Memorandum

RE: A phase I/II study of human placental hematopoietic stem cell derived natural killer cells (CYNK-001) for the treatment of adults with COVID-19 (Application: CLIN2COVID19-11857)

This memo is intended to provide additional information to address concerns raised by the GWG members during application review regarding the scientific rationale and potential toxicity.

1. It was shown by Zheng et al, 2020 (reference see below) that the total number of NK cells was decreased markedly in patients with SARS-CoV-2 infection. Besides, increased expression of exhaustion marker on NK cells implies a decreased NK function in COVID-19 patients. These results suggest that SARS-CoV-2 infection may hamper innate antiviral immunity at an early stage of infection, thereby justifying supplementation of CYNK-001 cells to provide the antiviral activities in those with SARS-CoV-2 infection. Several publications of SARS/MERS animal models suggest NK cells are dispensable for viral clearance in favor of T cell immunity. However, these models in young mice mimic an effective recovery to infection. While SARS-CoV-2 infection in young macaques is similar to mouse models, aged macaques shows a higher viral burden in the lung and extended recovery time (Rockx B et al, Science 2020), consistent with observations from the high-risk COVID-19 population (Liu Y et al, Lancet 2020).

   Zheng et al Rockx et al Liu et al

2. To date, no human has been treated with CYNK-001 drug product. However, a comparable investigational product, PNK-007, has been investigated under IND #016792 in patients who have relapsed and/or refractory acute myeloid leukemia (AML) and IND #017030 multiple myeloma (MM). Based on the available safety data from these two PNK-007 clinical studies in patient populations that are susceptible to pulmonary events, it is concluded that no potential lung injury cases related to PNK-007 were reported during the dose limiting toxicity (DLT) period of these studies. Furthermore, no PNK-007 infusion-induced increase of pro-inflammatory cytokines was noted in AML or MM patients.

   It is imperative to note that the currently proposed CYNK-001-COVID-19 clinical study is designed with a Day 14 safety stopping rule along with close monitoring of subjects until the Day 28 DLT period. One of the key exclusion criteria includes patients who are admitted to intensive care unit or pulmonary acute care unit with pneumonia, acute respiratory distress syndrome (ARDS) and sepsis. As part of further risk mitigation strategy, any potential treatment emergent adverse events (TEAEs) under Respiratory, Thoracic, and Mediastinal Disorder that may occur with CYNK-001 infusion shall be evaluated in comparison to the underlying pulmonary complications due to COVID-19 and presented for Data Monitoring Committee's review and recommendation.