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ESCAPE trial: Preliminary data on the effect of vafidemstat treatment in the COVID-19 induced immune response in hospitalized patients

M. ARÉVALO[1], R. RUÍZ-RODRÍGUEZ[1], L. FERNÁNDEZ DE ORUETA[2], J. SANZ[3], B. ALMIRANTE[4], J.P. HORCAJADA[5], A. CASTRO-GUARDIOLA[6], F. CICERI[1], S. GUTIÉRREZ[1], J. XAUS[1] AND C. BUESA[1].

[1] Oryzon Genomics SA - Cornellà De Llobregat (Spain); [2] Hospital Universitario de Getafe - Getafe (Spain); [3] Hospital de la Princesa - Madrid (Spain); [4] Hospital de la Vall d'Hebron - Barcelona (Spain), [5] Hospital del Mar - Barcelona (Spain), [6] Hospital Josep Trueta - Girona (Spain).

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INTRODUCTION

In some patients, SARS-CoV-2 infection elicits an exacerbated immune response responsible for a rapid progression to Acute Respiratory Distress Syndrome (ARDS), a severe and often fatal complication. Ex-vivo, LSD1 inhibition has been reported to control the expression of pro-inflammatory cytokine genes in severe COVID-19 patients' PBMCs[1]. Vafidemstat is an LSD1 inhibitor in clinical development in several Phase II studies. Vafidemstat has demonstrated to be safe and to have immunomodulatory properties that can be of interest in the management of ARDS.

AIM

ESCAPE is a randomized, open-label, multicenter trial that aimed to evaluate the efficacy and tolerability of vafidemstat in combination with standard of care (SoC) treatment to prevent ARDS in adult CoVID-19 patients. The trial also aims to evaluate the immune response induced by CoVID-19 and characterize the effect of vafidemstat treatment, which is the focus of this poster.

METHODS

ESCAPE eligible population comprised CoVID-19 patients at risk of rapidly becoming critical, developing ADRS or being transferred to ICU. The initial sample size of 40 patients was further extended up to 60. Patients received either SoC medication alone or in combination with oral vafidemstat (2.4 mg/day for 5 days). Primary and secondary endpoints included the incidence of patients requiring mechanical ventilation, development of ADRS, referral to ICU, decrease in mortality, and respiratory function, among others. Immune response was assessed by (a) immunophenotyping of PBMCs by mass cytometry and (b) determination of cytokine levels in plasma. In addition, LSD1 target engagement was assessed in all patients (**Figure 1**).

RESULTS

Results presented in this poster are preliminary and based on non-curated data after soft lock of the trial database on May 18th, 2021. Bioanalytical data have been audited by Oryzon Genomics' Quality Assurance Department.

Sixty patients were randomized to the trial from May 2020 to March 2021. No baseline differences in age, body mass index or disease severity and risk factors between study arms were observed (**Table 1**). Only the number of female subjects was not proportionally represented in the vafidemstat arm.

Most of the patients (69%) were discharged before the first week of treatment in both arms and only four patients were admitted in ICU (2 in each arm). One patient treated with SoC died due to CoVID morbidities. Glucocorticoids were the most frequent SoC treatment (83% of patients, equally represented in both arms).

RESULTS

Treatment was well tolerated, with only 13 AEs in 11 subjects reported during the study, none of them severe nor serious. Of those, 9 AEs were recorded in the vafidemstat +SoC arm, all mild and considered not treatment-related. The most frequent AEs were GI disorders (n=4, 6.7%), including gingival bleeding, nausea, and diarrhea.

