Ensuring Patient Safety And Data Integrity In Clinical Trials for The Treatment Of Bronchiolitis Obliterans Syndrome (BOS) During The COVID-19 Pandemic

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Introduction & Objectives

- On March 11th 2020, the World Health Organization (WHO) assessed the COVID-19 outbreak as a pandemic. This situation brought about new challenges such as country-wide lockdowns, quarantine, social distancing, and travel limitations.
- The pandemic also greatly impacted clinical research. In March 2020, 170 company sponsored clinical trials were suspended worldwide; thousands of trials, around 80% of non-COVID-19 studies, were stopped or interrupted; furthermore, new patient enrolment dropped 65% on a year-on-year basis.
- If we take into consideration the setting of CLAD patients with BOS phenotype, the current situation is especially challenging as many studies indicate that transplant recipients are at increased risk of severe COVID-19 and increased mortality on top of the logistical difficulties of reaching their reference transplant center.
- BOSTON-1 and BOSTON-2 are two ongoing phase III, prospective, multicenter, randomized, controlled clinical trials aimed at demonstrating the effectiveness and safety of inhaled liposomal cyclosporinA in patients with CLAD-BOS following single (BOSTON-1) or double (BOSTON-2) lung transplantation. BOSTON-3 is an open label extension trial for patients who have completed the 48-week treatment period in BOSTON-1 and BOSTON-2 trials.
- The trial Sponsor conducted a risk assessment to address challenges for trial conduct during restrictions posed by the pandemic and developed a contingency plan ensuring patient safety, data integrity and treatment continuation.

Materials and Methods

Due to possible restrictions of protocol-scheduled on-site visits, a contingency plan centered around remote visits has been implemented. Patients are contacted by the Investigator and/or appropriately qualified site personnel to assess the patients' overall status, wellbeing, and document any potential adverse events (AEs). Of the utmost importance, the protocols have been amended to include spirometry assessments carried out through a portable spirometer with standardized guidance by study staff by the patients themselves.

References

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4. Guidance from the International Society of Heart and Lung Transplantation regarding the SARS CoV-2 pandemic - REVISED: April 4, 2020
5. EMA: Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic Version 2 (27 March 2020)
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7. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic - Guidance for Industry, Investigators, and Institutional Review Boards (March 2020, Updated on March 27, April 16, 2020 and May 11, 2020)

Results

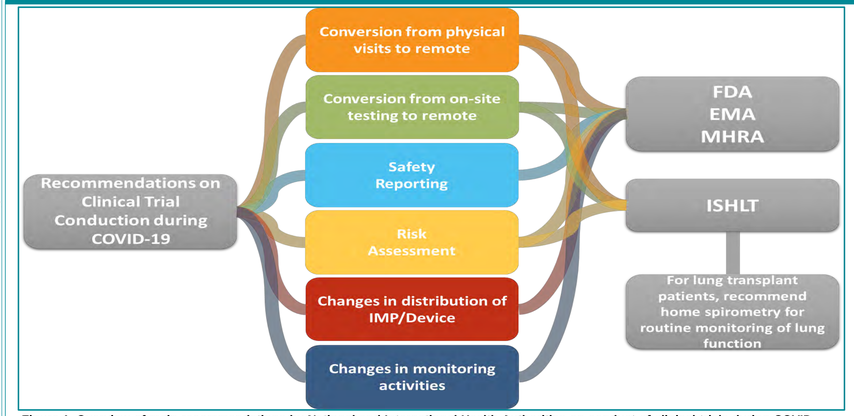

Figure 1. Overview of main recommendations by National and International Health Authorities on conduct of clinical trials during COVID-19 pandemic. The main goal is to ensure patient safety and efficacy data collection during COVID-19 outbreak. In addition to National and International Health Authorities, ISHLT also provided guidance for lung and heart transplant donors and recipients. One of the main points recommended by ISHLT for lung transplant patients is the use of home spirometry for routine monitoring of lung function. The Sponsor of BOSTON-1 and BOSTON-2 has implemented this, by providing portable spirometers (Hand-Held In2itive™) for all enrolled patients. For remote visits, the clinical trial personnel will telephone the patient and guide them through performing spirometry on the In2itive device.

