SUPPLEMENTARY APPENDIX

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1. PARTICIPATING INVESTIGATORS, FORCE STUDY GROUP

Primary Study Investigator / Coordinator	**Nicolas Schleinitz, Julien Carvelli**
Enrolling Center	**Investigators and Coordinators**
CHU Timone Marseille	**Nicolas Schleinitz, Julien Carvelli,** Marc Gainnier, Jérémy Bourenne, Amandine Bichon, Audrey Le Saux, Fouad Bouzana, Antoine Tilmont, Emi Cauchois, Charlotte Coularet, Nicolas Bruder, **Lionel Velly**, Mikael Ebbo, Véronique Veit, Estelle Jean, Pierre Simeone, Valéry Blasco, **Frédéric Vely, Christelle Piperoglou**, Bruno Coutard, Boris Pastorino, Maria Saba Villaroel, Emilie Garrido-Pradalie, Kahéna Amichi, Aurélie Larosa, Aurélie Blondelon, Imane Inal, Kahéna Amichi, Jean Dhorne, Frédérique Durieux, Julie Brunet, Anita Cohen, Bénédicte Deluca, Richard Malkoun
CHU Nice	**Jean Dellamonica**, Matthieu Buscot, Clément Saccheri, **Michel Carles**, Elisa Demonchy, Eric Cua, David Chirio, Johan Courjon, Karine Risso, Marie-Christine Rigault, Loïc Gazoppi, Virginie Salas, Nadège Bouskila, Irit Touitou, Sophie

	Breaud, Nihed Boughdiri, Guillaume Marrane
CHU Strasbourg	**Ferhat Meziani**, Hamid Merdji, Julie Helms, Alexandra Monier, Julien Demiselle, Louise-Marie Jandeaux, Antoine Studer, Hayat Allam, Léonie Thiebaut, Anne Hutt-Clauss
HIA Laveran Marseille	**Erwan Le Dault**, **Pierre-Yves Cordier**, Hélène Savini, Axelle Clerc, Sophie Spadoni, Emilie Javelle, Axelle Clerc, Nassima Chouaki-Benmansour, Patrick Le Garlantezec, Sarah Le Tohic
Hôpital Européen Marseille	**Jérôme Allardet-Servent,** Lucas Benarous, Corinne Madjarian, Assia Aouadenne-Mesbah, Amélie Rognon
Centre Hospitalier Victor Dupouy Argenteuil	**Megan Fraisse**, Gaétan Plantefeve, Nasro Benrezzak, Emeline Dubief, Olivia Chauvel, Charlotte Jamet
CHU Nîmes	**Saber Davide Barbar,** Audrey Ambert, Sophie Lloret, Loubna Elotmani, Grégory Dubois, Séverine Meyrieux, Laurie Barthelemi
Hôpital Saint Joseph Marseille	**Samuel Lehingue**, Antoine Poulet, Kristina Bezirganyan, Belkacem Asselate, Vincent Provitolo

AP-HP, Hôpital Saint Antoine	**Karine Lacombe**, Diane Bollens, Cyrielle Letaillandier, Christian Tran, Manuela Sebire, Julie Lamarque, Anne Deguenel-Nguyen
CHU Orléans	**Maxime Desgrouas,** Sophie Jacquier, Grégoire Muller, Anne Bretagnol, Armelle Mathonnet, Dalila Benzekri, François Barbier, Nay Mai-Anh, Isabelle Runge, Toufik Kamel, Lucie Muller, Sophie Tellec
CHU Nord Marseille	**Christophe Guervilly,** Laurent Papazian, Jean-Marie Forel, Céline Sanz, Camille Pinglis, Sabine Valera, Nathalie Colombini
CHU Bordeaux Saint-André	**Fabrice Camou**, Gaelle Mourissoux, Olivier Guisset, Nahéma Issa, Delphine Pedenon-Peyrichout, Jean Delaune, Claire Langlade, Stéphane Pedeboscq
CHU Lille	Julien Poissy, Saadalla Nseir, Laure Mariller, Claire Delcoutre, Sylvie Brice
AP-HP, Hôpital Bichat	Xavier Lescure, Valentina Isernia, Antoine Bachelard, Odile Fleurot, Sylvie Le Gac, Olivia Da Conceicao, Zelie Julia, Lynda Chalal, Lynda Oualit, Laura Kramer, Jennifer Le Grand
AP-HP, Henri Mondor Créteil	Jean-Daniel Lelievre, Sébastien Gallien, Christine Cotellon, William Vindrios,

	Giovanna Melica, Pierre-André Natella, Marion Bourhis, Alaki Thiemele, Delphine Lefebvre De Nailly
CHU Bordeaux Pellegrin	Denis Malvy, Arnaud Desclaux, Mailys Ducours, Pauline Perreau, Alexandre Boyer, Benjamin Clouzeau, Hoang-Nam Bui, Nicolas Bourgoin, Anna Kabala, Bellabes Ghezzoul, Vincent Servant, Sarah Djabarouti

2. SUPPLEMENTARY METHODS

2.1. Selection of Dose

The choice of study drug regimen (avdoralimab loading dose of 500 mg IV followed by a 200 mg maintenance dose IV every 48 h) was based on PK/PD data and safety data collected in previous phase I/II studies of avdoralimab (NN8210-3926, NN8210-3927 and STELLAR-001).

In the dose escalation study NN8210-3926 – covering doses from 0.02 to 10 mg/kg – a single IV dose of avdoralimab (15-minute infusion) resulted in full receptor saturation (>90%) on blood neutrophils, for doses of 0.3 mg/kg dose and above, for only one to two days. The maximal concentration obtained at the end of the infusion time was 20.1 µg/mL (CV=16.6%) at the 1 mg/kg dose, 73.5 µg/mL (CV=16.4%) at the 3 mg/kg dose, and 201 µg/mL (CV=23.2%) at the 10 mg/kg dose.

Based on non-clinical data (IC_{50} of 1-2 µg/mL in *in vitro* efficacy assays), the target concentration of avdoralimab for optimal pharmacological activity is 20 µg/mL. Furthermore, studies assessing the biodistribution of therapeutic antibodies have shown that their concentration in the lungs is one fifth that in the bloodstream.

The PK results from phase I study NN8210-3926 showed that a loading dose of avdoralimab >5 mg/kg of avdoralimab was required to obtain a blood concentration above 100 µg/mL for at least 24 h, to ensure full C5aR saturation and optimal pharmacological activity of avdoralimab in the target organ, the lung, from the first administration. Daily maintenance doses >1 mg/kg would be expected to maintain blood concentrations of the drug at levels >100 µg/mL throughout the treatment period.

Previous clinical studies have shown that body weight has no impact on the PK data or safety profile of avdoralimab. Accordingly, to limit dosing errors, the drug regimen was defined as a loading dose of 500 mg, followed by a maintenance dose of 200 mg every 48 h. The selected

doses are lower than those tested in previous phase I studies of avdoralimab (NN8210-3926, NN8210-3927 and STELLAR-001, highest tested dose of 15 mg/kg).

For a patient weighing 75 kg, the total dose administered during the first week of treatment, 1100 mg, is lower than the weekly dose administered in STELLAR-001 (at the highest dose of 15 mg/kg dose). Furthermore, the target concentration of 100 µg/mL is lower than the highest concentration attained at the highest doses in previous clinical studies.

2.2. Additional Statistical Analysis Details

Secondary outcomes included cumulative hospital discharge and cumulative ICU discharge. Both were analyzed by the Kaplan-Meier method with a two-tailed 5% Gray test. Hazard ratios (HRs) were generated with a Fine and Gray proportional hazards model to avoid competitive risk bias. Kaplan-Meier curves were generated for overall survival before day 28.

2.2.1. Subgroup Analysis

Analyses of the treatment effect, on the WHO ordinal scale at day 14 (≤4 vs >5) and mortality at day 28, in known COVID-19 prognostic factor subgroups were performed with a logistic regression model and the calculation of odds ratios (ORs). Forest plots were generated to visualize the treatment impact in each subgroup.

2.3. Exploratory Laboratory Analyses

2.3.1. ADA (anti-drug antibody) determinations

ADA analysis was performed by electrochemiluminescence, with a bridging format. Human serum was incubated with a mixture of biotinylated IPH5401 and SULFO-TAG-labeled IPH5401. In this assay, anti-IPH5401 antibodies, if present, form bridges between the two types of labeled IPH5401. The mixture is then transferred to a blocked MSD GOLD 96-well Streptavidin QuickPlex plate; the complexes bind to the plate via the biotinylated IPH5401.

Bound complexes are detected with the SULFO-TAG-labeled-IPH5401, which emits light upon electrochemical stimulation initiated at the electrode surface in the MSD GOLD 96-well Streptavidin QuickPlex plate during reading on an MSD Meso QuickPlex SQ 120 instrument.

2.3.2. Pharmacokinetic analysis (PK)

The analysis was performed by ELISA. The pre-diluted serum samples (1:100 minimal required dilution (MRD)) were incubated on an anti-IPH5401 idiotypic fragment mAb-coated 96-well plate. Bound IPH5401 antibodies were detected with a second biotinylated anti-IPH5401 idiotypic mAb and streptavidin conjugated to horseradish peroxidase (HRP), in a fluorescence reaction (Quantablu substrate). The reaction was stopped and fluorescence intensity was measured at 420 nm after excitation at 325 nm, with microtiter plate reader. The signal obtained by this method is proportional to the amount of IPH5401 present in the sample.

2.3.3. Soluble factor assessment

Human IL-6, CXCL9, CCL2, CCL4, CXCL8, TNF-α and IL-1β levels were analyzed with the U-PLEX kit supplied by MSD (U-PLEX 10-Assay, 96-Well SECTOR Plate, ref: N05235A-1), according to the manufacturer's instructions. The U-PLEX plate was loaded into an MSD instrument to measure the intensity of emitted light, which is proportional to the amount of analyte present in the sample. Circulating C5a-desArg levels were analyzed with the BD OptEIATM huC5a ELISA test.

