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ADDENDUM TO PROTOCOL ID-078A303 -
Exceptional measures to ensure subject safety and counteract potential trial conduct disruption due to the COVID-19 pandemic

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ADDENDUM TO PROTOCOL
ID-078A303

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse Event of Special Interest
BWSQ	Benzodiazepine Withdrawal Symptoms Questionnaire
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
C-SSRS	Columbia Suicide Severity Rating Scale
DDI	Drug-drug interaction
ECG	Electrocardiogram/graphy
eCRF	Electronic case report form
EDS	Excessive Daytime Sleepiness
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HMA	Heads of Medicines Agencies
ICH	International Council for Harmonisation
IDSIQ	Insomnia Daytime Symptoms and Impact Questionnaire
IEC	Independent ethics committee
IRB	Institutional review board
PD	Protocol deviation
PI	Principle Investigator
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDS	Sheehan Disability Scale
SDV	Source data verification
VAS	Visual Analog Scale
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), Idorsia provided instructions and guidance in communication letters sent to investigators participating in the ID-078A303 study on 19 March 2020 and 31 March 2020. These measures and instructions are in line with health authority guidelines (FDA, HMA and individual national health authorities) released in March 2020 on how to address the challenges caused by the pandemic itself.

These measures, which also constitute PDs, are introduced to preserve subject safety, trial integrity and interpretability, as well as compliance with regulatory requirements.

Idorsia tracks all these deviations from the protocol as "PDs related to COVID-19". 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 instructions and measures included in this addendum continue to be collected as PDs as per original protocol definition, and will be identified as due to COVID-19 even after the implementation of this addendum.

The objective of this addendum is to document those measures and instructions in the protocol. 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.

The recommendations and instructions that have been provided to the investigators are described below with reference to the protocol section affected.

2 RECOMMENDATIONS AND INSTRUCTIONS

2.1 Flexibility regarding site visits for subjects who can still go to sites

For subjects ongoing in ID-078A303:

- If the subject can travel to the investigator's site, the investigator should:
  - Ensure the subject's safety on his/her way to the site by following local/country regulations (e.g., not using public transportation). Alternatively, subjects can use taxis or private cars, the cost of which will be reimbursed by Idorsia.
  - Perform the on-site visit assessments according to the protocol.
  - An on-site visit is always preferable. Therefore, this may mean that the visit windows need to be extended, as long as the subject has enough study treatment. Study treatment can be delivered to the subject's home, following the instructions as in Section 2.2. The reason for this delayed scheduled visit must be documented in the subject's medical charts.

For subjects potentially transitioning from ID-078A302 to ID-078A303 [protocol section 7.1.1]:

- New enrollment in the extension study is allowed only if Visit 1 in ID-078A303, as well as Visit 10 in ID-078A302 can happen on-site.

2.2 Conduct of remote visits for subjects who cannot, are not allowed to, or are not willing to travel to the investigator's site

- If the subject cannot, is not allowed to, or is not willing to travel to the investigator's site, the clinic visit(s) can be replaced by a **telephone call or video call**: to keep close contact with subjects (remote visits), these visits should be at least as frequent as the protocol-mandated clinic visits.
  - The investigator should notify the IEC / IRB in advance of remote visits if this is a local requirement.

Before the telephone call or video call visit:

- If the study treatment needs to be delivered to the subject's home, the investigator should ensure the following:
  - Obtain subject's verbal consent by telephone to provide his/her name and home address to the courier service responsible for delivering study treatment and pregnancy tests [protocol section 5.1.6.3].
  - The date and time that verbal consent was obtained is documented in the subject's medical records.
  - Make sure that women of childbearing potential have enough home urine pregnancy kits (send them along with study medications to the subject's home if necessary) and remind them to perform the test monthly [protocol section 7.2.4.2].
  - If the approval must be in writing, according to the site's local regulation, please act accordingly and document it in the subject's medical charts.
  - Arrange for the delivery of study treatment (in accordance with local regulation) to the subject's home in advance.
- Local laboratory assessments are not to be performed in study ID-078A303 at regions/sites that are impacted by the pandemic, unless it is judged by the investigator as unavoidable, to preserve the subjects' safety. Should a sample be analyzed by a local laboratory, the investigator should send a prescription to the subject's home to take to the laboratory to ensure that the protocol requirements, laboratory manual and eCRF completion guidelines are followed [protocol section 7.2.4].

During the telephone call or video call visit [protocol section 7]:

- The investigator will interview the subject for:
  - Occurrence of any new AEs or worsening of existing ones.

- When asking about the occurrence of AEs, please follow the same process as for a site visit, i.e., use an open-ended question, such as:
  - "Have you had any significant medical problems since the last study visit?"
- Collection of additional information about AESI as applicable. AESI include:
  - Narcolepsy-like symptoms (i.e., EDS, cataplexy and complex sleep behavior events including hallucinations / sleep paralysis),
  - Suicide / self-injury.
- Checking for next day residual effects [see Section 2.4].
- Assessing withdrawal and rebound (only applicable to Visit 6) [see Section 2.4].
- Completion of the C-SSRS questionnaire.
- If closer monitoring of any of the above symptoms is required but not possible, depending on the severity of the symptoms observed and the investigator's assessment of the benefit-risk for the subject participation in the trial, the investigator can consider discontinuing treatment while trying to maintain the subject in the study [protocol section 5.1.9].
- Changes in any ongoing medication or start of new medication(s).
- Check compliance with study medication and potential overdose or other medication error(s) [protocol sections 5.1.7 and 9.1.1].
- The telephone or video contact must be entered under the visit it replaces (e.g., if the assessments were intended for Visit 3, please use the Visit 3 form) and documented in detail (day, time and conversation) in the subject's medical charts. All assessments not performed must be entered as "Not done".
- Should any additional telephone calls be performed to ensure the subject's safety that are not part of the regular visit plan, the call must be entered as an unscheduled visit ('UNS') in the eCRF and documented in detail (day and reason for the 'UNS') in the subject's medical charts.
- For Visit 6 please also refer to Section 2.4

2.3 Provisions for subjects infected with SARS-CoV-2

Testing for SARS-CoV-2 should follow local guidance. Mandatory testing is not requested for this study.