	SoC	Vafidemstat + SoC	TOTAL
No. of patients:	31	29	60
Gender: n (% in arm)			
Male	16 (51.6%)	21 (72.4%)	37 (61.7%)
Female	15 (48.4%)	8 (27.3%)	23 (38.3%)
Age: mean (min-max)	56.5 (23-83)	58.5 (26-81)	57.5 (26-83)
Weight (Kg): mean (min-max)	79.3 (42-143)	80.8 (57-116)	80 (42-143)
Height (cm): mean (min-max)	162.4 (148-178)	165.2 (143-177)	163.7 (143-178)
BMI: mean (min-max)	30 (17.5-46.8)	29.6 (22-37.5)	29.8 (17.5-46.8)
IL-6 elevated: n (% in arm)	17 (54.8%)	15 (51.7%)	32 (53.3%)
Risk parameters: n (% in arm)	30 (96.8%)	28 (96.6%)	58 (96.7%)
D-dimer >1000 ug/L	4 (12.9%)	5 (17.2%)	9 (15%)
PCR >5 mg/dL	19 (61.3%)	16 (55.2%)	35 (58.3%)
LDH >300 UI/L	21 (67.7%)	16 (55.2%)	37 (61.7%)
Ferritin >200 ng/mL	26 (83.9%)	27 (93.1%)	53 (88.3%)
Total Lymphocytes <1000 mm^3	15 (48.4%)	12 (41.4%)	27 (45%)
WHO-7 diagnose: n (% in arm)			
3. Hospitalized with no O2 support	13 (41.9%)	12 (41.4%)	25 (41.7%)
4. Hospitalized with O2 support	18 (58.1%)	17 (58.6%)	35 (58.3%)

Tab. 1: Patient demographics.

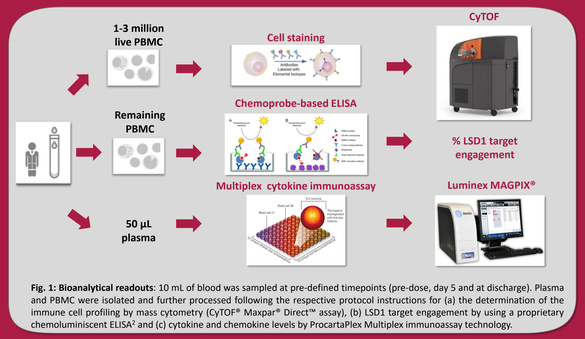

Fig. 1: Bioanalytical readouts: 10 mL of blood was sampled at pre-defined timepoints (pre-dose, day 5 and at discharge). Plasma and PBMC were isolated and further processed following the respective protocol instructions for (a) the determination of the immune cell profiling by mass cytometry (CyTOF® Maxpar® Direct™ assay), (b) LSD1 target engagement by using a proprietary chemoluminiscent ELISA[2] and (c) cytokine and chemokine levels by ProcartaPlex Multiplex immunoassay technology.

Twenty-four patients (77.4%) in the SoC group required mechanical ventilation versus 19 (65.5%) in the vafidemstat treated group. A total of 6 patients required rescue medication (Tocilizumab): 4 patients (67%) in SoC and 2 (33%) treated with vafidemstat. These 6 patients have been excluded from the analysis. Differences between treatment arms in clinical response, including days of hospitalization or respiratory parameters, will be analyzed later once the database is hard-locked.

Treatment with 2.4 mg/day vafidemstat for 5 days resulted in an almost complete occupancy (up to 97%; mean 86%) of the LSD1 target protein, which was sustained until day 7 and slowly declined afterwards (**Figure 2**).

Highlights

- Anti-inflammatory effects of vafidemstat confirmed in Covid-19 patients, in keeping with prior clinical and preclinical data.
- Vafidemstat reduced exacerbated CD4+ T cell activation and cytokine release.
- Fast recovery of patients was observed in both arms.

A mean value of 70% LSD1 target engagement was still observed on the day of discharge. LSD1 inhibition by vafidemstat resulted in significant effects on the immune response induced by CoVID-19 infection, in terms of both circulating immune cell populations and inflammatory mediators, including cytokines and chemokines.

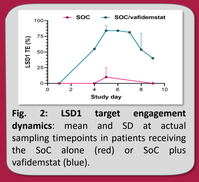

Fig. 2: LSD1 target engagement dynamics: mean and SD at actual sampling timepoints in patients receiving the SoC alone (red) or SoC plus vafidemstat (blue).