2.3.4. Real-time RT-PCR

We dispensed 100 µL of water in an S-Block (Qiagen) loaded with VXL lysis buffer containing proteinase K and RNA carrier. RNA extraction was performed with the Qiacube HT automat and the QIAamp 96 DNA kit HT in accordance with the manufacturer's instructions. Viral RNA was detected by real-time RT-qPCR (SuperScript III, Thermo Fisher Scientific), with 5 µL of extracted RNA and 20 µL of RT-qPCR mix. Standard cycling conditions were used: 15 min at 50°C, 2 min at 95°C and 45 amplification cycles (95°C for 15 s followed by a read step of 45 seconds at 60°C). RT-qPCR was performed on a CFX-96 (Biorad) and analyzed with CFX manager software v3.1. Primers and probe sequences have been reported elsewhere (Pezzi. L et al., PMID: 32630601).

2.3.5. Seroneutralization assay

Experiments were performed in BSL3 facilities with a clinical isolate of SARS-CoV-2. Virus neutralization tests (VNTs) were performed as previously described (PMID: 30587193). Briefly, VNTs were performed in a 96-well plate, with Vero-E6 cells and a SARS-CoV-2 strain (Ref-SKU:026V-03883 isolated at Charité University, Berlin, Germany; EVA-GLOBAL H2020 project; Grant Agreement 871029). Two-fold serial dilutions of serum samples (final serum dilutions of 1/20 to 1/160) were mixed with 100 $TCID_{50}$ of SARS-CoV-2 and dispensed on the confluent cell monolayer. The plates were incubated for four days and examined for the presence (no neutralization) or absence (neutralization) of CPE under an inverted microscope.

2.3.6. ELISA assay

ELISA (Euroimmun®, Lübeck, Germany) was used to detect anti-SARS-CoV-2 antibodies (IgG) directed against the S1 domain of the Spike protein. In accordance with the manufacturer's instructions, a serum was considered to be ELISA-positive if the optical density

ratio ≥ 1.1, ELISA-indeterminate if between 0.8 and 1.1, and ELISA-negative if < 0.8, relative to an internal standard.

3. SUPPLEMENTARY TABLES

3.1. Table S1 WHO Clinical Progression Scale (COVID-19)

Patient State	Descriptor	Score
Uninfected	Uninfected, no viral RNA detected	0
Ambulatory, mild disease	Asymptomatic, viral RNA detected	1
	Symptomatic, independent	2
	Symptomatic, assistance needed	3
Hospitalized: moderate disease	Hospitalized, no oxygen therapy	4
	Hospitalized, oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $PaO_2/FiO_2 \geq 150$ or $SpO_2 \geq 200$	7
	Mechanical ventilation $PaO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $PaO_2/FiO_2 < 150$ and vasopressors, dialysis or ECMO	9
Dead	Dead	10

3.2. Table S2 Withdrawals from the trial on or before day 28

	Cohort 1		Cohort 2		Cohort 3	
	AVDORALIMAB *N* **= 50** **No. (%)**	**PLACEBO** *N* **= 49** **No. (%)**	**AVDORALIMAB** *N* **= 24** **No. (%)**	**PLACEBO** *N* **= 25** **No. (%)**	**AVDORALIMAB** *N* **= 29** **No. (%)**	**PLACEBO** *N* **= 30** **No. (%)**
Completed the study	37 (74)	40 (82)	16 (67)	22 (88)	16 (52)	20 (67)
Died	9 (18)	5 (10)	7 (29)	2 (8)	12 (41)	9 (30)
Premature discontinuation*	3 (6)	3 (6)	1 (4)	1 (4)	1 (3)	1 (3)
Lost to follow-up	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Withdrawal of consent	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

***** Patients who left the hospital before day 28. No day 28 data were available for these patients. We therefore telephoned these patients or their doctors for more information. In the absence of WHO scale data for D28, the last WHO scale score obtained was extrapolated.

3.3. Table S3 Characteristics of the Total Population at Baseline

	Patients ***n* = 207**
Demographic data	
Age, years	63.7 (10.4)
≥ 65 years (*n*,%)	112 (54)
Sex - M (*n*, %)	147 (71)
BMI (kg/m^2)	30.2 (5.4)
Risk factors	
Obesity (*n*,%)	93 (45)
Hypertension (*n*,%)	105 (51)
Diabetes (*n*,%)	75 (36)
Tobacco use (*n*,%)	33 (16)
Comorbidities (chronic diseases)	
Cardiovascular disease (*n*,%)	50 (24)
COPD (*n*,%)	16 (8)

Chronic kidney disease (*n*,%)	11 (5)
Cirrhosis (*n*,%)	2 (1)
Cancer (*n*,%)	22 (11)
COVID-19 diagnosis	
Positive SARS-CoV-2 RT-PCR (*n*,%) ‡	205 (99)
Viral load at inclusion (Ct)	25.7 (6.1)
Time from first signs to inclusion (days)	10 (3.6)
Time from hospitalization to inclusion (days)	2.2 (1.9)
COVID-19 severity at inclusion	
WHO Scale (*n*,%)	
5: Hospitalized, oxygen by mask or nasal prongs	19 (9)
6: Hospitalized, oxygen by NIV or HFO	104 (50)
7: IMV and P/F ratio ≥ 150	15 (7)
8: IMV and P/F ratio < 150 or vasopressors	37 (18)
9: IMV and P/F ratio < 150 and vasopressors, RRT or ECMO	32(16)
SOFA	5.4 (2.5)

Illness severity on Simplified Acute Physiology Score 2 (IGS2) ‖	36.8 (11.6)
P/F ratio – ICU patients (HFO/NIV or IMV)	125 (56)
FiO_2 – ICU patients (HFO/NIV or IMV)	74 (22)
PEEP (cmH_2O) – IMV patients	12.4 (2.8)
Tidal volume (mL) – IMV patients	416 (48)
Prone positioning (*n*,%)	95 (46)
Number of prone positioning sessions (*n*)	2.8 (2.8)
At least one EMCO session (*n*)	10 (5)
Lesions on CT-scans, *n*(%)	
Limited	11 (5)
Moderate	57 (28)
Severe	55 (27)
CT-scan not done	84 (41)
Prior treatments, *n*(%)	
Antibiotics	21 (10)
Dexamethasone	130 (63)
Methylprednisolone	12 (6)
Concomitant drugs, *n*(%)	

Antibiotics	75 (36)
Dexamethasone	176 (85)
Methylprednisolone	49 (24)
Number of perfusions (avdoralimab or placebo)	5.9 (2.2)

3.4. Table S4 Biological Parameters at Baseline

	Cohort 1		Cohort 2		Cohort 3	
	AVDORALIMAB ***N* = 50**	**PLACEBO** ***N* = 49**	**AVDORALIMAB** ***N* = 24**	**PLACEBO** ***N* = 25**	**AVDORALIMAB** ***N* = 29**	**PLACEBO** ***N* = 30**
Neutrophils (10^9/L)	7.4 (5.7-9.8)	6.1 (4.9-7.5)	5.7 (4.2-8.2)	8.3 (6.6-9.0)	8.9 (6.7-12.1)	8.7 (5.8-11.1)
Lymphocytes (10^9/L)	0.7 (0.5-0.9)	0.7 (0.5-1.3)	0.7 (0.4-1.00)	0.8 (0.5-1.1)	0.7 (0.5-1.1)	0.6 (0.4-0.9)
Hemoglobin (g/L)	129 (115-138)	130 (122-141)	122 (111-130)	121 (114-138)	122 (112-130)	118 (111-127)
Platelets (10^9/L)	274 (207-378)	267 (210-339)	236 (199-339)	274 (187-336)	258 (213-327)	266 (194-336)
TP (%)	91 (83-94)	89 (80-99)	92 (78-96)	83 (77-91)	95 (82-100)	88 (76-95)
Fibrinogen (g/L)	6.5 (5.9-7.3)	6.6 (5.9-7.5)	7.3 (5.7-7.8)	7.7 (6.7-7.9)	6.6 (6.0-7.7)	6.8 (5.8-7.5)
Creatinine (µmol/L)	64 (54-75)	65 (55-81)	72 (63-84)	72 (63-112)	82 (67-114)	74 (58-88)
Bilirubin (µmol/L)	8.8 (7.0-10.4)	8 (6.0-9.6)	8.4 (5.7-10.2)	10 (7.0-13.0)	7.5 (5.9-9.0)	7.6 (6.0-9.9)
ASAT (IU/L)	40 (33-60)	39 (32-58)	45 (38-54)	56 (36-70)	53 (46-94)	48 (34-62)
ALAT (IU/L)	40 (30-57)	37 (26-70)	38 (25-57)	50 (27-75)	52 (30-69)	48 (26-76)
C-reactive protein (mg/L)	96 (53-142)	76 (44-163)	118 (59-252)	114 (56-243)	93 (56-173)	121 (55-168)
CPK (IU/L)	90 (48-134)	77 (56-120)	45 (34-110)	116 (42-159)	170 (29-387)	98 (48-392)
LDH (IU/L)	470 (392-691)	410 (358-570)	368 (340-428)	412 (368-504)	445 (362-587)	462 (418, 630)

Ferritin (ng/mL)	1041 (508-1498)	597 (402-1188)	1208 (462-1472)	1870 (1347-2154)	1527 (1228-1944)	1442 (1310-2928)
IL-6 (pg/mL)*	11 (4-36)	9 (4-36)	16 (8-47)	16 (4-66)	12 (4-24)	42 (15-103)
sC5a (mg/mL)*	106 (60-167)	86 (72-332)	69 (57-105)	91 (70-125)	95 (38-197)	71 (61-140)

* IL-6 and C5a determinations were performed only on patients enrolled at clinical sites in Marseille (*n*=109); the results are presented as medians (IQR).

