Cover page

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A Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of cenerimod in subjects with moderate to severe systemic lupus erythematosus (SLE)

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ADDENDUM 2 TO PROTOCOL
ID-064A202

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
BILAG	British Isles Lupus Assessment Group
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
DDI	Drug-drug interaction
eCRF	Electronic case report form
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
HMA	(EU) Heads of Medicines Agencies
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PD	Protocol deviation
PGA	Physician's Global Assessment
PRO	Patient Reported Outcome
QoL	Quality of Life
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index-2000
SRI	Systemic Lupus Erythematosus Responder Index
WBC	White blood cell
WHO	World Health Organization

UPDATE TO THE ADDENDUM

This amendment applies to the addendum, dated 8 April 2020, to the protocol ID-064A202, issued to implement "Exceptional measures to ensure subject safety and counteract potential trial conduct disruption due to the COVID-19 pandemic".

The resulting document is: Addendum 2 to protocol ID-064A202, dated 27 May 2020.

Rationale

The main reason for the changes to the addendum is to implement the IDMC recommendations sent to Idorsia on 18 May 2020, consisting of screening all new patients for SARS-CoV-2 prior to entry in study ID-064A202. Hence, subjects who test positive for SARS-CoV-2 should be considered as screen failures and discontinued from the study.

Changes to the Addendum

The section "Subjects infected with SARS-CoV-2"of the addendum is updated to include the following new instructions:

2.3 Subjects infected with SARS-CoV-2

- During screening, subjects must be tested for SARS-CoV-2 unless the subject has tested negative within a week prior to screening. Subjects will be screen failed and discontinued from screening if she/he tests positive for SARS-CoV-2.
- It is the responsibility of the investigator/delegate to obtain the subject's consent using a specific ICF if the testing for SARS-CoV-2 is performed as part of the trial-mandated procedures during screening. The SARS-CoV-2 test can be performed at the site or in a local laboratory using a prescription provided by the investigator.
- After subject randomization, testing for SARS-CoV-2 should follow local guidance.

Two versions of the updated addendum will be provided:

1) a clean version and 2) a comparison document showing deletions and insertions in comparison to the previous addendum version.

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 ID-064A202 (CARE) study investigators 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 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 sections affected:

2 RECOMMENDATIONS AND INSTRUCTIONS

2.1 Conduct of on-site visits

For subjects who are continuing to participate in the ID-064A202 (CARE) study, it is important that the protocol visit schedule is adhered to in order to ensure subject safety and trial integrity during the COVID-19 pandemic outbreak.

The preferred option is to maintain on-site visits, provided that the subject is allowed and can travel to the site [see protocol section 7.1]. 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.

On-site visits should be performed according to the protocol [see protocol section 7.2, table 4]. To facilitate on-site visits, scheduled visits might be brought forward or visit windows extended (e.g., ±7 days from scheduled visit, or even longer if the subject has enough study treatment). The reason for this delayed scheduled visit must be documented in the subject's medical chart.

If the subject can travel to the investigational site for his/her study site visit, the investigator should:

- Ensure the subject's safety on his/her way to the site in compliance with local/country instructions (e.g., not using public transportation).
- Perform the on-site visit assessments according to the protocol [protocol section 7.1 and 7.2].
- If blood and urine samples cannot be collected by the courier for shipment to the central laboratory, the analysis can be performed by the site's local laboratory*.

*If done by site local laboratory, the investigator should make sure that the site personnel has an "unblinded" staff member who is not involved in the conduct of ID-064A202 (CARE) study and who can check for any WBC (including differentials) and lymphocyte counts and redact these parameters from the laboratory report. If this option is not available, the site local laboratory analysis should still be performed.

Note that new subjects may be considered for screening only after thorough evaluation of the benefit-risk for the subject participation in the context of the COVID-19 pandemic. Screening visit should only take place if a complete on-site visit can be organized. If this is not possible, the preferred option is to reschedule the screening visit to a time when all components of the site visit can be performed in full compliance with the protocol.

2.2 Conduct of home visits or remote visits

If the subject cannot, is not allowed, or is not willing to travel to the investigational site due to the COVID-19 pandemic, **remote visits (telephone call or video call)** may be conducted as described below.

