Supplementary Material

Abbreviations:

6 MWD: 6-minute walk distance
AD-MSC: Adipose tissue derived mesenchymal stem cell
AE: adverse effects
BDI: Baseline Dyspnea Index
B-hCG: Beta human chorionic gonadotropin
CAT: COPD Assessment Test
COPD: chronic obstructive pulmonary disease
CRP: c-reactive protein
CSR: Clinical Study Report
DMC: Data Monitoring Committee
ELISA: enzyme-linked immunosorbent assay
FEV1: forced expiratory volume in one second
FVC: Forced vital capacity
GOLD: Global Initiative for Chronic Obstructive Lung Disease
ICH: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines
IFN-gamma: Interferon-gamma
IL-17: Interleukin-17
IL-6: Interleukin-6
IL-8: Interleukin-8
IRT: Interactive Response Technology
IWRS: Interactive Web Response System
mMRC: Modified Medical Research Council
MSCs: mesenchymal stem cells
QOL: quality of life
RT-PCR COVID-19: real time polymerase chain reaction for Coronavirus Disease from 2019
SAE: serious adverse event
SGOT : serum glutamic-oxaloacetic transaminase
SGPT: Serum Glutamic Pyruvic Transaminase.
SOBDA: Shortness of Breath with Daily Activities
SOC: standard of care
SOPs: standard operating procedures () and the
TDI: Transition Dyspnea Index
TLC: Total Lung Capacity
TNF-alpha: Tumor necrosis factor alpha
WBC: White blood cells

Table 1: PICOT strategy for this study

Acronym	Description	Explanation
P	Population	Patients with COPD GOLD 2 (50%≤FEV1<80% predicted) and Group D (two exacerbations or one hospitalization and mMRC>2 or CAT>10) from 35 to 60 years old.
I	Intervention	SOC plus AD-MSC IV infusion suspended in normal saline
C	Comparison	Patients under the SOC and IV placebo of 0.9% saline solution
O	Outcome	*FEV1-improvement (%) baseline (day 0) vs. day 90. **FVC, FEV1/FVC, TLC, 6MWD, number of hospitalizations or deaths in 2 years, SOBDA and QOL questionnaires, BDI/TDI.
T	Time	Follow-up for 2 years

COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: Modified Medical Research Council; CAT: COPD Assessment Test; AD-MSC: Adipose tissue derived mesenchymal stem cell; IV: intravenous; SOC: standard of care; FVC: Forced vital capacity; TLC: Total Lung Capacity; 6 MWD: 6-minute walk distance; SOBDA: Shortness of Breath with Daily Activities; QOL: quality of life; BDI: Baseline Dyspnea Index; TDI: Transition Dyspnea Index.

Table 2: Timeline

Timeline	Visit 1 Inclusion	Visit 2 Infusion	Visit 3 Infusion	Visit 4 Infusion	Visit 5 Day 30	Visit 6 Day 90	Visit 7 Day 180	Visit 8 Day 360	Visit 9 Day 720
Inclusion Criteria	x								
PE and MH	x	x	x	x	x	x	x	x	x
Intervention infusion		x	x	x					
6MWD	x					x	x	x	x
QOL questionnaire	x					x	x	x	x
SOBDA questionnaire	x					x	x	x	x
Baseline dyspnea index	x					x	x	x	x
Blood count/SGOT/ SGPT/CRP	x	x	x	x		x	x	x	x
RT-PCR COVID-19	x	x	x	x	x	x	x	x	x
Check adverse events		x	x	x	x	x	x	x	x
Spirometry	x				x	x	x	x	x
B-hCG (if female)	x	x	x	x					

PE: Physical exam; MH: medical history; FEV1: forced expiratory volume in one second; 6 MWD: 6-minute walk distance; QOL: quality of life; SOBDA: Shortness of Breath with Daily Activities; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; CRP: c-reactive protein; RT-PCR COVID-19: real time polymerase chain reaction for Coronavirus Disease from 2019; B-hCG: Beta human chorionic gonadotropin

Attachment 1: Symptoms diary

SYMPTOMS DIARY

Name:

Diary Receipt Date: __/__/____

Diary Return Date: __/__/____

How to fill

You will receive a symptom diary which is a calendar for you to fill in with the symptoms you experience over the course of the observation period, including need for hospitalization or use of additional therapies such as oxygen use.

Example:

Month: May Year: 2023

Month day	***Symptons***
1	*headache*
2	*headache*
3	*dyspnea requiring oxygen in the hospital*
4	*---*

Month: _____ Year: _____

Month Day	SYMPTOM
1	
2	

3	
4	
5	
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11	
12	
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