3.5. Table S5 Efficacy Analysis on the m-ITT population

	COHORT 1		COHORT 2		COHORT 3	
Outcomes	**AVDORALIMAB** ***N* = 45**	**PLACEBO** ***N* = 44**	**AVDORALIMAB** ***N* = 24**	**PLACEBO** ***N* = 25**	**AVDORALIMAB** ***N* = 29**	**PLACEBO** ***N* = 30**
Improvement in WHO scale score						
D14	1.2 (2.3)	1.3 (2.2)	0.7 (2.6)	1.4 (1.7)	1.2 (2.5)	1.4 (1.9)
Difference of the means (avdoralimab vs. placebo) (95% CI)	-0.1 (-1.1,0.8)		-0.7 (-2,0.6)		-0.2 (-1.3;1)	
p value†	*0.62*		*0.862*		*0.61*	
D28	1.7 (2.7)	1.9 (2.2)	0.5 (3.1)	2.7 (2.1)	1.7 (3)	1.9 (2.6)
Difference of the means (avdoralimab vs. placebo) (95% CI)	-0.2 (-1.2,0.9)		-2.2 (-3.7,-0.6)		-0.3 (-1.8,1.2)	
p value†	*0.63*		*0.99*		*0.65*	
VFD (ventilator-free days)						

	COHORT 1		COHORT 2		COHORT 3	
Outcomes	**AVDORALIMAB** ***N* = 45**	**PLACEBO** ***N* = 44**	**AVDORALIMAB** ***N* = 24**	**PLACEBO** ***N* = 25**	**AVDORALIMAB** ***N* = 29**	**PLACEBO** ***N* = 30**
VFD14	NA	NA	6.9 (6.7)	7.1 (6.4)	3.2 (4.4)	2.4 (4.2)
Difference of the means (avdoralimab vs. placebo) (95% CI)	-	-	-0.3 (-4,3.5)		0.8 (-1.4,3.1)	
p value†	-	-	*0.55*		*0.23*	
VFD28	NA	NA	12.1 (13.6)	18.4 (10.4)	8.8 (11.1)	7.7 (10.3)
Difference of the means (avdoralimab vs. placebo) (95%CI)	-	-	-6.3 (-13.2,0.7)		1 (-4.5,6.6)	
p value†	-	-	*0.96*		*0.36*	
Mortality at D28, *n*(%)	6 (12)	3 (6)	4 (17)	2 (8)	10 (35)	7 (23)
p value†	*0.32*		*0.36*		*0.35*	
Adverse events						
Sepsis	6 (12)	8 (16)	6 (24)	7 (29.2)	10 (35)	10 (33)
Related AE	9 (18)	13 (27)	8 (32)	9 (37.5)	7 (24)	9 (30)

	COHORT 1		COHORT 2		COHORT 3	
Outcomes	**AVDORALIMAB** ***N* = 45**	**PLACEBO** ***N* = 44**	**AVDORALIMAB** ***N* = 24**	**PLACEBO** ***N* = 25**	**AVDORALIMAB** ***N* = 29**	**PLACEBO** ***N* = 30**
Serious AE	18 (36)	13 (27)	13 (52)	11 (46)	19 (66)	20 (67)

† In a one-tailed Student's *t* test (avdoralimab – placebo > 0)

3.6. Table S6 Efficacy Analysis on the Per-Protocol population

	Cohort 1		**Cohort 2**		**Cohort 3**	
Outcomes	**AVDORALIMAB** ***N* = 47**	**PLACEBO** ***N* = 45**	**AVDORALIMAB** ***N* = 24**	**PLACEBO** ***N* = 24**	**AVDORALIMAB** ***N* = 29**	**PLACEBO** ***N* = 30**
Improvement in WHO scale score						
D14	1.1 (2.4)	1.4 (2.2)	0.9 (2.7)	1.3 (1.7)	1.2 (2.5)	1.4 (1.9)
Difference of the means (avdoralimab vs. placebo) (95% CI)	-0.3 (-1.3,0.6)		-0.4 (-1.7,0.9)		-0.2 (-1.3,1)	
p value§	*0.76*		*0.72*		*0.61*	
D28	1.5(2.7)	2 (2.1)	0.9 (3)	2.7 (2.2)	1.7 (3)	1.9 (2.6)
Difference of the means (avdoralimab vs. placebo) (95% CI)	-0.5 (-1.5,0.5)		-1.8 (-3.3,-0.2)		-0.3 (-1.8,1.2)	
p value§	*0.83*		*0.99*		*0.65*	
VFD (ventilator-free days)						
VFD14	NA	NA	6.8 (6.7)	6.9 (6.4)	3.2 (4.4)	2.4 (4.2)

Difference of the means (avdoralimab vs. placebo) (95% CI)	-	-	-0.1 (-3.9,3.7)		0.8 (-1.4,3.1)	
p value§	-	-	*0.53*		*0.23*	
VFD28	-	-	13.2 (13.6)	18.1 (10.5)	8.8 (11.1)	7.7 (10.3)
Difference of the means (avdoralimab vs. placebo) (95% CI)	-	-	-4.9 (-12,2.2)		1 (-4.5,6.6)	
p value§	-	-	*0.91*		*0.36*	
Mortality at D28, *n* (%)	6 (13)	3 (7)	3 (13)	2 (8)	10 (35)	7 (23)
p value†	*0.3*		*0.6*		*0.4*	
Cumulative incidence of hospital discharges, (95% CI)						
D7	10.6 (3.9,21.4)	15.6 (6.8,27.7)	4.2(0.3,18)	4.2(0.3,18)	0	0
D14	46.8 (32,60.3)	57.8 (41.8,70.8)	33.3 (15.5,52.3)	20.8 (7.3,39)	13.8 (4.2,29)	13.3 (4.1,28.1)
D21	61.7 (46,74)	66.7 (50.5,78.6)	45.8 (25.0,64.5)	50 (28.4,68.3)	31 (15.2,48.3)	16.7 (5.9,32.1)
D28	63.8 (48.1,75.9)	75.6 (59.7,85.9)	50 (28.4,68.3)	54.2 (31.9,72)	34.5 (17.8,51.9)	30 (14.7,47)
p-value†	*0.26*		*0.07*		*0.50*	
HR‡	*0.76 (0.49-1.16)*		*0.62 (0.32-1.19)*		*0.84 (0.44-1.58)*	
Cumulative incidence of ICU discharges, (95% CI)						

D7	38.2 (22.1,54.3)	37.5 (21,54)	29.2 (12.6,48)	25 (9.9,43.5)	10.3 (2.5,24.6)	10 (2.5,23.9)
D14	58.8 (40.1,73.5)	65.6 (46,79.6)	45.8 (25,64.5)	41.7 (21.8,60.5)	34.5 (17.9,51.8)	23.3 (10.1,39.7)
D21	67.6 (48.6,80.9)	75 (55.3,86.9)	50 (28.4-68.3)	62.5 (39.4-78.9)	34.5 (17.9,51.8)	26.7 (12.4,43.3)
D28	70.6 (51.5,83.3)	81.3 (61.7,91.5)	50 (28.4,68.3)	75 (51.1,88.4)	37.9 (20.5,55.3)	36.7 (19.8,53.7)
p-value†	*0.45*		*0.06*		*0.67*	
HR‡	*0.79 (0.47-1.31)*		*0.6 (0.31-1.17)*		*0.87 (0.46-1.62)*	
SOFA score at D14	n = 11	n = 11	n = 9	n = 10	n=13	n=18
SOFA score at D14, mean (SD)	6.3 (4.2)	5.5 (1.9)	6. 6(3.2)	5.4 (2.8)	7.9(3.71)	5.5(3.09)
Difference of the means	0.7 (-2.2,3.4)		1.2 (-1.8,4.1)		2.4 (-0.1,4.9)	
p-value§	*0.7*		*0.79*		*0.97*	

† In a two-tailed Gray test
‡ Fine and Gray proportional hazards model
§ One-tailed Student's *t* test

3.7. Table S7: Other Prespecified Secondary Outcomes: Cumulative Hospital and ICU Discharges and SOFA Score Improvement at D14 (ITT population)

	Cohort 1		**Cohort 2**		**Cohort 3**	
	AVDORALIMAB *N* **= 50** **No. (%)**	**PLACEBO** *N* **= 49** **No. (%)**	**AVDORALIMAB** *N* **= 24** **No. (%)**	**PLACEBO** *N* **= 25** **No. (%)**	**AVDORALIMAB** *N* **= 29** **No. (%)**	**PLACEBO** *N* **= 30** **No. (%)**
FROM START OF TREATMENT TO HOSPITAL DISCHARGE						
Hospital discharges	41 (82)	44 (90)	17 (71)	23 (92)	17 (59)	21 (70)
Deaths	9 (18)	5 (10)	7 (29)	2 (8)	12 (41)	9 (30)
Cumulative incidence of hospital discharges, (95% CI)						
D7	10 (3.6,20.2)	14.3 (6.2,25.6)	4.2 (0.3,18)	4 (0.3,17.4)	0	0
D14	44 (29.9,57.2)	55.1 (40,67.9)	29.2 (12.6,48)	24 (9.5,42.1)	13.8 (4.2,29)	13.3 (4.1,28.1)
D21	62 (46.9,74)	63.3 (47.9-75.2)	41.7 (21.7,60.6)	52 (30.5,69.7)	31 (15.2,48.3)	16.7 (5.9,32.1)
D28	64 (48.8-75.7)	73.5 (58.3-83.8)	45.8 (25,64.5)	56 (34,73.2)	34.5 (17.8,51.9)	30 (14.7,47)
p-value†	*0.33*		*0.03*		*0.5*	
HR‡	0.77 (0.51-1.16)		0.53 (0.27-1.03)		0.84 (0.44-1.58)	
FROM START OF TREATMENT TO ICU DISCHARGE						
ICU discharges	30 (60)	31 (63)	17 (71)	23 (92)	17 (59)	21 (70)

Deaths	8 (16)	4 (8)	7 (29)	2 (8)	12 (41)	9 (30)
Cumulative incidence of ICU discharges, (95% CI)						
D7	36.8 (21.8,52)	34.3 (19.1,50)	25 (9.9,43.6)	28 (12.2,46.3)	10.3 (2.5,24.6)	10 (2.5,23.9)
D14	57.9 (40.4,71.9)	62.9 (44.3,76.7)	41.7 (21.7,60.6)	44 (24.1,62.3)	34.5 (17.9,51.8)	23.3 (10.1,39.7)
D21	68.4 (50.6,80.9)	71.4 (52.8,83.8)	45.8 (25,64.5)	64 (41.4,79.8)	34.5 (17.9,51.8)	26.7 (12.4,43.3)
D28	73.7 (56,85.2)	77.1 (58.6,88.2)	45.8 (25,64.5)	76 (52.8,88.9)	37.9 (20.5,55.3)	36.7 (19.8,53.7)
p-value†	0.69		0.02		0.67	
HR‡	0.84 (0.52-1.35)		0.52 (0.27-1.02)		0.87 (0.46-1.62)	
SOFA score at D14	*n*=13	*n*=13	*n*=10	*n*=10	*n*=13	*n*=18
SOFA score at D14, mean (SD)	5.8 (4.3)	5.5 (1.8)	6.8 (3.2)	5.4 (2.8)	7.9(3.71)	5.5(3.09)
Difference of the means	0.31 (-2.33,2.95)		1.4 (-1.4,4.2)		2.42 (-0.1,4.9)	
p-value§	*0.59*		*0.86*		*0.97*	