- If possible, it is preferable to have the remote visit performed as a **video call** instead of a telephone call.
- The IEC or IRB must be notified in advance of remote visits if this is a local requirement.
- **During the remote visit**, the investigator will interview the subject to:
  - Check for the occurrence of any new AE or worsening of existing ones. When asking for AEs, the same process as that used for site visits is to be followed [see protocol section 9.3], i.e., use open-ended questions such as "Have you had any new symptoms or experienced any worsening of your disease since the last study visit?".
    - If the subject spontaneously reports symptoms of worsening of disease activity or symptoms that could be related to the safety areas of special interest [refer to protocol appendix 5] follow the instructions below, as relevant:

- Symptoms potentially related to SLE flare: a visit by site staff / or home nurse to the subject's home should take place if allowed or the subject should be asked to come to the site if this is allowed in emergency cases.
- Bradycardia (e.g., dizziness, vertigo, syncope): treatment medication interruption and restart should be verified, and the subject should be asked to check their pulse. If severe bradycardia is suspected, a visit by site staff / home nurse to the subject's home should take place if allowed.
- Hypertension/hypotension (e.g., severe headache, fatigue, confusion, vision problems, chest pain, difficulty breathing, irregular heartbeat, dizziness or lightheadedness, fainting): the subject should be asked about availability of a home-based automated blood pressure instrument for self-assessment or such a device should be delivered to the subject's home.
- Dyspnea: if severe dyspnea is observed, the subject should be asked about other potential symptoms that could be linked to COVID-19 (e.g., fever) to act accordingly. If this is not possible a home nurse service should be organized to perform spirometry at the subject's home.
- Visual disturbances: if reduced or blurred vision is reported, the investigator should consider whether waiting for site to return to normal site operation is acceptable. The investigator may consult the study ophthalmologist for the most appropriate action to be taken.
- Symptoms that may indicate hepatotoxicity: (e.g., unusual lethargy or fatigue, nausea, vomiting, upper right quadrant pain or tenderness, jaundice, anorexia, dark urine, fever, rash, itching) blood sampling at home is to be conducted.

– Check for changes in any ongoing medication or start of new medication(s)
– Check if the subject has enough study medication to ensure no study medication holiday.
– Make sure that subjects who are women of childbearing potential have enough home pregnancy kits (send them along with study medications to subject's home if necessary) and remind them to perform the test monthly.
– Ask the subject to perform the blood and urine sampling in a local laboratory for analysis using a prescription provided by the investigator**.

** If possible, in this situation laboratory results and reports should be sent to an "unblinded" site staff member who is not involved in the conduct of (ID-064A202) CARE study and who can check for any WBC (including differential) and lymphocyte count and redact these parameters from local laboratory report. If this option is not available, site local laboratory analysis results and reports should still be sent to the site.

- If closer monitoring of any of the above symptoms is not possible within the foreseeable future, depending on the severity of the symptoms observed and on the

investigator's assessment of the benefit-risk for the subject's participation in the trial, the investigator may consider discontinuing the study medication.

- A subject who permanently discontinues study treatment is not considered as having withdrawn from the study, provided that the subject's consent to participate in the study has not been withdrawn. Hence, the subject remains in the study, and study protocol assessments should continue to be performed until the end of the study following the planned scheduled of assessments. This will reduce the amount of missing data and should ensure data accuracy and scientific relevance of the study results.
- The site staff should organize the delivery of study treatment and pregnancy tests (if applicable) to the subject's home using either the institutional internal process or a home nurse, if allowed by local laws and regulation or by using the express courier service contracted by the sponsor. Shipment to subject's home can only occur after obtaining subject's consent [see Section 2.2.1].
- For those subjects for whom study medication is provided at home due to the inability to perform on-site visits, a solution must be identified to perform, at a minimum, the WBC and lymphocyte count assessments (preferably the entire chemistry and hematology panel) as close as possible to the original protocol schedule, preferably using the study central laboratory, or a local laboratory if necessary.
- During the remote visit, the investigator also ensures that the subject understands that the new study medication kit is to be used instead of the one used previously, even if there is remaining medication. The unused medication will have to be brought back to the center at the next safe opportunity.
- The **remote visit** must be entered as an Unscheduled visit in the eCRF and documented in detail (day, time and conversation) in the subject's medical charts.
- The remote visit is not meant to replace an on-site visit. If in the foreseeable future on-site visits can be resumed, planned on-site visits can be re-scheduled as long as the subject has enough study treatment and SLE background therapy. As soon as possible following the remote visit, the corresponding on-site visit must be performed. If the corresponding on-site visit can only be scheduled relatively close to the next scheduled study visit (e.g. within 1 week of the next study visit), this study visit will be skipped to the next scheduled on-site visit.