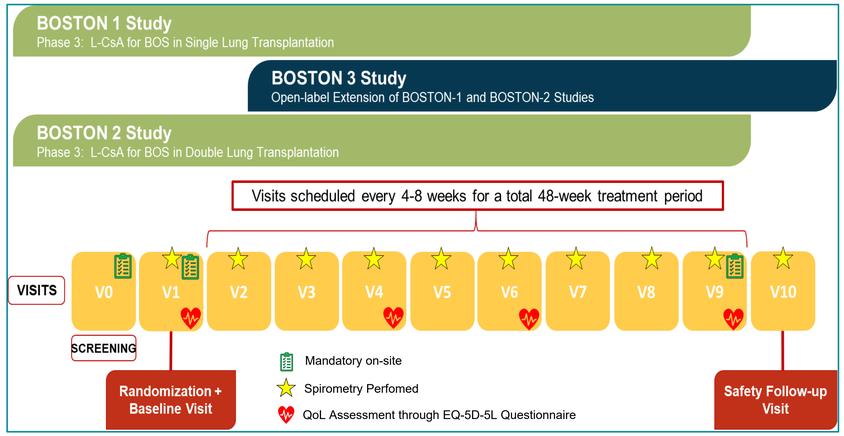

Figure 2. Overview of BOSTON-1 and BOSTON-2 clinical study program and new visit schedule implemented with COVID-19 risk assessment measures. Mandatory on-site visits remain Screening, Visit V1 and Visit 9. After finishing 48-week treatment, the patient during Visit 9 will be assessed for eligibility to enroll in the long-term safety trial follow-up study (BOSTON-3). Visit 2 through Visit 8 can be performed remotely, if the patient is unable to travel to the clinical site due to COVID-19. During remote visits, the following procedures are requested to be completed: check of investigational drug supply with patient (if required and allowed re-supply needs to be arranged); check of patient treatment compliance; capture any potential adverse events and confirm the patient's status and wellbeing; capture any changes in concomitant medication; provide refresher training for In2itive, if needed; guide the patient through a spirometry session using the In2itive device.

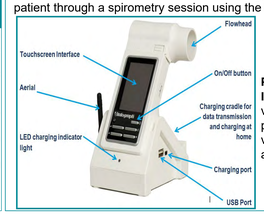

Figure 3. The Sponsor of BOSTON-1 and BOSTON-2 provided portable spirometers (Hand-Held In2itive TM) for all enrolled patients. Portable spirometers are also used by all patients at the screening visit. In addition to the spirometry performed on the COMPACT spirometer at clinical site, all patients will perform spirometry using the In2itive device at every on-site study visit as well. If patients cannot attend visits on-site due to COVID-19, remote visits with guided home spirometry will be performed (FEV_1, FEF_{25-75}, and FVC) using the In2itive device.

RISKS	CONSEQUENCES	ACTIONS
Inability to visit the study center	**Patient cannot perform follow-up visits**	If necessary, patients can request to be provided with a **private driver for the follow-up visits at sites**. In the event that **on-site visits are not possible or patients decide not to attend the hospital/clinic visit**, specific instructions for alternative procedures to be used to collect critical safety and/or efficacy variables are provided for the following anticipated possible cases: ▪Patient visits not possible at study site and visit is performed at patient's home using **portable spirometers (Hand-Held In2itive™)**. In2itive device will also be used by all patients at the screening visit. In addition to the Spirometry performed on the COMPACT, all patients will perform spirometry using the In2itive device at every on-site study visit. If patients cannot attend visits on site due to COVID-19, remote visits with guided home spirometry will be performed (FEV_1, FEF_{25-75}, and FVC) using the In2itive device.
Insufficient IMP supply	**Patient is unable to continue treatment because of shortage in IMP supply**	▪ In cases where approval is given to **extend home-treatment for a patient**, and the patient does not have sufficient IMP to enable continued treatment until the next rescheduled visit date, the **study site will be required to ship additional IMP to the patient**. ▪ All shipments from study sites to patients must be performed by the Sponsor contracted courier. The couriers are qualified as suitable, and all measures were contractually established to maintain the pseudonymization. The processes for the transportation, including temperature control requirements, handover conditions for IMP, and **maintaining the privacy and personal data protection of the trial patients**, are contractually regulated. ▪ It is advised that when a patient receives study drug, he/she should take a photo to ensure the study drug quality and then send the photo to site staff.
Inadequate monitoring of clinical study	**Protocol deviations, or inconsistencies in study conduct are not adequately managed**	If CRA is unable to perform on-site monitoring visits: ▪Source Data Verification (SDV) activities must be postponed until on-site monitoring visit restrictions have been lifted. ▪Remote monitoring activities are initiated and will be documented in a monitoring visit report. The DMC (Data Monitoring Committee) will perform a comparison between the rate of observed COVID-19 cases, rate of COVID-19 related SAEs, rate of patients' withdrawal, and rate of missing data among trial participants in both treatment arms.

Table 1. Overview of BOSTON-1 and BOSTON-2 clinical trials risk assessment plan implemented by the study Sponsor for study conduct during COVID-19 pandemic.

Conclusions

- Through the risk assessment plan implemented, the Sponsor's priority was to ensure patients' safety, address any limitations to travel and access to investigational sites, while reducing the amount of missing data.
- Therefore, despite the challenges posed by the current COVID-19 pandemic, the BOSTON-1, BOSTON-2 and BOSTON-3 clinical studies' Sponsor determined that the medical value of this research is compelling as these studies are the first large Phase III trials evaluating the safety and efficacy of inhaled liposomal cyclosporinA for the treatment of CLAD patients with BOS phenotype after single- or double-lung transplantation, as currently no approved therapy for this setting exists.