† Two-tailed Gray test
‡ Fine and Gray proportional hazards model
§ One-tailed Student's *t* test

3.8. Table S8. All Recorded Adverse Events (AEs), by Cohort (Safety Population)

	Cohort 1		Cohort 2		Cohort 3	
	AVDORALIMAB ***N* = 50** **No. (%)**	**PLACEBO** ***N* = 49** **No. (%)**	**AVDORALIMAB** ***N* = 24** **No. (%)**	**PLACEBO** ***N* = 25** **No. (%)**	**AVDORALIMAB** ***N* = 29** **No. (%)**	**PLACEBO** ***N* = 30** **No. (%)**
GENERAL DATA						
At least one AE	25 (50)	26 (53)	16 (64)	13 (54)	24 (83)	25 (83)
At least one related AE	9 (18)	13 (27)	8 (32)	9 (38)	7 (24)	9 (30)
At least one AE of grade 3 or higher	21 (42)	15 (31)	12 (48)	11 (46)	19 (66)	21 (70)
At least one serious AE (SAE)	18 (36)	13 (27)	13 (52)	11 (46)	19 (66)	20 (67)
At least one fatal AE	9 (18)	5 (10)	7 (28)	2 (8)	12 (41)	9 (30)
MAIN AEs						
Allergy	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)	1(3)
Sepsis	6 (12)	8 (16)	6 (24)	7 (29)	10 (35)	9 (30)
Cardiac disorders*	3 (6)	0 (0)	3 (12)	0 (0)	4 (14)	3 (10)

Hepatobiliary disorders*	4 (8)	2 (4)	0 (0)	0 (0)	0 (0)	1 (3)
Acute kidney injury*	2 (4)	3 (6)	4 (16)	1 (4)	5 (17)	2 (7)
Thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	2 (7)

*Full AE details are listed in the final report generated by the IDDI

3.9. Table S9: Causes of Death

	Cohort 1		Cohort 2		Cohort 3	
	AVDORALIMAB	**PLACEBO**	**AVDORALIMAB**	**PLACEBO**	**AVDORALIMAB**	**PLACEBO**
	***N* = 9**	***N* = 5**	***N* = 7**	***N* = 2**	***N* = 12**	***N* = 9**
COVID-19-related death	**5**	**2**	**5**	**1**	**5**	**7**
Sepsis or bacterial secondary infection	**3**	**2**	**1**	**0**	**6**	**2**
Endocarditis	*1*	*0*	*0*	*0*	*0*	*0*
Ventilator-acquired pneumonia	*2*	*2*	*1*	*0*	*6*	*2*
Cardiac arrest or failure	**1**	**0**	**1**	**0**	**0**	**0**
Acute kidney injury	**0**	**1**	**0**	**0**	**0**	**0**
Stroke	**0**	**0**	**0**	**1**	**0**	**0**
Pneumothorax	**0**	**0**	**0**	**0**	**1**	**0**

3.10. Table S10: Viremia, Serology and Neutralizing Antibodies

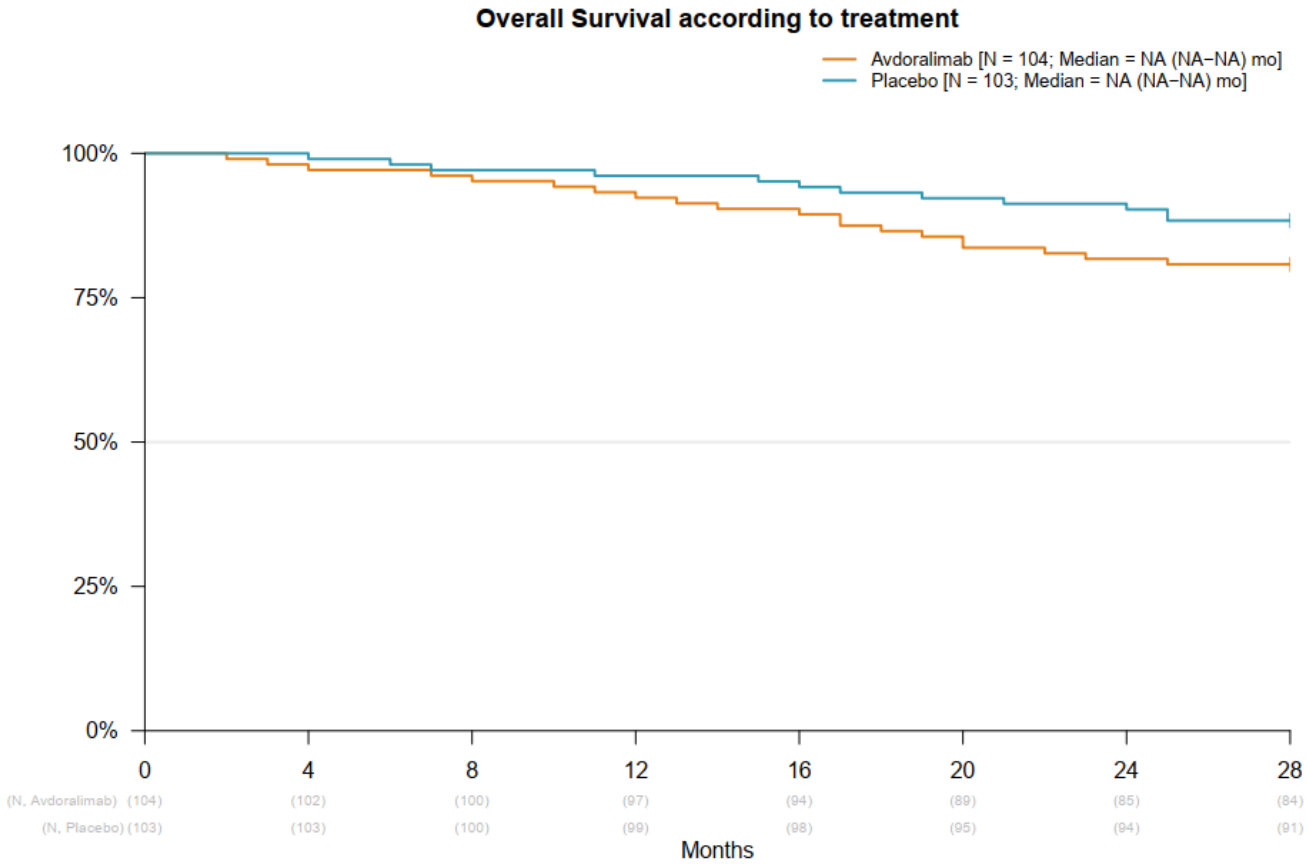
	AVDORALIMAB **D0 : *N* = 54** **> D7: *N* = 49**	**PLACEBO** **D0 : *N* = 54** **> D7: *N* = 49**
POSITIVE VIREMIA (RT-PCR on blood samples)		
D0	16 (30%)	12 (22%)
> D7	1 (2.0%)	0 (0%)
POSITIVE SEROLOGY (circulating IgG against Spike)		
D0	32 (59%)	32 (59%)
> D7	48 (98%)	49 (100%)
BLOOD NEUTRALIZING ANTIBODIES		
D0	48 (89%)	47 (87%)
> D7	49 (100%)	49 (100%)

3.11. Table S11: Study Drug Exposure, by Cohort

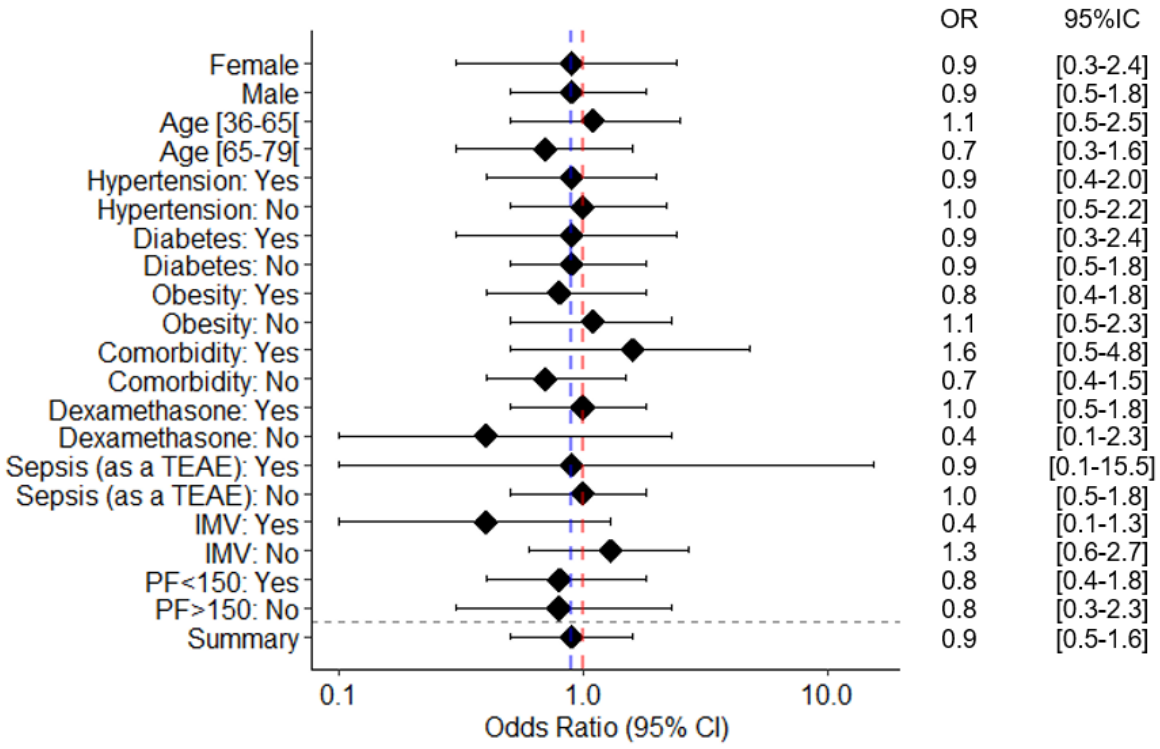
	Cohort 1		Cohort 2		Cohort 3	
	AVDORALIMAB *N* **= 50** **No. (%)**	**PLACEBO** *N* **= 49** **No. (%)**	**AVDORALIMAB** *N* **= 25** **No. (%)**	**PLACEBO** *N* **= 24** **No. (%)**	**AVDORALIMAB** *N* **= 29** **No. (%)**	**PLACEBO** *N* **= 30** **No. (%)**
1 dose	1 (2)	0 (0)	2 (8)	0 (0)	2 (7)	1 (3)
2 doses	2 (4)	3 (6)	1 (4)	3 (13)	1 (3)	0 (0)
3 doses	4 (8)	12 (25)	0 (0)	1 (4)	2 (7)	3 (10)
4 doses	12 (24)	6 (12)	3(12)	3 (12)	4 (14)	1 (3)
5 doses	5 (10)	7 (14)	4 (16)	4 (17)	1 (3)	1 (3)
6 doses	7 (14)	4 (8)	1 (4)	1 (4)	1 (3)	1 (3)
7 doses	1 (2)	1 (2)	2 (8)	0 (0)	3 (10)	4 (13)
8 doses	18 (36)	16 (33)	12 (48)	12 (50)	15 (52)	19 (63)
Number of doses administered, mean (SD)	**5.7 (2.1)**	**5.3 (2.2)**	**6.1 (2.3)**	**6 (2.3)**	**6.1 (2.4)**	**6.8 (2)**

