Safety of IL-17A blockade with secukinumab in Covid-19 hospitalized patients – interim data from the BISHOP study.

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Background
The new coronavirus (SARS-CoV-2) pandemic has spread across the planet and threatens all health systems in the world. The most severe patients, who progress to acute respiratory distress syndrome (ARDS), seem to have a combination of deficient antiviral immunity (type 1 immune response) with hyperinflammation. IL-17A is an inflammatory cytokine with a major role in immune protection against extra-cellular pathogens (signature of type 3 immune response) and is a potent neutrophil attractor and activator through chemokines such as CXCL8 and growth factors such as G-CSF. There were already some previous attempts to block IL-17A in animal models of viral infections, but to our knowledge, there is no study published of IL-17A inhibition in COVID-19. We hypothesized that the use of secukinumab (SEK), a monoclonal antibody anti-IL17A, could prevent or mitigate the hyperinflammation and its deleterious consequences in severe Covid-19 patients.

Methods
The BISHOP study is an ongoing open-label, single-center, phase 2, controlled clinical trial, which is recruiting since September 2020. Adult patients with SARS-CoV-2 infection confirmed by RT-PCR, admitted in Hospital Risoleta Tolentino Neves in severe acute respiratory syndrome (SARS) according to the Brazilian Ministry of Health definition are randomized 1:1 to receive a dose of 300mg of secukinumab subcutaneously at D0 (group A) in addition to standard of care (SoC) or follow the SoC alone (group B). A second dose of 300mg could be administered at D7 for those included in group A, according to attending medical team judgment and if the study´s inclusion and exclusion criteria remain applicable. The primary endpoint is the ventilator-free days in 28 days (VFD28). Here, we present the interim data of the first 20 patients included (40% of the expected sample) with interest in the safety profile of secukinumab in this population. This research was supported by Novartis Brazil. Novartis Brazil also provided expert input in the development of the project as drug supply, data management and monitoring.

Results
With 10 patients included in each group, the number of serious adverse events (SAE) in group A and group B, were respectively, 11 and 5. The incidence rate of SAE (per 100 patients-day) were 3.9 (group A), and 2.0 (group B). There were three diagnosis of pulmonary embolisms in group B and one in group A. Septic shock, defined as hemodynamic instability and the identification of an infectious focus by culture, occurred in two patients from group A and one from group B. Only one patient discontinued the study (group B) because for not tolerating the consecutive nasopharyngeal swab procedures. There was only one death in each group, both due to septic shock secondary to ventilator-associated pneumonia (VAP). No fungal infections nor injections site reactions were observed. The viral clearance defined by the fold change ($2^{-\Delta\Delta CT}$) in viral RNA, quantified by RT-PCR of nasopharyngeal swab, was remarkably similar between the two groups (0,10 from day-0 to day-5 in group A and 0,07 in group B).

Conclusions
The addition of Secukinumab in the SoC treatment seems to have, based on the analysis of this interim data, an acceptable safety profile in severely ill Covid-19 patients. No significant difference between groups was demonstrated regarding the occurrence of serious adverse events, pulmonary thromboembolism, septic shock, and deaths. The IL-17A blockade also does not seem to interfere with the viral clearance in the upper airways.