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ID-054-304

Addendum to protocol: Exceptional measures to ensure subject safety and counteract potential trial conduct disruption due to the COVID-19 pandemic

Official Title:

A Prospective, Multi-center, Double-blind, Randomized, Placebo-controlled, Parallel-group, Phase 3 Study to Assess the Efficacy and Safety of Clazosentan in Preventing Clinical Deterioration Due to Delayed Cerebral Ischemia (DCI), in Adult Subjects With Aneurysmal Subarachnoid Hemorrhage (aSAH)

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ADDENDUM TO PROTOCOL
ID-054-304

Exceptional measures to ensure subject safety and counteract potential trial conduct disruption due to the COVID-19 pandemic

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
eCRF	Electronic case report form
EOS	End-of-Study
GCP	Good Clinical Practice
GOSE/mRS	Glasgow Outcome Scale / Modified Rankin Scale
ICH	International Council for Harmonisation
ICU	Intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MoCA	Montreal Cognitive Assessment
PD	Protocol deviation
QoLs	Quality of life assessments
SAE	Serious adverse events
SDV	Source data verification
WHO	World Health Organization

1 INTRODUCTION

As a consequence of the pandemic of respiratory infectious disease (COVID-19; declared a pandemic by the WHO on 11 March 2020) caused by a novel coronavirus (SARS-CoV-2), on 19 March 2020 Idorsia put the recruitment for the ID-054-304 (REACT) study on hold temporarily. Health authorities and IECs/IRBs have been informed, as required. This decision was a precautionary measure taken to spare intensive care resources at the participating sites. As a result, subject safety, trial integrity and interpretability can also be preserved.

A recruitment hold communication letter was sent to the study investigators on 20 March 2020.

Sites were informed that patients who had already signed an informed consent form and were therefore in screening could still be randomized. Investigators were instructed that any randomized subjects, including the ones in the treatment period, should continue their study participation. This was recommended as for the few subjects with treatment ongoing the monitoring of safety during ICU/hospital stay was ensured, and the risk of any of these subjects getting infected with COVID-19 during the maximum 14 days of treatment administration plus 24-hour follow-up period was considered minimal. Therefore, the overall benefit/risk of continuing study drug was considered favorable. At the time of issuing this protocol addendum, all subjects have completed their study treatment and no COVID-19 related complications were reported by the sites.

Data collection for subjects enrolled was asked to be completed to the extent possible in accordance with the study protocol. Instructions were issued to record PDs due to the COVID-19 situation and continuing to report them as per clinical trial requirements to Idorsia, IEC/IRB, regulatory authority, and/or any other applicable parties.

Sites were reminded that the Week 12 and Week 24 visits can be done remotely as per protocol.

Instructions regarding the Week 12 MoCA testing, and instances when the entire Week 12 visit and the safety follow-up at either at Week 12 or Week 24 post-aSAH become compromised due to COVID-19 restrictions are provided in Section 2.

Additionally, provisions are given for subjects infected with SARS-CoV-2 after recruitment has resumed by emphasizing applicable sections already present in the protocol.

All PDs related to the COVID-19 crisis will be identified and tracked by Idorsia. This will allow, at the end of the trial, a reconstruction of the impact that such deviations had on the trial integrity and interpretability. This requires that the PDs continue to be collected as per original protocol definition, and will be identified as due to COVID-19 pandemic even after the implementation of this addendum.

The addendum applies to those sites affected by the COVID-19 outbreak and is limited to the time during which such sites are affected. This addendum is therefore limited in scope and in duration.

2 RECOMMENDATIONS AND INSTRUCTIONS

2.1 MoCA testing and outcome assessments at the Week 12 visit

The preferred option is to maintain the Week 12 visit as a face-to-face on-site visit, provided that the subject is allowed as per COVID-19 restrictions and can travel to the site. To ensure safety of the subject on his/her way to the site, the site staff will remind the subject to adhere to local laws and recommendations (e.g., not using public transportation). Alternatively, subjects can use taxis or private cars, the cost of which will be reimbursed by Idorsia.