4. SUPPLEMENTARY FIGURES

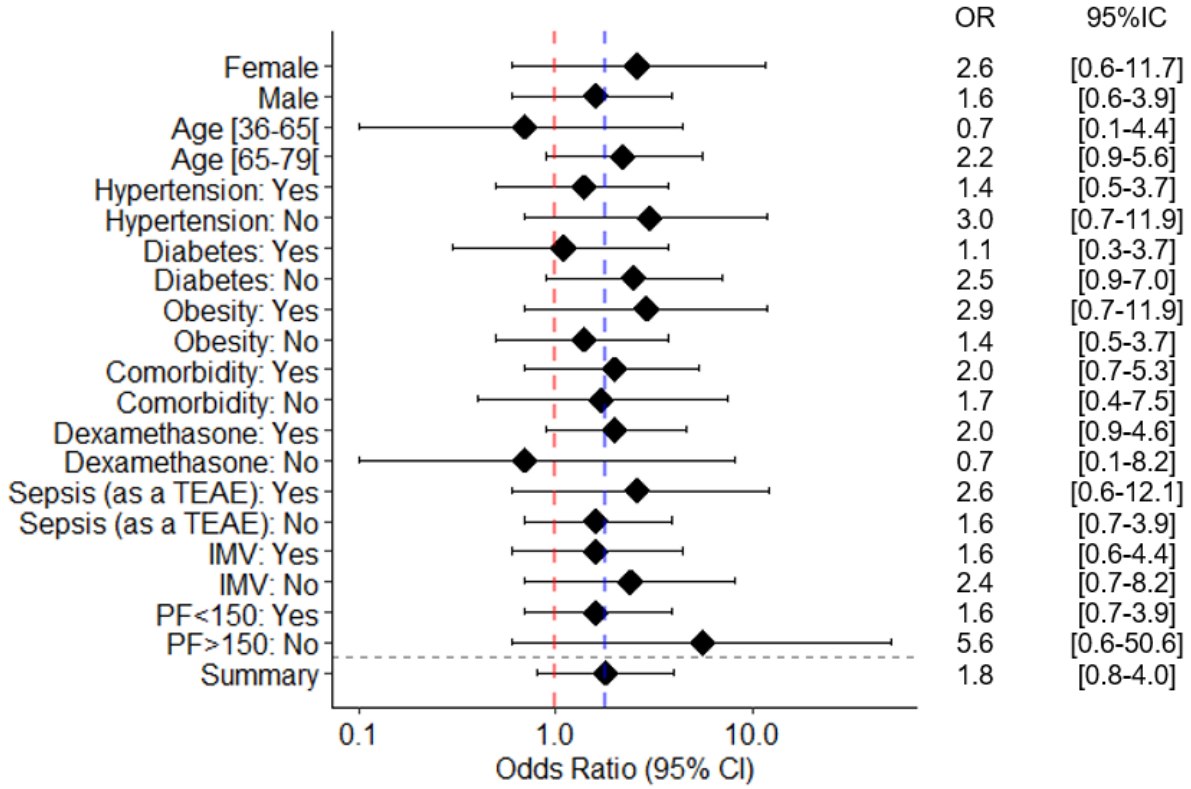
4.1. Figure S1: Kaplan-Meier Plot for overall survival at D28



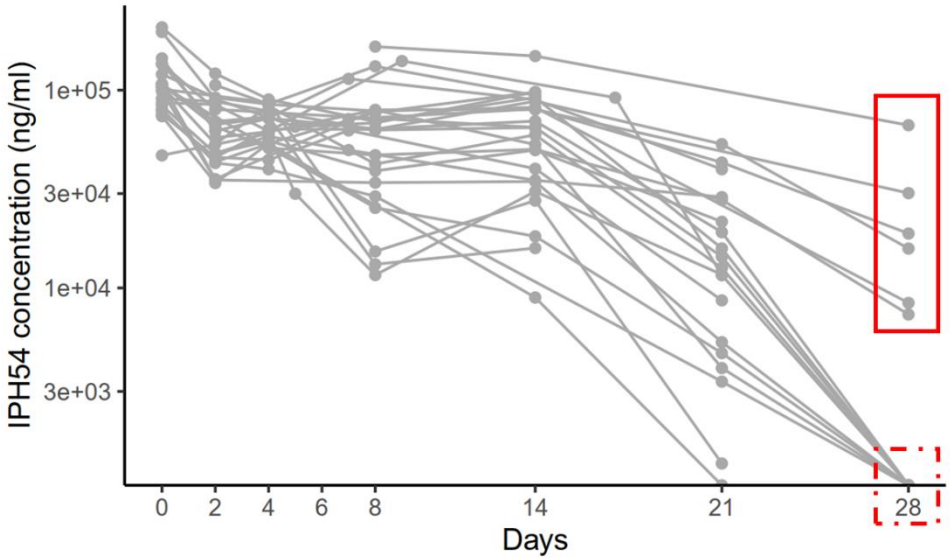
4.2. Figure S2: Subgroup Analyses – WHO Score on Day 14



4.3. Figure S3: Subgroup Analyses – Death by Day 28

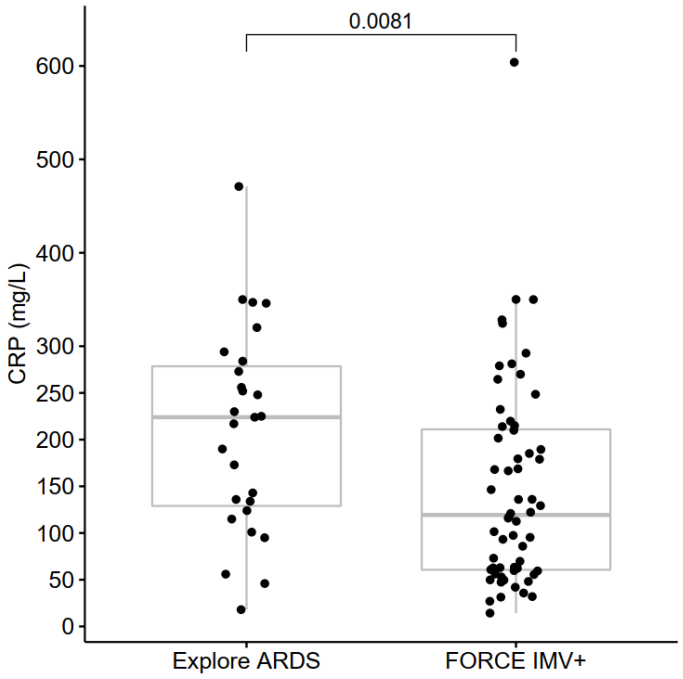


4.4. Figure S4: PK curves



PK Analysis of the patients who received eight doses of avdoralimab. All patients with detectable high levels of avdoralimab in the bloodstream (*n*=6, full red line) were discharged from hospital. One of these patients had sepsis during hospitalization. For the patients with no detectable avdoralimab in the bloodstream at the end of the study (D28) (*n*=10, dotted red line), five had died and five had sepsis.

4.5. Figure S5: CRP levels in COVID patients from the first wave compared to those in the FORCE patients (IMV+ patients).



5. PROTOCOL DETAILS

This supplement contains the following items:

1. Summary of original protocol with statistical analysis plan
2. Summary of final protocol with statistical analysis plan
3. Summary of main protocol amendments

ORIGINAL PROTOCOL - SUMMARY

Title: A randomized, double-blind study, placebo controlled, multicenter study to evaluate the safety and efficacy of Avdoralimab (IPH54) in patients with severe COVID-19 pneumonia

Protocol Number: 2020-21

Version Number: 1.0

EudraCT Number: 2020-001686-36

Compound: Avdoralimab (IPH5401)

Study Phase: II

Principal Investigator: Nicolas Schleinitiz

Sponsor: Assistance Publique Hopitaux de Marseille (AP-HM)

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1. Target Population

Inclusion Criteria

Participants are eligible to be included in the study if they are aged between 18 and 80 years at the time of randomization. They will be enrolled in one of 2 cohorts:

Cohort 1: Patients with severe COVID-19 pneumonia:

- Requiring oxygen therapy ≥ 5L/min to maintain SpO2 > 93% (conventional oxygen therapy and/or HFO).
- With presence of a positive SARS-Cov-2 RT-PCR at the time of or prior to enrollment; or presence of a radiographic imaging typical of COVID-19 (Chest CT scan showing peripheral ground glass opacity)

Cohort 2: Patients with severe COVID-19 pneumonia admitted to the ICU:

- On IMV, with a PaO2/FiO2 < 300mmHg for over 24hours.
- With presence of a positive SARS-Cov-2 RT-PCR at the time of or prior to enrollment; or presence of a radiographic imaging typical of COVID-19 (Chest CT scan showing peripheral ground glass opacity)

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding
- Refusing to participate to the study
- Currently participating in other drug clinical trial or was part of a clinical trial in the last 2 weeks preceding randomization
- Presenting active bacterial or fungal sepsis at enrollment
- Having contraindications preventing admission to the ICU

2. Study Endpoints

Primary Efficacy Objectives

The primary efficacy objectives of the study FORCE are to improve:

- **In Cohort 1:** The hospital discharge rate by day 14 of alive patients in patients treated with avdoralimab versus placebo
- **In Cohort 2:** The number of ventilator-free days at day 28 (VFD28) in ICU patients on IMV or HFO in patients treated with avdoralimab versus placebo

The number of participants required for this study is calculated based on these primary efficacy objectives.

