

Supplementary Material

Plitidepsin in Adult Patients with COVID-19 Requiring Hospital Admission: A Long-term Follow-up Analysis

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Supplementary Tables

Supplementary Table 1. Prevalent post-COVID-19 complications previously reported in published analysis.

List of COVID-19 complications
Fatigue/asthenia
General malaise
Headaches
Low mood
Muscle aches and pains
Joint pains
Attention deficit
Chest pressure
Anxiety
Febricula
Cough
Memory lapses
Diarrhea
Palpitations
Dizziness
Tingling in extremity
Others (specify)

Supplementary Table 2. Pharmacological treatments at study entry

Pharmacological treatment		1.5 mg		2 mg		2.5 mg		Total	
		N	%	N	%	N	%	N	%
Has the patient received any pharmacological treatment?		7	77.8	12	85.7	10	90.9	29	85.3
Alimentary tract and metabolism	Drugs for acid-related disorders	2	22.2	3	21.4	1	9.1	6	17.6
	Drugs used in diabetes	2	22.2	6	42.9	4	36.4	12	35.3
	Vitamins	2	22.2	2	14.3	1	9.1	5	14.7
Anti-infectives for systemic use	Antibacterials for systemic use	1	11.1	1	7.1	.	.	2	5.9
	Antivirals for systemic use	1	9.1	1	2.9
Blood and blood-forming organs	Antithrombotic agents	3	33.3	3	21.4	.	.	6	17.6
	Antianemic preparations	.	.	1	7.1	.	.	1	2.9
Cardiovascular system	Beta blocking agents	1	11.1	1	7.1	.	.	2	5.9
	Cardiac therapy	1	11.1	1	7.1	.	.	2	5.9
	Lipid modifying agents	5	55.6	4	28.6	4	36.4	13	38.2
	Agents acting on the renin-angiotensin system	.	.	3	21.4	2	18.2	5	14.7
	Antihypertensives	.	.	1	7.1	.	.	1	2.9
	Calcium channel blockers	.	.	2	14.3	2	18.2	4	11.8
	Diuretics	.	.	2	14.3	.	.	2	5.9
Dermatologicals	Antifungals for dermatological use	1	11.1	1	7.1	.	.	2	5.9
Musculo-skeletal system	Anti-inflammatory and antirheumatic products	2	22.2	3	21.4	3	27.3	8	23.5
	Drugs for treatment of bone diseases	1	11.1	1	2.9
	Muscle relaxants	1	11.1	2	14.3	.	.	3	8.8
	Antigout preparations	1	11.1	2	14.3	1	9.1	4	11.8
Nervous system	Analgesics	2	22.2	4	28.6	2	18.2	8	23.5
	Psychoanaleptics	2	22.2	1	7.1	1	9.1	4	11.8

Pharmacological treatment		1.5 mg		2 mg		2.5 mg		Total			
		N	%	N	%	N	%	N	%		
Pharmacological treatment		Psycoleptics		1	11.1	1	7.1	.	.	2	5.9
		Anti-Parkinson drugs		.	.	1	7.1	.	.	1	2.9
Respiratory system		Antihistamines for systemic use		1	11.1	.	.	2	18.2	3	8.8
		Drugs for obstructive airway diseases		1	11.1	1	7.1	2	18.2	4	11.8
		Nasal preparations		.	.	1	7.1	.	.	1	2.9
Systemic hormonal preparations, excluding sex hormones and insulins		Corticosteroids for systemic use		2	22.2	2	14.3	.	.	4	11.8
		Thyroid therapy		1	11.1	2	14.3	1	9.1	4	11.8
Genitourinary system and hormones		Urologicals		.	.	2	14.3	2	18.2	4	11.8
		Other gynecologicals		1	9.1	1	2.9

