Cover page

Official Title:

Multi-center, blinded, randomized, parallel-group, Phase 3 study with aprocitentan in subjects with resistant hypertension (RHT).

ClinicalTrials.gov Identifier:

NCT03541174

Brief Title:

A Research Study to Show the Effect of Aprocitentan in the Treatment of Difficult to Control (Resistant) High Blood Pressure (Hypertension) and Find Out More About Its Safety

(PRECISION)

Date of protocol addendum document:

8 April 2020

ADDENDUM TO PROTOCOL

ID-080A301 (PRECISION)

Multi-center, blinded, randomized, **P**a**R**all**E**l-group, Phase 3 study with apro**CI**tentan in **S**ubjects with Res**I**stant Hypertensi**ON** (RHT)

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

Document Number: D-20.063

8 April 2020

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LIST OF ABBREVIATIONS AND ACRONYMS

ALT	Alanine aminotransferase
AOBPM	Automated office blood pressure measurement
AST	Aspartate aminotransferase
BP	Blood pressure
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
GCP	Good Clinical Practice
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IFN	Interferon
IRB	Institutional review board
MCAR	Missing completely at random
NT-proBNP	N-terminal pro-brain natriuretic peptide
PD	Protocol deviation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBAT	Standardized background antihypertensive therapy
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), Idorsia provided instructions and guidance in communication letters sent to ID-080A301 (PRECISION) study investigators on 19 March 2020 and 31 March 2020. These measures and instructions are in line with health authority guidelines (FDA, EMA and individual national health authorities) released in March 2020 on how to address the challenges caused by the pandemic itself.

These measures, which 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(s) affected.

2 RECOMMENDATIONS AND INSTRUCTIONS

New subjects may be considered for screening only after thorough evaluation of the risk-benefit for the subject's participation in the context of the COVID-19 pandemic. The 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 re-schedule the Screening visit at a time when all components of the site visit can be performed in full compliance with the protocol [see protocol section 7.1.1.1].

2.1 Guidance on flexibility of study visits and safety assessments for subjects ongoing in the study

2.1.1 Site visits for subjects who can still travel to the site

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.

- **Study visits, protocol section 7:** On-site visits are the preferred option. If a site faces difficulty (e.g., limited site staff) scheduling visits according to the protocol, the visits can be re-scheduled with the provision that the subject has enough study medication, i.e., study treatment and SBAT. The reason for the delayed protocol visit (i.e., re-scheduling) must be documented in the subject's medical chart. The instructions below are to be followed:
  - **Screening period, protocol section 3.1.1.1:** The flexibility is high as the protocol allows visits to be scheduled as needed. If it is not certain that the on-site visits can be performed in the near future, the subject can be discontinued and declared as a screen failure. Subjects who are screen failures due to COVID-19 can be re-screened when it can be ensured that the study protocol can be followed again [protocol section 7.1.1.2]. This also applies to subjects who have already switched to the SBAT.
  - **Run-in period, protocol section 3.1.1.2:** Visit 3 can be skipped if it cannot be conducted. In addition, the duration of the run-in period can be between 3 and 8 weeks based on the principal investigator's judgment, by taking into consideration the subject's medical conditions.
  - **Double-blind part 1, protocol section 3.1.1.3:** The key visits are Visit 4 (Randomization) and Visit 6 (Week 4) as BP measurements collected during these two visits are needed to derive the study primary endpoint. The visit window for Visit 6 can be ±1 week. If this is not possible, the site staff should contact the Idorsia study team as soon as possible to evaluate potential alternatives.
  - **Single-blind part 2, protocol section 3.1.1.3:** The key visits are Visit 7 (Week 6) and Visit 11 (Week 36).
    - Visit 7 can be performed within a −2 days / +1 week window.
    - Visit 11 can be performed within a −12 days / +8 weeks window.
    - Other visits can be performed within a ±3 weeks window.
      - Due to the current circumstances, even more flexibility is allowed (e.g., skipping visits) based on the investigator's judgment by taking into consideration a subject's medical condition (e.g., BP level, ongoing adverse events).
  - **Double-blind withdrawal part 3, protocol section 3.1.1.3:** The key visits are Visit 13 (Re-randomization) and Visit 15 (Week 40) as BP measurements collected during these two visits are needed to derive the study key secondary endpoint. The visit window for these two visits can be ±1 week. If this is not possible, the Idorsia study team must be contacted as soon as possible to evaluate potential alternatives.