Secondary Efficacy Objectives

The secondary efficacy objectives of the study FORCE are to:

- Improve the WHO Score at day 14 and day 28
- Improve the number of VFD at days 14 and 28 in ICU patients
- Lower the mortality at day 28
- Improve the SOFA Score at day 14 in ICU patients
- Evaluate the safety of avdoralimab as assessed by the number of adverse events occurring in patients treated with avdoralimab versus placebo

VFD14 and VFD28 are assessed at days 14 and 28 post enrollment, respectively. VFD is defined as the number of days during which the patients are alive and have had complete IMV weaning for at least 48h. Patients who die by day 28 are considered to have had zero ventilator-free days, even if they had IMV weaning for a few days. Short IMV weaning periods (of less than 24h) for surgical procedures are not taken into consideration. If a patient has repeated IMV weaning periods longer than 48h, VFD28 is calculated starting from the last weaning period and until day 28.

3. Study Intervention

Measures to Minimize Bias: Randomization and Blinding

This is a randomized, double-blind, placebo controlled study. The randomization process will be performed by means of a secure web-based case report form system (eCRF, RedCap). After initial informed consent is obtained, each patient will be assigned an identification number ensuring anonymity (trial site number – patient inclusion number). Once eligibility is established, the study site will proceed to randomization and treatment assignment via RedCap.

Patients will be randomly assigned at a 1:1 ratio to receive either avdoralimab and best supportive care or placebo and best supportive care. Randomization will occur in blocks of 4 to ensure a balanced assignment of placebo and avdoralimab in each trial site; and will be stratified according to trial site and admission type (ICU or general hospital).

Randomization will result in the attribution of a number (1 – 208) to each enrolled patient. Only trial site pharmacists will be aware of the correspondence between a patient's identification number and their assigned treatment. All other trial site personnel and patients will be blinded to treatment assignment during the study. The sponsor and its agents will also be blinded to treatment assignment.

Study Intervention Administered

Avdoralimab is a fully human Fc-silent monoclonal antibody that prevents the binding of C5a to its receptor C5aR1. Avdoralimab will be supplied by Innate Pharma as a lyophilized powder, in 10mL vials containing 100mg each, for reconstitution with 1,1 mL of sterile water for injection. The reconstituted solution has a pH of 6,5; and contains 100mg/ml of IPH5401 (active ingredient), 5,33mg of Histidine, 86,0 mg/mL of sucrose and 0,34/mL of polysorbate 80. The maximum amount of solution that can be withdrawn from each vial is 1mL.

Patients assigned to the treatment arm will receive a 500 mg loading dose of avdoralimab on day 1, followed by a 200 mg maintenance dose administered by IV infusion every 48hours for 14 days (maximum of 8 injections); independently from the patient's body weight. Treatment will be stopped prior to day 14 if oxygen therapy is no longer needed. Patients assigned to the placebo arm will receive normal saline in 100mL infusion bags.

Depending on the assigned treatment arm (experimental or placebo), avdoralimab will either be added to the infusion bag (500mg or 200mg doses) or not (placebo):

- For the 500mg loading dose, 5mL of the reconstituted avdoralimab solution will be added to the 100mL infusion bag.
- For the 200mg loading dose, 2mL of the reconstituted avdoralimab solution will be added to the 100mL infusion bag.

The entire 100mL-content of the infusion bag must be administered, and must be completed in 1 hour.

A full manual (Trial Material Manual, TMM) containing information on the formulation, handling and conservation of avdoralimab is provided to the trial site pharmacists.

Concomitant Therapies

All patients will receive standard of care per local practice for the treatment of COVID-19 pneumonia. In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Of note:

- Currently used antiviral agents include: hydroxychloroquine, lopinavir/ritonavir, remdesvir. Patients are allowed to receive such therapies, but this should mandatorily be notified in the eCRF.
- Concomitant treatment with immunomodulatory agents whose efficacy is not demonstrated in patients with COVID-19 pneumonia (such as tocilizumab, anakinra or corticosteroids) is prohibited.

4. Statistical Considerations and Analysis Plan

Study Design

For Cohort 1, the statistical trial design is based on a binomial test for comparing the success rate at day 14 between treatment arms. Success being defined as a patient being alive at day 14 after randomization, and discharged from the hospital (or being ready for discharge, and not receiving any oxygen support). The test statistic, assuming separate variances for each arm, is:

$$Z_j = \frac{\hat{\pi}_{ej} - \hat{\pi}_{cj}}{\sqrt{\frac{\hat{\pi}_{ej}(1-\hat{\pi}_{ej})}{n_{ej}} + \frac{\hat{\pi}_{cj}(1-\hat{\pi}_{cj})}{n_{cj}}}}$$

$\hat{\pi}_{ej}$ and $\hat{\pi}_{cj}$ being the estimations of success rates in the experimental arm (e), and control arm (c) respectively at analysis number *j* (*j*=1 for the interim analysis, and *j*=2 for the final analysis); n_{ej} and n_{cj} being the number of patients treated in both arms.

For Cohort 2, the statistical trial design is based on a Gaussian test for comparing between treatment arms the number of VFD at day 28 starting from the time of randomization. The date of first treatment administration (V0) will be used in the calculation to ensure that the actual VFD28 number ranges between 0 and 28.

The Gaussian test is based on the below statistical test, assuming a population standard deviation of $\sigma = 2$ in each arm:

$$Z_j = \sqrt{n_j/n}\frac{\bar{X}_{ej} - \bar{X}_{cj}}{2\sqrt{\sigma^2/n_j}} = \frac{n_j}{\sqrt{n}}\frac{\left(\bar{X}_{ej} - \bar{X}_{cj}\right)}{4}$$

$\bar{X}_{ej}$ and $\bar{X}_{cj}$ being the mean number of VFD in the experimental (e) and control (c) groups respectively; at analysis number *j* (*j*=1 for the interim analysis, and *j*=2 for the final analysis); n_j being the number of patients treated in both arms, and n the total number of patients treated at the end of the trial (60).

Each test will be performed with a total type I error probability $\alpha \leq 0.05$ and a total type II error probability $\beta \leq 0{,}20$.

Statistical trial design was performed using East 6 software (Cytel Inc.)

Statistical Hypotheses

Cohort 1: The rate of alive patients discharged from the hospital by day 14 is expected to be of 40% in the control arm. We aim for a rate of 75% in the experimental arm.

Cohort 2: An improvement of at least 2 days in the number of ventilator-free days by day 28 is considered to be clinically relevant.

Interim Analysis

An interim analysis will be performed in each cohort when two-thirds of the total number of patients has been enrolled. (40 out of 60 in cohort 1, and 32 out of 48 in cohort 2). Calculation of the futility and efficacy boundaries will be done based on the Lan-Demets method with O'Brien Fleming error probability spending function, with a total type I error probability set to 0.016.

Cohort	n_1	α spending	β spending	Z limits		Probability of early termination			
						For efficacy		For futility	
				Efficay	Futility	Under H_0	Under H_1	Under H_0	Under H_1
1	40	0,016	0,051	**2,135**	**0,759**	1,6%	60,2%	77,6%	5,1%
2	32	0,016	0,011	**2,135**	**0,549**	1,6%	75,6%	70,8%	1,1%

Final Analysis

Boundaries for rejecting or not rejecting the null hypothesis during final analysis are reported in the below table:

Cohort	n_1	α spending	β spending	Z limits		Probability of early termination			
						For efficacy		Par futilité	
				Efficay	Futility	Sous H_0	Sous H_1	Sous H_0	Sous H_1
1	60	0,050	0,111	**1,655**	**1,655**	3,4%	28,7%	17,4%	6,0%
2	48	0,050	0,039	**1.676**	**1.676**	3,4%	20,5%	24,2%	2,7%

Determination of Sample Size

Cohort 1: We plan to enroll **60 patients** in this cohort. An intermediate analysis will be performed when 40 patients are enrolled; providing the trial with a power of 89% to detect an increase of the success rate from 40% in the control arm to 75% in the experimental arm. Early trial termination either for futility or for efficacy is estimated to range between 65% (H_1) and 80% (H_0). Taking into account the probability of early termination, the mean number of patients enrolled in this cohort is expected to be about 45.

Cohort 2: We plan to enroll **48 patients** in this cohort. An intermediate analysis will be performed when 32 patients are enrolled; providing the trial with a power of 96% to increase the number of VFD by 2 in the experimental arm compared to the control arm. Early trial termination either for futility of for efficacy is estimated to range between 72% (H_0) and 77% (H_1). Taking into account the probability of early termination, the mean number of patients enrolled in this cohort is expected to be about 36.

Statistical Methodology

Statistical analysis will be performed separately for each cohort. For each cohort, descriptive statistics of patients characteristics will be performed and will include for each variable: the mean, standard deviation and associated 95% confidence intervals, median and quartiles, minimum, maximum and number of missing values. Categorical data will be expressed as a frequency distribution and its associated 95% confidence intervals.

For treatment comparison of quantitative characteristics, the Student t-test or the non-parametric Wilcoxon-Mann-Whitney test will be used.

For treatment comparison of qualitative characteristics, the Chi-square test or the Fisher's exact test will be used. A p value of $< 0,05$ will be considered to be significant.

