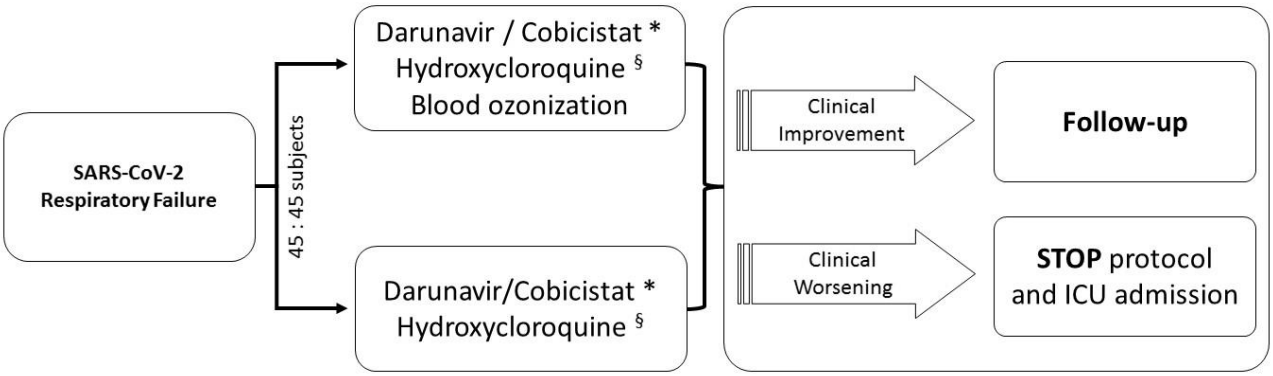
CIG: Z7C2CA5837

Blood Ozonization in Patients With SARS-CoV-2 Respiratory Failure

NCT number: Pending.

Flow chart of CORMOR study



Legend: * = Darunavir/Cobicistat 800/150 mg BD; § = 400 mg BD at Day 1, after 200 mg BD for 4 days; BD = every 12 hours; ICU: intensive care unit.

Schedule of assessments of CORMOR study

	T_0	T_3	T_{10}
Informed consent	X		
Inclusionand exclusion criteria	X		
Demography and physical examination (including height and weight)	X	X	X
SOFA score	X		
Charlson Comorbidity Index	X		
Medical history	X		
Concomitant systemic therapy	X		
Arterial Blood Gas analysis	X	X	X
P/F ratio and respiratory assistance assessment	X	X	X
Thoracic CT scan or Chest XR or Chest echo*	X	X	X
12-lead ECG	X		
Laboratory assessment §	X	X	X
IL-6, HLA-DR, lymphocyte typing °	X	X	X
2019-nCoV testing by RT-PCR by upper respiratory tract and expectorated sputum	X	X	X
AE review	X	X	X
Concomitant medical review	X	X	X
Survival follow-up			X

Legend: T_0 – study inclusion; T_3 – after the 3rd blood ozonization treatment; T_{10} – follow-up visit at one week after the end of blood ozonization; * - if it is not possible to perform a thoracic CT scan is recommended to perform a chest x-ray and/or chest ultrasound (POCUS - Point-of-Care Ultrasound); § - blood count, bilirubin, AST, ALT, LDH, creatinine, PCR, PCT, CPK, PT, aPTT, D-dimer, fibrinogen, serum electrolytes; ° - lymphocyte typing for CD4, CD3, CD8, HLA-DR, CD45.

Statistical analyses

Variables are described as means ± standard deviation, median and interquartile range, or proportion (depending on distribution). To compare categorical variables, we used a 2-tailed paired test, Mann-Whitney U test, and $\chi 2$ test. The $\chi 2$ test was used through Yates continuity correction or Fisher test, as required by the specific case. Normality of the variables was assessed with a nonparametric Kolmogorov-Smirnov test.

In order to identify the risk factors associations, and to adjust the results respect to the different clinical conditions, a multivariate regression will be calculated on the subjects enrol on the two study arms. This regression will be calculated with two distinct methodological approaches (multivariate Cox regression and survival random forest [Breiman L. Random Forests. Machine Learning. 2001; 45: 5-32]); the results of each method will be compared on the basis of predictive accuracy, calculated with cross-validation and ROC survival curve.

Furthermore, the number of events that occurred to each patient during follow-up will be calculated, comparing it between the different treatment groups with a $\chi 2$ test. About the biomarkers, recorded longitudinally, a two-way analysis of variance for repeated measurements will be performed, followed by the appropriate post-hoc test. If the distributions are nonlinear, Friedman's non-parametric test will be performed. The parameters of adherence to therapy in the different treatment groups will be studied with one-way analysis of variance, followed by the appropriate post-hoc test. If the distributions are nonlinear, the non-parametric Kruskal-Wallis or chi-square test will be performed. Persistence of treatment will be assessed using the classic survival analysis methods [Marubini E., Valsecchi M.G., Emmerson M., Analysing Survival Data from Clinical Trials and Observational Studies. John Wiley & Sons, 1995, New-York.].

Along with an unbiased estimation of prediction accuracy, a ranking of variable importance and a measure of similarity between any couple of patients were produced. The similarity measure was used for risk stratification, following a model-based clustering approach. Multiple comparisons were adjusted with the Bonferroni method.

We used the statistical software R (R Foundation for Statistical Computing, Vienna) for all statistical analyses, and we considered a P value less than 0.05 statistically significant [R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria. 2013. http://www.R-project.org/].

The comparison between the two groups will be carried out with a $\chi 2$ test with Yate correction. We calculate to enrol 45 patients per arm to obtain a statistical power of 80% with a significance level of 95%.