETHERAL and in the three REIMAGINE psychiatric patient populations. Findings support that vafidemstat controlled agitation and aggression symptoms of AD patients, as well as improved caregiver burden after 6 months of treatment. Interesting anecdotal findings in the moderate subjects included a concomitant increase in memory performance on the MMSE in 2 out of 4 subjects at 6 months. These data are preliminary but support further clinical investigations in this difficult to treat disease with limited treatment options.

CONFLICT OF INTERESTS: *RB, SG, JX, MR and CB are employees of ORYZON GENOMICS S.A. MB is advisory board and has received consultancy honoraria from several pharma, including Biogen, Eisai, Grifols, Lilly, Merck, Servier and Roche. CA has received honoraria from Zambon and Schwabe. CB is the Chief Executive Officer and shareholder of ORYZON GENOMICS S.A. This study was sponsored by ORYZON GENOMICS S.A.*