Analyzed Populations

Intention to treat Population (ITT)

Will include all randomized patients, assigned to a treatment arm

Per Protocol Population (PP)

Will include all randomized patients with the exception of:

- Patients who do not meet inclusion criteria, based on the investigator's objective evaluation, or based on an evaluation made prior to the time of randomization. Non-adherence to inclusion criteria must be determined prior to data unblinding.
- Patients who do not receive any treatment (avdoralimab or placebo), not based on a decision from their side nor from their investigator; and for reasons unrelated to their overall health status.
  Reasons for not receiving treatment leading to exclusion of the PP population may include: early termination of trial, unavailability of the drug product, administrative reasons etc..

Safety Population

Will include all patients who have received at least one dose of avdoralimab or placebo (including patients who do not received their assigned treatment).

Efficacy Assessment

Efficacy analysis will be performed in the ITT population; a sensitivity analysis for evaluating efficacy will also be performed in the PP population.

Handling of Missing Data and Sensitivity Analyses

In case a patient is lost to follow up prior to day 28, VFD28 will be considered as per the least favorable hypothesis; the days being lost to follow up being considered as being under IMV.

Two sensitivity analyses will be performed:

- One analysis will include only patients who complete the trial and are followed until day 28. All other patients will be excluded.
- Another analysis will input VFD according to the least-favorable hypothesis as described above (lost to follow up days are considered as being under IMV).

Secondary Efficacy Objectives

The below secondary objectives will be described per cohort and per treatment arm:

- Respiratory score at days 14 and 28
- ICU admission rates (Cohort 1)
- Length of hospital stay
- Length of ICU stay
- VFD14 for ICU patients
- Mortality at day 28
- SOFA Score at day 14 (=24 for deceased patients).

FINAL PROTOCOL - SUMMARY

Title: A randomized, double-blind study, placebo controlled, multicenter study to evaluate the safety and efficacy of Avdoralimab (IPH54) in patients with severe COVID-19 pneumonia

Protocol Number: 2020-21

Version Number: 10.0

EudraCT Number: 2020-001686-36

Compound: Avdoralimab (IPH5401)

Study Phase: II

Principal Investigator: Nicolas Schleinitiz

Sponsor: Assistance Publique Hopitaux de Marseille (AP-HM)

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5. Target Population

Inclusion Criteria

Participants are eligible to be included in the study if they are aged between 18 and 80 years at the time of randomization. They will be enrolled in one of 3 cohorts:

Cohort 1: Patients with severe COVID-19 pneumonia:

- Requiring oxygen therapy ≥ 5L/min to maintain SpO2 > 93% (conventional oxygen therapy and/or HFO).
- With presence of a positive SARS-Cov-2 RT-PCR at the time of or prior to enrollment.

Cohort 2: Patients with severe COVID-19 pneumonia admitted to the ICU:

- Requiring HFO, NIV or IMV with a PaO2/FiO2 < 300mmHg for over 24hours.
- With presence of a positive SARS-Cov-2 RT-PCR at the time of or prior to enrollment; or presence of a radiographic imaging typical of COVID-19 (Chest CT scan showing peripheral ground glass opacity)

Cohort 3: Patients with severe COVID-19 pneumonia admitted to the ICU:

- Requiring IMV or under IMV for less than 72 hours.
- Having a PaO2/FiO2 ranging between 60 and 200mmHg at the time of randomization.
- With presence of a positive SARS-Cov-2 RT-PCR at the time of or prior to enrollment.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding
- Refusing to participate to the study
- Currently participating in other drug clinical trial or was part of a clinical trial in the last 2 weeks preceding randomization
- Presenting active bacterial or fungal sepsis at enrollment
- Having contraindications preventing admission to the ICU

Additional exclusion criteria for **Cohort 1:**

- Receiving chloroquine or hydroxychloroquine treatment at the time of randomization
- Receiving conventional oxygen therapy at enrollment, but already under NIV or HFO at the time of randomization
- Have received IMV prior to randomization

Additional exclusion criteria for **Cohort 3:**

- Receiving IMV for over 72h
- Receiving ECMO at the time of randomization

Additional exclusion criteria for **cohorts 1 and 3:**

- Receiving chloroquine or hydroxychloroquine treatment at the time of randomization
- With chronic pulmonary disease: COPD, asthma, cystic fibrosis.

- With liver cirrhosis, Child-Pugh Class B or C
- Under chronic dialysis or receiving renal dialysis at the time of randomization
- Have received an organ transplant in the three-months period preceding the time of randomization
- With NYHA Class III or IV congestive heart failure
- Have had a cardiac arrest in the two-week period preceding the time of randomization

Number of Patients

This study aims to enroll 208 hospitalized patients with severe COVID-19 pneumonia.

Cohort 1: 100 patients.
Treatment arm (Avdoralimab + best supportive care); n= 50 patients
Control arm (Placebo + best supportive care); n=50 patients

Cohort 2: 48 patients.
Treatment arm (Avdoralimab + best supportive care); n= 24 patients
Control arm (Placebo + best supportive care); n= 24 patients

Cohort 3: 60 patients.
Treatment arm (Avdoralimab + best supportive care); n= 30 patients
Control arm (Placebo + best supportive care); n= 30 patients

6. Study Endpoints

Primary Efficacy Objectives

The primary efficacy objectives of the study FORCE are to evaluate:

- **In Cohort 1:** The clinical status improvement on the WHO ordinal scale at days 14 and 28 in patients treated with Avdoralimab versus placebo
- **In Cohort 2:** The number of ventilator-free days at day 28 (VFD28) in patients treated with Avdoralimab versus placebo
- **In Cohort 3:** The clinical status improvement on the WHO ordinal scale at days 14 and 28 in patients treated with Avdoralimab versus placebo

The number of participants required for this study is calculated based on these primary efficacy objectives.

Secondary Efficacy Objectives

The secondary efficacy objectives of the study FORCE are to evaluate:

- The ratio of patients discharged alive from the hospital by day 14 **(Cohort 1)**
- The clinical status on the WHO ordinal scale at days 14 and 28 **(Cohort 2)**
- The number of ICU transfers **(Cohort 1)**
- The length of hospital stays
- The length of ICU stays
- The number of VFD at days 14 and 28 in ICU patients

- The mortality at day 28
- The SOFA Score at day 14 in ICU patients
- The number of septic events
- The safety of Avdoralimab as assessed by the number of adverse events occurring in patients treated with Avdoralimab versus placebo

VFD14 and VFD28 are assessed at days 14 and 28 post enrollment, respectively. VFD is defined as the number of days during which the patients are alive and have had complete IMV weaning for at least 48h. Patients who die by day 28 are considered to have had zero ventilator-free days, even if they had IMV weaning for a few days. Short IMV weaning periods (of less than 24h) for surgical procedures are not taken into consideration. If a patient has repeated IMV weaning periods longer than 48h, VFD28 is calculated starting from the last weaning period and until day 28.

7. Study Intervention

Measures to Minimize Bias: Randomization and Blinding

This is a randomized, double-blind, placebo controlled study. The randomization process will be performed by means of a secure web-based case report form system (eCRF, RedCap). After initial informed consent is obtained, each patient will be assigned an identification number ensuring anonymity (trial site number – patient inclusion number). Once eligibility is established, the study site will proceed to randomization and treatment assignment via RedCap.

Patients will be randomly assigned at a 1:1 ratio to receive either avdoralimab and best supportive care or placebo and best supportive care. Randomization will occur in blocks of 4 to ensure a balanced assignment of placebo and avdoralimab in each trial site; and will be stratified according to trial site and admission type (ICU or general hospital).

Randomization will result in the attribution of a number (1 – 208) to each enrolled patient. Only trial site pharmacists will be aware of the correspondence between a patient's identification number and their assigned treatment. All other trial site personnel and patients will be blinded to treatment assignment during the study. The sponsor and its agents will also be blinded to treatment assignment.

Study Intervention Administered

Avdoralimab is a fully human Fc-silent monoclonal antibody that prevents the binding of C5a to its receptor C5aR1. Avdoralimab will be supplied by Innate Pharma as a lyophilized powder, in 10mL vials containing 100mg each, for reconstitution with 1,1 mL of sterile water for injection. The reconstituted solution has a pH of 6,5; and contains 100mg/ml of IPH5401 (active ingredient), 5,33mg of Histidine, 86,0 mg/mL of sucrose and 0,34/mL of polysorbate 80. The maximum amount of solution that can be withdrawn from each vial is 1mL.

Patients assigned to the treatment arm will receive a 500 mg loading dose of avdoralimab on day 1, followed by a 200 mg maintenance dose administered by IV infusion every 48hours for 14 days (maximum of 8 injections); independently from the patient's body weight. Treatment will be stopped prior to day 14 if oxygen therapy is no longer needed. Patients assigned to the placebo arm will receive normal saline in 100mL infusion bags.

Depending on the assigned treatment arm (experimental or placebo), avdoralimab will either be added to the infusion bag (500mg or 200mg doses) or not (placebo):

- For the 500mg loading dose, 5mL of the reconstituted avdoralimab solution will be added to the 100mL infusion bag.
- For the 200mg loading dose, 2mL of the reconstituted avdoralimab solution will be added to the 100mL infusion bag.

The entire 100mL-content of the infusion bag must be administered, and must be completed in 1 hour.

A full manual (Trial Material Manual, TMM) containing information on the formulation, handling and conservation of avdoralimab is provided to the trial site pharmacists.

Concomitant Therapies

All patients will receive standard of care per local practice for the treatment of COVID-19 pneumonia. In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Of note:

- Concomitant treatment with immunomodulatory or antiviral agents (such as tocilizumab, anakinra, hydroxycholoquine) is prohibited. **Patients are allowed to receive Remdesivir – but this should mandatorily be notified in the eCRF.**
- If not contra-indicated, concomitant treatment with dexamethasone is allowed and recommended given the positive preliminary results of the RECOVERY trial in severe COVID-19 patients.

8. Statistical Considerations and Analysis Plan

Study Design

The statistical trial design is based on a Gaussian test for comparing between treatment arms:

- The mean improvement in the WHO score compared to the score at enrollment **(for cohorts 1 and 3)**
- The number of VFD at day 28 starting from the time of randomization **(for cohort 2)**. The date of first treatment administration (V0) will be used in the calculation to ensure that the actual VFD28 number ranges between 0 and 28.