- **Laboratory assessments, protocol section 7.2.3.5:** If blood and urine samples cannot be collected by the courier for shipment to the central laboratory, site staff should make sure that, in addition to freezing the samples for delayed assessments, a portion of the sample is used to measure the following safety parameters by the site's local laboratory:
  - Hemoglobin, NT-proBNP, serum creatinine, eGFR, ALT, AST, and total bilirubin.

2.1.2 Conduct of remote visits for subjects who are not allowed or not willing to travel to the investigators site

- **Study visits, protocol section 7:** As an alternative to an on-site visit, a telephone call or video call can be performed. Video call is the preferred option, if possible. A telephone call or video call does not replace an on-site visit. As soon as possible following the call, the corresponding on-site visit must be completed. If the (corresponding) on-site visit can only be scheduled relatively close to the next scheduled study visit (i.e., within 1 week of the next study visit), the corresponding study visit should be skipped and only the next scheduled study visit per protocol should be performed.

1) Scheduling the call

- When scheduling the date and time of the call, ensure that adequate time is planned to perform all the assessments listed below, including the risk-benefit evaluation for the subject regarding his/her continuation of study medications.
- The subject should be asked to perform the following assessments on the day before the call:
  - BP measurements according to the protocol section 7.2.2.3 with the home BP device provided to her/him for the study, or, if not delivered, with her/his own BP device.
  - Body weight measurement according to protocol section 7.2.3.3.
  - Subject should be instructed to record the BP, body weight values and last study treatment/SBAT intake date and time in the home BP monitoring card or in a notebook. This will be the source document.

2) During the call

- Ask the subject for the measured BP and body weight values and record them in the subject's medical chart.
  - Remind the subject to bring the home BP monitoring card or the notebook to the next on-site visit for verification.
- Ask for adverse events, follow the same process as for site visit, i.e., use an open-ended question such as: "Have you had any medical problem since the last study visit?"

- Ask whether any new medication has been taken or other medication has been modified.

- **Study treatment, protocol section 5:**
  - Remind the subject about the importance of taking study medications according to the protocol.
  - Check if the subject has enough study treatment and SBAT to ensure no study treatment and/or SBAT holiday. If the subject does not have enough study treatment and/or SBAT to last until the next visit, follow the instructions below:
    - If possible, the subject or a relative can collect study treatment and/or SBAT from the site (e.g., at a specific site delivery point / at the gate of the clinic).
    - If the above option is not possible, study treatment and/or SBAT may be sent to the subject's home using a local courier organized by site or through the site's CRA.
    - If neither of the above options are possible, the site's CRA is to be contacted. Idorsia will support the site and the CRA to find the best solution for the subject (e.g., collect SBAT from the local pharmacy).

- **Laboratory assessments, protocol section 7.2.3.5:**
  - For subjects with a medical history of heart disease and/or fluid retention/edema, ongoing adverse events related to cardiovascular diseases, or eGFR between 15 and 30 mL/min/1.73 m^2, the following blood parameters must be measured: hemoglobin, NT-proBNP, serum creatinine, eGFR, ALT, AST, and total bilirubin.
    - If a subject is allowed to leave the house according to the local regulations, assist him/her to find a local laboratory close to his/her home for the above measurements. Provide a prescription for the tests to be performed. Costs incurred will be reimbursed by Idorsia.
    - If a subject is not allowed to leave the house according to the current local regulations, organize the drawing of blood samples at the subject's home. In the event of difficulties, the site's CRA can be contacted for support.
    - Ask the subject to report back to the site as soon as results are received and to keep the local laboratory report. This will be used as the source document and must be given to the site at the next visit.
    - If neither of the above options are possible, a thorough risk-benefit evaluation of the treatment and the study in the COVID-19 context must be performed to decide whether this subject should remain in the study.

  - For women of childbearing potential: make sure the subject has enough home urine pregnancy kits (send them along with study medications to subject's home if necessary), remind them to perform the test monthly and ask for results.