If the subject cannot return to the site due to COVID-19 pandemic-related reasons, the visit should be conducted remotely within the protocol-defined time window. However, as per protocol the MoCA can only be performed face-to-face. Remote administration will not be allowed during the COVID-19 pandemic. Instead, if MoCA face-to-face testing could not be done at the time of the Week 12 visit, the testing should be performed at the earliest face-to-face opportunity, even if it is outside of the protocol-defined time window, as soon as possible, and at the latest at the time of the EOS visit at 24 weeks post-aSAH. If at the due time of the visit the MoCA assessment could not be performed because the condition of the subject does not allow for testing (e.g., Glasgow Coma Scale estimated as ≤ 13), the assessment should be considered as not done and the corresponding reason(s) must be entered into the applicable eCRF form(s).

Should the self-completion of the QoLs (Stroke Specific Quality of Life, Oxford Participation and Activities Questionnaire, EQ-5D) be compromised given the circumstances (e.g., questionnaires cannot be delivered by post), any of the assessments can be performed out-of-window, as soon as possible before the EOS visit at 24 weeks post-aSAH, either remotely or face-to-face.

Postponing the Week 12 assessments is only allowed because of logistical restrictions due to the COVID-19 pandemic.

2.2 Safety follow-up at Week 12 and Week 24

If an ongoing AE requires follow-up as per protocol sections 9.2.1 and 9.2.2 at either the Week 12 or Week 24 visit, including follow-up of laboratory abnormalities, the subject should be asked to return to the hospital following evaluation of the risk with regards to safety of the travel. If the subject cannot or is not willing to return because of the COVID-19 pandemic, the option of referring the patient for follow-up to an alternative hospital or local laboratory should be evaluated.

If the urine pregnancy test for women of childbearing potential due at the Week 12 visit cannot be delivered to the subject's home, the use of a self-purchased pregnancy test is allowed, for which the subject will be reimbursed.

2.3 Provisions for subjects infected with SARS-CoV-2 during recruitment hold

Testing for SARS-CoV-2 should follow local guidance. Mandatory testing is not required for this study. No specific provisions are foreseen if a subject is found positive for SARS-CoV-2, during hospitalization or the period between discharge from the hospital and EOS.

Idorsia has evaluated the potential drug-drug interactions with the current available most frequently used medications for COVID-19 (e.g., remdesivir, lopinavir/ritonavir, IFN beta1b, corticosteroids, hydroxychloroquine). Clazosentan is a substrate of OATP1B1/1B3, therefore inhibitors/inducers, i.e.: lopinavir/ritonavir is contraindicated. As already defined in the protocol, subjects for whom the use of OATP inhibitors is foreseen are excluded from the study [protocol section 4.4]. Additionally, OATP inhibitor administration is forbidden until Day 14 post-study drug initiation [protocol section 5.2.4]. If their use is inevitable, study drug must be permanently discontinued [protocol section 5.1.3.4.1].

Based on our current knowledge, the rest of the assessed anti-COVID-19 drugs are not expected to mutually affect their PKproperties based on an effect on metabolizing enzymes or transporters. Clazosentan has no perpetrator potential on enzymes or transporters.

Information about COVID-19, whether confirmed with a positive SARS-CoV-2 test result or not, and its corresponding diagnosis (symptoms) as well as administered medications will be collected on the AE and Concomitant Medication pages of the eCRF [see protocol sections 9 and 5.2.5 for reporting procedures].

2.4 Reporting of protocol deviations related to the COVID-19 pandemic

PDs due to the COVID-19 pandemic are expected to occur during the pandemic and fall under ICH GCP section 4.5.4: "The investigator may implement a deviation from, or change of, the protocol to eliminate an immediate hazard(s) to trial subjects". Any PD occurring due to the COVID-19 pandemic must be documented according to ICH GCP section 4.5.3 and clearly recorded as related to the COVID-19 pandemic. All PDs will be reported to the sponsor, IEC/IRB, regulatory authorities and/or any other applicable parties, according to local requirements.

2.5 Monitoring

If on-site monitoring cannot be performed by the CRA as described in protocol section 12.8, and if acceptable under local law and with the IEC/IRB, the CRA will conduct remote monitoring and remote SDV, provided that subject confidentiality is maintained

throughout the process [as per protocol Section 11.2] and all local approvals to do so are in place, as applicable. If remote monitoring or remote SDV are not allowed, alternatives as applicable according to local regulations may be agreed with the principal investigator to ensure data integrity.