The Gaussian test is based on the below statistical test, assuming a population standard deviation of $\sigma = 2$ in each arm:

$$Z = \frac{\bar{X}_e - \bar{X}_c}{2\sqrt{\sigma^2/n}} = \frac{(\bar{X}_e - \bar{X}_c)}{4}$$

$\bar{X}_e$ and $\bar{X}_c$ being the means in the experimental (e) and control (c) groups respectively ; and *n* being the total number of patients treated in both treatment arms.

Statistical trial design was performed using East 6 software (Cytel Inc.)

Cohort 1

Statistical Hypothesis

The mean WHO score at enrollment is expected to be around 6. We may expect an improvement in the control arm of about 0,5 points at day 14 and 1,0 point at day 28.

In the experimental treatment arm, we expect an improvement compared to enrollment of at least 1,5 points at day 14 and at least 2,2 points at day 28.

Statistical Hypothesis Testing

Testing will proceed in a sequential fashion following the Wiens *Fallback* procedure. Tests at days 14 and 28 will each be performed with a nominal significance level of 0.05 (one-sided). If significance is met for either test, the second test will be repeated at the nominal significance level of 0,10 (one-sided), thereby allowing a global significance level of 0,10 (one-sided) for both tests.

Determination of Sample Size

The inclusion of 90 patients will provide the trial with:

- A power $\geq$ 76% to detect a 1,0-point difference between treatment arms at day 14
- A power $\geq$ 88% to detect a 1,2-points difference between treatment arms at day 28

At the nominal significance level $\alpha \leq 0,05$

Primary Efficacy Analysis and Sensitivity Analysis

Upon protocol amendment, the inclusion criteria and the primary endpoint were modified for this cohort; thus only the 90 patients included prospectively after this amendment will be included in the primary efficacy analysis.
A sensitivity analysis that includes the first 10 patients previously enrolled in Cohort 1 under previous protocol versions will be performed.

Subgroup Analysis

A subgroup analysis including patients under HFO at the time of enrollment will be performed.

Cohort 2

Statistical Hypothesis

An improvement of at least 2 days in the number of ventilator-free days by day 28 is considered to be clinically relevant.

Statistical Hypothesis Testing

The test will be performed at the one-sided nominal significance level of $\alpha \leq 0,05$

Determination of Sample Size

The inclusion of 48 patients will provide the trial with a power $\geq$ 96% to detect a clinically significant improvement of at least 2 days in the number of ventilator-free days at day 28.

Subgroup Analysis

The primary efficacy analysis will be performed on all patients enrolled in Cohort 2.

A subgroup analysis including only patients under IMV at the time of enrollment will be performed.

In the subgroup of patients not under IMV at enrollment, a second subgroup analysis will be performed to compare patients who required IMV post-enrollment to patients who did not require any IMV.

Cohort 3

Statistical Hypothesis

The mean WHO score at enrollment is expected to be around 7,5/10. We may expect an improvement in the control arm of about 0,7 points at day 14 and 1,5 points at day 28.

In the experimental treatment arm, we expect an improvement compared to enrollment of at least 2,0 points at day 14 and at least 3,0 points at day 28.

Statistical Hypothesis Testing

Testing will proceed in a sequential fashion following the Wiens *Fallback* procedure. Tests at days 14 and 28 will each be performed with a nominal significance level of 0.05 (one-sided). If significance is met for either test, the second test will be repeated at the nominal significance level of 0,10 (one-sided), thereby allowing a global significance level of 0,10 (one-sided) for both tests.

Determination of Sample Size

The inclusion of 60 patients will provide the trial with:

- A power $\geq$ 80% to detect a 1,3-point difference between treatment arms at day 14
- A power $\geq$ 89% to detect a 1,5-points difference between treatment arms at day 28

At the nominal significance level $\alpha \leq 0,05$

Sensitivity Analysis

None

Statistical Methodology

Statistical analysis will be performed separately for each of three cohorts. For each cohort, descriptive statistics of patients characteristics will be performed and will include for each variable: the mean, standard deviation and associated 95% confidence intervals, median and quartiles, minimum, maximum and number of missing values. Categorical data will be expressed as a frequency distribution and its associated 95% confidence intervals.

For treatment comparison of quantitative characteristics, the Student t-test or the non-parametric Wilcoxon-Mann-Whitney test will be used.

For treatment comparison of qualitative characteristics, the Chi-square test or the Fisher's exact test will be used. A p value of $< 0,05$ will be considered to be significant.

Analyzed Populations

Intention to treat Population (ITT)

Will include all randomized patients, assigned to a treatment arm

Per Protocol Population (PP)

Will include all randomized patients with the exception of:

- Patients who do not meet inclusion criteria, based on the investigator's objective evaluation, or based on an evaluation made prior to the time of randomization
- Patients who do not receive any treatment (avdoralimab or placebo), not based on a decision from their side nor from their investigator; and for reasons unrelated to their overall health status.
  Reasons for not receiving treatment leading to exclusion of the PP population may include: early termination of trial, unavailability of the drug product, administrative reasons etc..

Safety Population

Will include all patients who have received at least one dose of avdoralimab or placebo (including patients who do not received their assigned treatment).

Efficacy Assessment

Efficacy analysis will be performed in the ITT population; a sensitivity analysis for evaluating efficacy will also be performed in the PP population.
Sub-group analysis will be performed for the primary and the secondary endpoints.

Primary Efficacy Objectives

Cohorts 1 and 3: WHO Score Improvement at Days 14 and 28

For cohorts 1 and 3, the WHO score will be recorded at enrollment and at days 14 and 28. For each patient, clinical score improvement at days 14 and 28 compared to the time of enrollment will be calculated.

Mean improvement of the WHO Score will be calculated using the Gaussian test based on the main statistical test described in sections 4.1, 4.1.1 (for cohort 1) and 4.1.3 above. Both tests (at days 14 and 28) will be done at the one-sided nominal significance level $\alpha \leq 0{,}05$.

In addition to the above mentioned Gaussian test, the nonparametric Wilcoxon-Mann-Whitney test will be performed for comparing probability distributions.

Cohort 2: Number of VFD at Day 28

In Cohort 2, the number (mean, standard deviation, mean, minimum and maximum) of VFD by day 28 will be recorded for each treatment arm. VFD is defined in section 2.2 above.

The mean difference between treatment arms will be calculated using the Gaussian test (p-value and associated 95% confidence interval). The Gaussian test will be calculated based on the main statistical test described in section 4.1, assuming a population standard deviation of $\sigma = 2$ in each arm:

$$Zj = \sqrt{n_j/n}\,\frac{\bar{X}_{ej} - \bar{X}_{cj}}{2\sqrt{\sigma^2/n_j}} = \frac{n_j}{\sqrt{n}}\,\frac{\left(\bar{X}_{ej} - \bar{X}_{cj}\right)}{4}$$

$\bar{X}_{ej}$ and $\bar{X}_{cj}$ being the means of VFD in the experimental (e) and control (c) groups respectively, at analysis number *j* (*j*=1 for the intermediate analysis, and *j*=2 for the final analysis); n_j being the number of patients treated in both treatment arms, and *n* being the total number of patients at trial termination.

In addition to the above mentioned Gaussian test, the nonparametric Wilcoxon-Mann-Whitney test will be performed for comparing probability distributions.

Handling of Missing Data and Sensitivity Analyses

In case a patient is lost to follow up prior to day 28, VFD28 will be considered as per the least favorable hypothesis; the days being lost to follow up being considered as being under IMV.

Two sensitivity analyses will be performed:

- One analysis will include only patients who complete the trial and are followed until day 28. All other patients will be excluded.
- Another analysis will input VFD according to the least-favorable hypothesis as described above (lost to follow up days are considered as being under IMV).

Secondary Efficacy Objectives

The below secondary objectives will be described per cohort and per treatment arm:

- WHO Scale at days 14 and 28
- ICU admission rates (Cohort 1)
- Length of hospital stay
- Length of ICU stay
- VFD14 for ICU patients
- Mortality at day 28
- SOFA Score at day 14 (=24 for deceased patients).

The length of hospital and ICU stays will be analyzed by estimating a cumulative incidence function based on a competing risk model. This model will take into account the potential risk of death prior to discharge from the hospital/ICU.

Cumulative incidence plots will be generated for each cohort and for each treatment arm.

Cumulative mortality will be calculated using the Kaplan-Meier estimate. Survival curves will be generated for each cohort and for each treatment arm.

Multivariate Analyses

An efficacy analysis will be performed on groups of patients as such:

- One group that includes all Cohort 1 patients and
  Cohort 2 patients not under IMV at enrollment time.
- One group that includes all Cohort 3 patients and
  Cohort 2 patients under IMV at enrollment time.

Subgroup analyses will be performed on all patients enrolled in the study according to the PaO2/FiO2 ratio at enrollment and according to the treatment arm. For this exploratory analysis, three thresholds will be evaluated: 100, 150 and 200. Other thresholds ranging between 100 and 200 may be analyzed using a ROC curve.

A Multivariate analysis on all enrolled patients (across the 3 cohorts) will be performed by adjusting the models on the patients' characteristics at enrollment, namely IMV status.

SUMMARY OF SUBSTANTIAL CHANGES TO TRIAL PROTOCOL AND SAP

Protocol version	Date	Amendment
V5.0	15/06/2020	- Extension of enrollment period (until December 2020), due to the low number of patients enrolled at that time
V7.0	02/09/2020	- Allowing concomitant treatment with corticosteroids including dexamethasone based on RECOVERY results. - Concomitant treatment with anti-IL6 (tocilizumab) or anti-ILR (anakinra) is prohibited
V9.0	30/09/2020	- Addition of a new cohort (3), which aims to enroll 60 ICU patients, on IMV for less than 72hours. - New inclusion criteria defined for cohort 1: patients on HFO may be enrolled in this cohort - Primary endpoint of cohorts 1 and 3 modified to clinical status on the WHO ordinal scale at days 14 and 28. The previous primary endpoint of cohort 1 (rate of alive patients discharged from the hospital at day 14) becomes a secondary endpoint. - No interim analysis will be performed for cohort 2
V10.0	10/11/2020	- Increasing the number of patients to be enrolled in cohort 1 to 100 patients in total