Supplementary Table 3. Blood laboratory parameters at study entry

	1.5 mg N=9	2.0 mg N=14	2.5 mg N=11	Total N=34
Leukocytes-10⁹/L, median (IQR)	6.67 (5.45-7.7)	6 (5.36-7.88)	7.06 (5.54-7.78)	6.35 (5.45-7.72)
Lymphocytes-10⁹/L, median (IQR)	1.8 (1.51-2.3)	2 (1.63-2.56)	2.09 (1.56-2.6)	1.98 (1.56-2.56)
Neutrophils - 10⁹/L, median (IQR)	3.93 (3.00-4.37)	3.36 (2.90-4.10)	3.92 (3.10-4.72)	3.72 (3.00-4.52)
Hemoglobin - g/dL, median (IQR)	14.40 (13.80-15.00)	14.95 (14.50-15.90)	14.00 (13.40-15.40)	14.60 (13.80-15.40)
Platelets - 10⁹/L, median (IQR)	233 (188-337)	237 (172-278)	247 (215-316)	240.5 (182-309)
Ferritin (ng/mL), median (IQR)	153 (82-196)	183 (80.5-223)	173.3 (62.5-323.1)	172 (65-223)
Creatinine (mg/dL), median (IQR)	0.79 (0.74-1.00)	0.71 (0.65-0.89)	0.9 (0.66-0.98)	0.8 (0.66-0.93)
CRP (mg/dL), median (IQR)	1.10 (0.62-1.2)	1.79 (0.9-2.9)	1.9 (1.1-4.37)	1.36 (0.9-2.9)
ALT (ULN), median (IQR)	0.44 (0.39-0.57)	0.50 (0.45-0.78)	0.51 (0.41-0.67)	0.50 (0.41-0.67)
AST(ULN), median (IQR)	0.51 (0.46-0.52)	0.51 (0.45-0.78)	0.51 (0.48-0.59)	0.51 (0.46-0.61)
LDH (ULN), median (IQR)	0.73 (0.59-0.79)	0.78 (0.62-0.91)	0.94 (0.83-1.01)	0.82 (0.65-0.95)
D-dimer (ng/mL), median (IQR)	203 (156-247)	310 (215-408)	304 (200-500)	240.5 (201-343)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; dL: decilitre; IQR: interquartile range; IU: international unit; L: liter; LDH: lactate dehydrogenase; mg: milligram; N: number; ng: nanogram; x ULN: normalized value respect to the Upper Limit of the Normal range.

Supplementary Table 4. Summary of post-COVID-19 complications, regardless of relationship, by dose cohort and overall. Worst per patient.

Post-COVID-19 complications - Regardless of relationship	1.5 mg		2 mg		2.5 mg		Total	
	N	%	N	%	N	%	N	%
Alanine aminotransferase increased	1	11.1	1	2.9
Aspartate aminotransferase increased	1	11.1	1	2.9
Asthenia	2	22.2	8	57.1	5	45.5	15	44.1
Attention deficit	2	22.2	4	28.6	4	36.4	10	29.4
Blood triglycerides increased	1	11.1	1	7.1	.	.	2	5.9
COVID-19 pneumonia	1	11.1	1	2.9
Cough	1	11.1	3	21.4	2	18.2	6	17.6
Diarrhea	1	11.1	2	14.3	1	9.1	4	11.8
Dizziness	1	11.1	2	14.3	2	18.2	5	14.7
Fibrin D dimer increased	1	11.1	1	2.9
Gamma-glutamyltransferase increased	1	11.1	1	7.1	.	.	2	5.9
Interstitial lung disease	1	11.1	1	2.9
Joint pains	1	11.1	3	21.4	4	36.4	8	23.5
Low density lipoprotein increased	1	11.1	1	2.9
Memory lapses	1	11.1	6	42.9	3	27.3	10	29.4
Muscle aches and pains	2	22.2	3	21.4	2	18.2	7	20.6
Palpitations	2	22.2	1	7.1	1	9.1	4	11.8
Serum ferritin increased	1	11.1	1	7.1	.	.	2	5.9
Tingling in extremity	4	44.4	6	42.9	1	9.1	11	32.4
Anxiety	.	.	5	35.7	.	.	5	14.7
Back pain	.	.	1	7.1	.	.	1	2.9
Blood cholesterol increased	.	.	1	7.1	.	.	1	2.9
Chest pressure	.	.	1	7.1	.	.	1	2.9

Post-COVID-19 complications - Regardless of relationship	1.5 mg		2 mg		2.5 mg		Total	
	N	%	N	%	N	%	N	%
Chloasma	.	.	1	7.1	.	.	1	2.9
Epistaxis	.	.	1	7.1	.	.	1	2.9
Febricula	.	.	1	7.1	.	.	1	2.9
General malaise	.	.	3	21.4	2	18.2	5	14.7
Headaches	.	.	2	14.3	2	18.2	4	11.8
Libido decreased	.	.	1	7.1	.	.	1	2.9
Low mood	.	.	5	35.7	.	.	5	14.7
Male sexual dysfunction	.	.	1	7.1	.	.	1	2.9
Nasal congestion	.	.	1	7.1	.	.	1	2.9
Oropharyngeal pain	.	.	1	7.1	.	.	1	2.9
Tremor	.	.	1	7.1	.	.	1	2.9
Urinary tract infection	.	.	1	7.1	.	.	1	2.9
Alopecia	1	9.1	1	2.9
Diabetic metabolic decompensation	1	9.1	1	2.9
Dyspnea	1	9.1	1	2.9
Hyperglycaemia	1	9.1	1	2.9
Phlebitis	1	9.1	1	2.9

mg: milligram; N: number.