Should a subject become infected with SARS-CoV-2 / contract COVID-19:

- Information about COVID-19 infection, whether positively confirmed with a SARS-CoV-2 test or not, and its corresponding diagnosis (symptoms or pneumonia related to COVID-19) as well as administered medications will be collected on the AE and Concomitant Medication pages of the eCRF.

- If a subject is without symptoms and remains asymptomatic, study treatment can be continued as per protocol.
- If a subject is presenting mild symptoms, study treatment can be continued as per protocol and the subject should be closely monitored. Should the symptoms worsen, study treatment should be interrupted.
- If a subject develops severe symptoms or requires hospitalization for COVID-19, the subject should be discontinued from study treatment.
- When shipping blood samples from subjects who tested positive or had high potential to test positive for SARS-CoV-2 virus infection to the Study Central Laboratory, the central laboratory manual and the most up-to-date COVID-19 regional guidance should be followed.

Drug-drug interaction with medications used to treat COVID-19

Certain treatments used for COVID-19, such as lopinavir/ritonavir (strong CYP3A4 inhibitor) are contraindicated in association with daridorexant. Please refer to the Investigator's Brochure and the protocol for more details on potential DDIs with daridorexant. Please try to avoid using such treatments for at least 24 h after last dose intake of daridorexant.

2.4 Evaluation of the study endpoints

2.4.1 Safety endpoints

If the investigators are not able to arrange site visits to perform the safety evaluations planned at each visit during the period that the site is affected by the COVID-19 pandemic, the following should be implemented:

2.4.1.1 Withdrawal effects (only at run-out Visit 6) [protocol sections 7.2.2.6 and 7.2.2.8]

Withdrawal effects are assessed via BWSQ scores, occurrence of relevant AEs and marked ECG abnormalities upon treatment discontinuation. If no on-site visits are possible, withdrawal effects will only be assessed by relevant AEs upon treatment discontinuation.

2.4.1.2 Rebound insomnia (only at run-out Visit 6) [protocol section 7.2.3.1]

Rebound insomnia is assessed via subjective sleep parameters collected through the subject's sleep diary. The hand-held device is automatically programmed to display the sleep diary when entries are expected from the subject, therefore, those data can still be collected and analyzed without disruption.

2.4.1.3 Next day residual effects [protocol sections 7.2.2.4 and 7.2.3.1.2]

Next day residual effects are assessed via the SDS questionnaire and VAS scores collected in the hand-held device. The SDS requires manual activation at each visit. As no remote activation can be performed, if an on-site visit cannot be performed, those data will not be

collected and analyzed. The VAS is automatically programmed to be displayed when entries are expected from the subject, therefore, those data can still be collected and analyzed without disruption.

2.4.1.4 Occurrence of AESIs [protocol section 7.2.2.5]

If an on-site visit is replaced by a telephone/video call, investigators should collect any new occurrence or worsening of AE, including AESIs (as defined above). The C-SSRS should also be completed during this call. Therefore, no disruption should be noted in the evaluation of this safety endpoint.

2.4.2 Efficacy endpoints [protocol section 7.2.3]

Efficacy endpoints are collected through the subject's entries in the sleep diary and the completion of the IDSIQ questionnaire. The hand-held device is automatically programmed to display the sleep diary when entries are expected from the subject, therefore, those data can still be collected and analyzed without disruption. The investigator/delegate is encouraged to remind the subject to complete the sleep diary and IDSIQ at each call performed.

2.4.3 Impact on statistical analyses [protocol section 10]

The sample size in ID-078A303 is driven by subjects rolling over from ID-078A301 / ID-078A302. The number of subjects rolling over from ID-078A302 may be impacted during the COVID-19 pandemic: subjects who are unable to perform their visit (Visit 10) in ID-078A302 and did not have their eligibility criteria assessed at the site for this extension study cannot roll over.

No changes to the current planned analyses are foreseen. All observed data will be summarized as planned. The missing-at-random assumption of the linear mixed-effects model is considered appropriate for any missing data due to the COVID-19 pandemic.

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

Protocol deviations due to COVID-19 are expected to occur during the pandemic and fall under the ICH GCP 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 protocol deviation occurring due to COVID-19 must be documented according to ICH GCP 4.5.3 and be clearly recorded as related to COVID-19. All protocol deviations will be reported to the sponsor, IEC/IRB and regulatory authorities according to local requirements.

2.6 Monitoring

If on-site monitoring cannot be performed by the CRA as described in protocol section 12.8 and if acceptable under local law with the IEC/IRB, the CRA will conduct remote monitoring and remote SDV, provided that the subject's confidentiality is maintained throughout the process [as per protocol section 11.2] and all local approvals to do so are in place. If remote monitoring or remote SDV are not allowed, alternatives as applicable, according to local regulations, might be agreed with the PI to ensure data integrity.