- **Data collection, protocol section 11.1:** The telephone or video contact must be entered as an unscheduled visit in the eCRF and documented in detail (date, time and conversation) in the subject's medical charts.

- **Informed consent, protocol section 12.3:** If study treatment, SBAT and/or pregnancy kits need to be shipped to subject's home, ensure the following:

  - Obtain the subject's verbal consent by telephone to provide his/her name and home address to the courier service responsible for delivering study medications and pregnancy test. The date and time that verbal consent was obtained must be documented in the subject's medical records.

  - If, according to your local regulation, the subject's consent must be in writing, act accordingly (e.g., request consent by email) and document it in the subject's medical charts.

2.2 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:

- Information about positivity for SARS-CoV-2 and its corresponding diagnosis (symptoms) as well as administered medications will be collected on the Adverse Events and Concomitant Medication pages of the eCRF.

- If a subject becomes infected, study treatment should be continued as there is no reason to believe that aprocitentan could have a negative impact on SARS-CoV-2 infection or its complications. In addition, abruptly stopping a potentially active treatment may destabilize the control of BP and contribute to a worse prognosis in the event of COVID-19. This also applies to the SBAT: "EMA advises continued use of medicines for hypertension, heart or kidney disease during COVID-19 pandemic" (EMA/143324/2020).

- In the event of infection with SARS-CoV-2, on the basis of our current knowledge, a subject can be treated with the currently available most frequently used medications for COVID-19 (e.g., remdesivir, lopinavir/ritonavir, IFN beta1b, corticosteroids, hydroxychloroquine) given that aprocitentan and the anti-COVID-19 drugs are not expected to mutually affect their pharmacokinetic or pharmacodynamic properties based on an effect on metabolizing enzymes or transporters. The full description of potential drug-drug interactions with aprocitentan is provided the Investigator's Brochure.

- 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 Q Squared Solutions should be followed.

2.3 Evaluation of primary efficacy endpoint

2.3.1 Efficacy / primary endpoint

It is expected that investigators will not be able to perform all on-site visits while the site is affected by the COVID-19 pandemic.

2.3.1.1 Blood pressure analysis (primary and secondary endpoints)

The primary and key secondary efficacy endpoints of this study need to be measured at on-site visits (i.e., at Visits 4, 6, 11 and 13) with an unattended AOBPM device [see protocol sections 6.1.1 and 6.1.2]. If these measurements cannot be performed due to missing on-site visits because of the COVID-19 pandemic, the BP should be measured at home [see Section 2.1.2].

2.3.1.2 Impact on statistical analyses

It is expected that the amount of missing data will increase due to the COVID-19 pandemic. Missing data due to missed on-site visits are assumed to be MCAR. Thus, data missing due to the COVID-19 pandemic should not introduce bias in the statistical analyses.

The analysis of the primary endpoint [protocol section 10.3.2] is based on AOBPM data collected at Randomization (Visit 4) and Week 4 (Visit 6). Data missing because of on-site Visits 4 and 6 were missed due to the COVID-19 pandemic will not be imputed but will be handled by the mixed model specified for the primary endpoint analysis.

The analysis of the key secondary endpoint [protocol section 10.3.3] is based on AOBPM data collected at Re-randomization (Visit 11) and Week 40 (Visit 13). Data missing because on-site Visits 11 and 13 were missed due to the COVID-19 pandemic will be handled by the mixed model specified for the key secondary endpoint analysis.

If the amount of missing AOBPM data at Visits 4, 6, 11 and 13 due to the COVID-19 pandemic is high (e.g., double the expectations in the protocol), home BP values may be included in the main analysis of the primary and/or key secondary endpoints. The home BP values will in any case be included in a supportive analysis. This will be described in an update of the statistical analysis plan.

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

PDs due to COVID-19 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 COVID-19 must be documented according to ICH GCP section 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.

2.5 Monitoring

If on-site monitoring cannot be performed by the CRA as described in protocol section 12.8, and if acceptable under local law 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. If remote monitoring or remote SDV are not allowed, alternatives as applicable according to local regulations might be agreed with the principal investigator to ensure data integrity.