Official Title : Effects of low-dose corticosteroids on survival of severe community-acquired pneumonia

MAJOR CHANGES IN THE ORIGINAL PROTOCOL – DESIGNS ISUES	Methodological issues are the following: - Cape-COVID is planned as a group sequential randomized trial - The primary outcome is different as the one of the original trial. We will now consider failure at Day 21 were failure corresponds to death or dependence from respiratory support, including mechanical ventilation or high-flow oxygen therapy. This outcome makes sense at both individual and community levels. Indeed, prolongation of respiratory support, especially mechanical ventilation, is associated with several complications (e.g. ventilator-associated pneumonia, ventilator-induced lung injury, acquired muscle weakness or sleep deprivation) and increase ICU stay. Moreover, in the context of rapidly progressive pandemic with a risk of exceeding critical care capacities, diminishing the duration of respiratory support will permit to decrease ICU length-of-stay and to liberate ICU-beds for other patients. This beneficial effect of CTx is consistent with previous studies in non-severe community-acquired pneumonia who have shown that CTx decrease the time for clinical stability and hospital length-of-stay. - The sample size has been calculated with an assumption on the failure rate associated to the control group which is no well documented. We will therefore allow ourselves to revise this sample size while the trial is going on - Therapeutic units will be those we planned to use for the original trial. However, we presently have about 290 therapeutic units, knowing that about 50 COVID19 patients have already been included. It is presently impossible to obtain new placebo units. As a consequence, the trial is planned as being blinded, but in case we need to include more patients than we have units, we plan to end the trial as an open trial.
SAMPLE SIZE	The event rate is assumed to be 30% in the control group. The trial is designed to demonstrate superiority of experimental treatment over control with an assumed event rate of 15% in the experimental group with 80% power and a one-sided Type I error rate of 2.5. Symmetric two-sided group sequential, requires sample size 290, for 6 interim analyses (5 during the trial and one final). Bounds were determined using a Kim-DeMets alpha spending function (Lan et al, Biometrika 1983;70:659-63; kim et al Biometrics 1987;4:857-64; DeMets et al Statist Medicine 1994;13:1341-52) with a conservative bound for efficacy and an aggressive bound for futility. That is, stopping for high

	evidence of superiority while stopping early if the experimental treatment is not effective and can be potentially harmful for patients. Due to uncertainty of the failure rate in the control group, we plan to re-calculate this sample size while the trial is going-on. Indeed, data about mortality rate of COVID patients in ICU are diverging and ranging from 50% to 5%. We choose to assume a 30% rate considering mortality or need of respiratory support for the control arm but this is uncertain. This is why sample size re-estimation could be necessary during the trial when up-dated knowledge will be available.
STATISTICAL ANALYSIS	The statistical design for this phase III two arms clinical trial will follow a group sequential design with a total of 6 analyses (5 interim analyses and a final). The group sequential will use a Kim-DeMets alpha spending function with a conservative bound for efficacy and an aggressive bound for futility. That is, a conservative O'Brien Fleming type of bound for superiority bound and a an aggressive bound for futility design. The alpha spending function has the advantage to be a continuous function of the information time in group sequential procedures for interim analyses. As inclusions can be fast during this pandemic or that data monitoring will be more complex than usual, it can be possible that interim analysis will not follow the initial plan. So, using a continuous function will allow to re-calculate the boundaries if necessary. At each interim analysis, the Z statistics (for a difference of binary endpoints) is computed from the data of the two arms and will be compared to the efficacy and futility bounds. If the value of Z is higher than the interim analysis specific upper bound (or lower than the lower bound), the trial is stopped for reasons of demonstrated efficacy (or futility); otherwise the trial will continue. For interpretability, the plots and the results will be displayed on the maximum likelihood estimation (MLE) scale, but the final p-value will be computed using the log-odd-ratio normalized Z statistics. Analysis will be performed using R version 3.6.3 and the package gsDesign version 3.0-1.