Idorsia is providing the option to have home nurses visiting the subject at home (also called "flying nurses")

In addition to the remote visit, Idorsia will support the sites to organize home nurses to visit the subjects at home if allowed. Home nurse visits can be performed in order to keep close contact with the subjects at least as frequently as required by the protocol mandated on-site visits:

The home nurses will:

- Handle the shipping logistics of the central laboratory kits for blood and urine sampling.
- Handle the delivery of the study medication to subject's home.
- Assess blood pressure measurement at subject's home.
- Make sure that subjects who are women of childbearing potential have enough home pregnancy kits (send them or bring them along with study medications to subject's home if necessary) and remind them to perform the test monthly.
- Perform the blood and urine sampling and will organize the shipping logistics to the central laboratory. If blood and urine samples cannot be collected by the courier for shipment to the central laboratory, the analysis will be performed by the site local laboratory**.
- Provide PRO and QoL questionnaires to the subject at home.

2.2.1 Obtaining subject's consent to provide his/her name and home address to a third party

In line with the protocol section 12.3, it is the responsibility of the investigator/delegate to obtain the subject`s consent to provide his/her name and home address to any third party (e.g., courier service, home nurse) responsible for delivering study treatment (and pregnancy tests if applicable). In the event of verbal consent, the date and time verbal consent was obtained must be documented in the subject's medical chart. If according to the local regulation the subject's consent must be obtained in writing, investigator must act accordingly (e.g., request subject's consent by mail) and document it in the subject medical charts.

2.3 Subjects infected with SARS-CoV-2

- During screening, subjects must be tested for SARS-CoV-2 unless the subject has tested negative within a week prior to screening. Subjects will be screen failed and discontinued from screening if she/he tests positive for SARS-CoV-2.
- It is the responsibility of the investigator/delegate to obtain the subject's consent using a specific ICF if the testing for SARS-CoV-2 is performed as part of the trial-mandated procedures during screening. The SARS-CoV-2 test can be performed at the site or in a local laboratory using a prescription provided by the investigator.
- After subject randomization, testing for SARS-CoV-2 should follow local guidance.

In addition to the provisions described in Sections 2.1 and 2.2, should a subject become infected with SARS-CoV-2 / contract COVID-19:

- Information about COVID-19 positivity to SARS-CoV-2, 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 (refer to protocol sections 9 and 5.2, respectively).

- If a subject is confirmed to be infected with SARS-CoV-2, the precautionary principle suggests that study treatment should be stopped. No unblinding is deemed necessary. In the event that the subject is on active therapy, the effect of cenerimod will disappear gradually.
- Given the long half-life of cenerimod (12–22 days) [see section 1.4.2 of the Cenerimod IB], Idorsia has evaluated the potential DDI with the current, available, most frequently used medications for COVID-19 (e.g., remdesivir, lopinavir/ritonavir, IFN beta1b, corticosteroids, hydroxychloroquine). Based on our current knowledge, cenerimod and the anti-COVID-19 drugs are not expected to mutually affect their PK properties based on an effect on metabolizing enzymes or transporters, therefore subjects can be treated as per current practice. Refer to the IB for full description of potential DDIs with cenerimod [Cenerimod IB].
- When shipping 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 updated COVID-19 regional guidance provided by [redacted] should be followed.

2.4 Efficacy assessments

2.4.1 Study assessments related to the primary and secondary endpoints.

It is important to ensure that efficacy assessments, especially assessments related to primary (SLEDAI-2K) and secondary endpoints (i.e., BILAG and SRI-4) are performed as per protocol. They should ideally not be performed later than one month after the protocol planned schedule of assessment [see protocol section 7].

If the investigator is not able to arrange on-site visits to perform the planned efficacy evaluations, the following should be implemented:

- Organize the remote visit as described above, at approximately the time of the planned visit assessment.
- During the remote visit, the investigator should collect the SLEDAI-2K components even if not all assessments are possible [protocol section 7.2.6]. Record the outcome of the SLEDAI-2K assessment in the eCRF and report a PD related to COVID-19 in the event of missing values. If this is not possible, the investigator should contact the CRA or sponsor study team.
- The same procedures should be followed to perform the assessments (e.g., BILAG, PGA, SLE Flare Index) related to the secondary efficacy endpoints. These measurements should be collected at that time as well [protocol section 7.2.6].

Very important note: as soon as the study site can resume activity, ask the subject to come to the site at the closest scheduled visit, to perform a full SLEDAI-2K assessment and all other assessments (such as BILAG, PGA, ...) which will be recorded in the eCRF.

2.5 Reporting of protocol deviations related to COVID-19 pandemic

PDs 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 PD occurring due to COVID-19 must be documented according to ICH GCP 4.5.3 and clearly recorded as related to COVID-19. All PDs 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 source data verification, 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 source data verification are not allowed, alternatives as applicable according to local regulations might be agreed with the investigator to ensure data integrity.

3 REFERENCES

[Cenerimod IB] Investigator's Brochure for cenerimod (ACT-334441), version 10. Idorsia Pharmaceuticals, Ltd, January 2020.