In particular, a clear tendency for decreased plasma levels of most of the cytokines evaluated was observed after 5 days of vafidemstat treatment compared to the immunosuppressor effect already observed with the SoC alone (**Figure 3**). Despite the small population size, statistical significancy ($p<0.05$) was reached for IL-12p70, IL-17A and IFNγ, and the p-values of the rest were mostly <0.2. Regarding chemokines, vafidemstat treatment did not lead to any significant improvements in IP-10 or MCP-1 plasma levels compared to the inhibitory effects of the SoC alone. Interestingly, a trend towards elevation of RANTES, known to play an important role in protecting CoVID-19 patients from developing severe illness[3], was observed in patients treated with vafidemstat compared to SoC alone. Similar results were observed when treatment arms were compared on the day of discharge. Furthermore, distinct changes in the frequency of several circulating immune cell populations were also observed (**Figure 4**). These were most significantly affecting CD4+ T cell subsets and revealed that vafidemstat in combination with SoC treatment might help to control T-cell activation by significantly reducing the % of terminal effector (TE), effector memory (EM) and regulatory T (Treg) cells, which have been previously shown to be elevated in patients with CoVID-19 pneumonia[4]. This reduction in activated CD4+ T subsets was coupled to an increase in naïve cells (not shown). The % of monocytes was also consistently increased upon vafidemstat treatment, but the differences observed were not statistically significant. No significant effects were observed on the CD8+ T cell subsets.

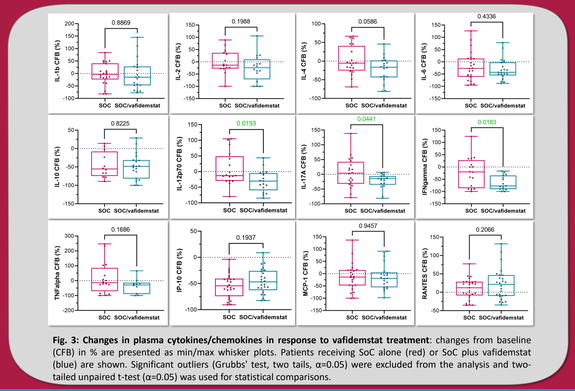

Fig. 3: Changes in plasma cytokines/chemokines in response to vafidemstat treatment: changes from baseline (CFB) in % are presented as min/max whisker plots. Patients receiving SoC alone (red) or SoC plus vafidemstat (blue) are shown. Significant outliers (Grubbs' test, two tails, α=0.05) were excluded from the analysis and two-tailed unpaired t-test (α=0.05) was used for statistical comparisons.

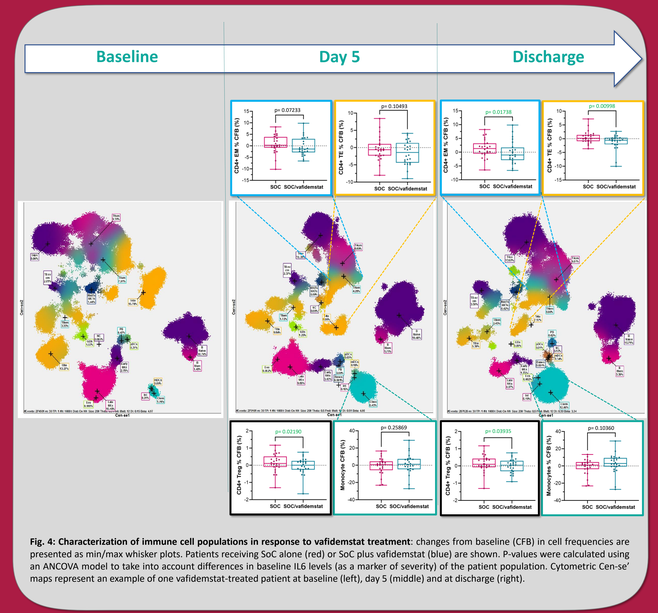

Fig. 4: Characterization of immune cell populations in response to vafidemstat treatment: changes from baseline (CFB) in cell frequencies are presented as min/max whisker plots. Patients receiving SoC alone (red) or SoC plus vafidemstat (blue) are shown. P-values were calculated using an ANCOVA model to take into account differences in baseline IL6 levels (as a marker of severity) of the patient population. Cytometric Cen-se' maps represent an example of one vafidemstat-treated patient at baseline (left), day 5 (middle) and at discharge (right).

CONCLUSIONS

Vafidemstat treatment in combination with SoC (mainly corticoids) is safe and well-tolerated and modulates the immune response of CoVID-19 patients at risk of rapidly becoming critical by controlling exacerbated CD4+ T cell activation and the subsequent release of inflammatory cytokines.

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DISCLOSURES

MA, RRR, FC, SG, JX and CB are employees of Oryzon Genomics S.A. CB is the Chief Executive Officer and holds equity of Oryzon Genomics S.A. Oryzon Genomics S.A. sponsors the ESCAPE clinical trial.

CONTACT

cbuesa@oryzon.com (www.oryzon.com)