Supplementary Table 5. Summary of post-COVID-19 complications, regardless of relationship, by severity of disease. Worst per patient.

Post-COVID-19 complications - Regardless of relationship	Severity							
	Mild		Moderate		Severe		Total	
	N	%	N	%	N	%	N	%
Anxiety	2	40.0	2	10.5	1	10.0	5	14.7
Asthenia	3	60.0	7	36.8	5	50.0	15	44.1
Attention deficit	2	40.0	6	31.6	2	20.0	10	29.4
Chloasma	1	20.0	1	2.9
Diarrhea	2	40.0	1	5.3	1	10.0	4	11.8
General malaise	1	20.0	3	15.8	1	10.0	5	14.7
Joint pains	2	40.0	4	21.1	2	20.0	8	23.5
Low mood	1	20.0	2	10.5	2	20.0	5	14.7
Memory lapses	2	40.0	6	31.6	2	20.0	10	29.4
Muscle aches and pains	2	40.0	3	15.8	2	20.0	7	20.6
Oropharyngeal pain	1	20.0	1	2.9
Tingling in extremity	3	60.0	5	26.3	3	30.0	11	32.4
Alopecia	.	.	1	5.3	.	.	1	2.9
Back pain	.	.	1	5.3	.	.	1	2.9
Chest pressure	.	.	1	5.3	.	.	1	2.9
Cough	.	.	4	21.1	2	20.0	6	17.6
Diabetic metabolic decompensation	.	.	1	5.3	.	.	1	2.9
Dizziness	.	.	2	10.5	3	30.0	5	14.7
Dyspnea	.	.	1	5.3	.	.	1	2.9
Febricula	.	.	1	5.3	.	.	1	2.9
Headaches	.	.	3	15.8	1	10.0	4	11.8
Libido decreased	.	.	1	5.3	.	.	1	2.9

Post-COVID-19 complications - Regardless of relationship	Severity							
	Mild		Moderate		Severe		Total	
	N	%	N	%	N	%	N	%
Male sexual dysfunction	.	.	1	5.3	.	.	1	2.9
Palpitations	.	.	1	5.3	3	30.0	4	11.8
Phlebitis	.	.	1	5.3	.	.	1	2.9
Tremor	.	.	1	5.3	.	.	1	2.9
Urinary tract infection	.	.	1	5.3	.	.	1	2.9
Alanine aminotransferase increased	1	10.0	1	2.9
Aspartate aminotransferase increased	1	10.0	1	2.9
Blood cholesterol increased	1	10.0	1	2.9
Blood triglycerides increased	2	20.0	2	5.9
COVID-19 pneumonia	1	10.0	1	2.9
Epistaxis	1	10.0	1	2.9
Fibrin D dimer increased	1	10.0	1	2.9
Gamma-glutamyltransferase increased	2	20.0	2	5.9
Hyperglycemia	1	10.0	1	2.9
Interstitial lung disease	1	10.0	1	2.9
Low density lipoprotein increased	1	10.0	1	2.9
Nasal congestion	1	10.0	1	2.9
Serum ferritin increased	2	20.0	2	5.9

N: number.

Supplementary Table 6. Six-minute walk test by severity of disease.

Categorical Endpoints (6MWT)			Mild		Moderate		Severe		Total	
			N	%	N	%	N	%	N	%
Pre-TEST	Borg scale of dyspnea and fatigue at basal (1)	0	5	100.0	16	84.2	10	100.0	31	91.2
		1	.	.	1	5.3	.	.	1	2.9
		2	.	.	2	10.5	.	.	2	5.9
Post-TEST	Borg scale of dyspnea and fatigue after test (1)	0	1	20.0	5	26.3	5	50.0	11	32.4
		1	2	40.0	3	15.8	1	10.0	6	17.6
		1.5	1	10.0	1	2.9
		2	.	.	5	26.3	1	10.0	6	17.6
		2.5	1	20.0	1	2.9
		3	.	.	3	15.8	1	10.0	4	11.8
		4	.	.	1	5.3	.	.	1	2.9
		5	.	.	1	5.3	.	.	1	2.9
		6	1	20.0	1	5.3	.	.	2	5.9
		9	1	10.0	1	2.9
Results	Stopped or paused	No	5	100.0	18	94.7	9	90.0	32	94.1
		Yes	.	.	1	5.3	1	10.0	2	5.9
	Symptoms at the end of the exercise	None	5	100.0	19	100.0	10	100.0	34	100.0

(1) 0 (None); 0.5 (Very, very slight), 1 (Very slight); 2 (Slight); 3 (Moderate); 4 (Somewhat severe); 5 (Severe); 6 (Severe); 7 (Very severe); 8 (Very severe); 9 (Very very severe); 10 (Maximal).

6MWT: 6-minute walk test.

