# BARDOXOLONE METHYL (RTA 402)

## 402-C-1603 [redacted]

**EUDRACT NUMBER: 2016-004395-22**

# A PHASE 2/3 TRIAL OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH ALPORT SYNDROME

# US/AUS ADDENDUM 1.0
# DATED 05 JUNE 2020
# TO
# PROTOCOL VERSION 4.0 – 22 APR 2019

# SPONSOR APPROVAL AND SIGNATURE PAGE

[redacted]

Date

[redacted]

Date

[redacted]

Date

# INVESTIGATOR'S AGREEMENT

I have received and read the addendum to the protocol v4 dated 22 Apr 2019 aimed at managing the study during the COVID-19 emergency and agree to conduct the study according the mitigation measures put in place. I agree to maintain the confidentiality of all information received or developed in connection with this addendum.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

# 2. TABLE OF CONTENTS

# 3. JUSTIFICATION FOR THE ADDENDUM

Since the WHO declared the COVID-19 pandemic, various challenges exist which result in restrictions of visits to healthcare facilities, increased demands on the health services and changes to trial staff availability and resources. Study participants may also be required to self-isolate, which introduces difficulties for Investigators to maintain medical oversight. These challenges could have an impact on the conduct of trials and data integrity, such as the completion of trial assessments, completion of trial visits, continued patient safety oversight and the provision of Investigational Products (IPs).

As a sponsor, Reata Pharmaceuticals is committed to ensuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity.

To face this evolving situation, Reata Pharmaceuticals has put in place some pragmatic actions to address the challenges of conducting research, while ensuring the rights, safety and wellbeing of participants.

This addendum outlines Reata Pharmaceuticals' strategies to be implemented during the COVID-19 pandemic, to maintain ongoing safety reporting, access to study drug, continuity of patient care, and oversight of clinical site performance and quality.

This document is being presented in an effort to make available information regarding the mitigation strategies that have been implemented for the CARDINAL study as a result of COVID-19. Since the nature and scope of this outbreak is rapidly evolving, Reata continues to monitor the situation and adjust its response as appropriate.

The main activities this addendum addresses are:

- ongoing safety monitoring of the trial participants
- continuity of IP supply for subjects
- preservation of trial integrity through the collection of critical data

# 4. CHANGES TO THE CURRENT APPROVED PROTOCOL

THE FOLLOWING CHANGES ARE IMPLEMENTED DURING THE COVID-19 PANDEMIC. AS THE IMPACTS OF COVID RESOLVE, THE CURRENTLY APPROVED VERSION OF THE PROTOCOL WILL BE FULLY REIMPLEMENTED FOR STUDY CONDUCT. AS SUCH, THESE CHANGES ARE PRESENTED AS AN ADDENDUM TO BE FOLLOWED, AS NEEDED, AND DURING THIS GIVEN PERIOD ONLY.

| | | VERSION NUMBER | VERSION DATE |
|---|---|---|---|
| **CURRENT APPROVED PROTOCOL:** | | 4.0 | 22 Apr 2019 |
| **CHANGES TO THE CURRENT APPROVED PROTOCOL** | | | |
| **1.** | **SECTION NO., SECTION TITLE, PAGE NO.(S):** | **7. INVESTIGATIONAL PLAN** page 34 | |
| | **OLD TEXT:** | No changes | |
| | **NEW TEXT:** | Added subparagraph ***7.6. Home Health Provider Use***<br>Due to the COVID-19 outbreak and the resulting restrictive measures put in place by the different national and regional governments that, in many cases, resulted in travel restrictions, limited availability of site access and personnel, and local limitation on the movement of delegated individuals, the use of home health services has been implemented to assist with the collection of study required visits and laboratory assessments while also guaranteeing the rights, safety and wellbeing of participants and of the trial sites' staff. The use of a company specialized in home health services ensures the ongoing safety monitoring of trial participants and maintaining trial integrity through the collection of critical data, in accordance with FDA and local guidelines about the COVID-19 pandemic management. For each hired home health nurse/professional, the site will be provided with the following documentation: signed and dated CV, current Nursing Licensure, GCP training certificate, and protocol training certificate. The home health nurse/professional will also be included in the Delegation of Activities log of the site.<br>The tasks delegated to the home health nurse/professional at the patient's home will be: collection of vital signs and weight measurements, collection of information about adverse events and concomitant medications, collection of laboratory samples (blood and urine), supply urine pregnancy test for self-reading, drug accountability, and diary collection. The laboratory samples are collected using the laboratory kit provided by the centralized laboratory, normally used for the study visit conduct, and are processed and shipped according to the laboratory manual of the study. All costs relevant to these additional services will be covered by Reata Pharmaceuticals. |
| | **REASON FOR CHANGE:** | Mitigation measures taken by the sponsor to ensure safety of subjects and trial's integrity during the COVID outbreak. | |

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| **2.** | **SECTION NO., SECTION TITLE, PAGE NO.(S):** | **8.5 Patient Discontinuation and Termination** page 42 |
| | **OLD TEXT:** | No changes |
| | **NEW TEXT:** | Added sub-paragraph ***8.5.3 SARS-COV-2 Testing and Investigational Product Use***<br><br>If a patient tests positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, the investigational product (IP) RTA-402 (bardoxolone methyl) must be temporarily discontinued until the patient no longer presents an active infection, as assessed by the Investigator and/or the patient's physician(s). The Sponsor must be notified immediately for additional guidance.<br><br>When the investigator deems that the patient can safely return to the site for an in-person visit, the investigator should conduct an unscheduled visit and perform a full clinical assessment with labs:<br>• Safety labs<br>o Clinical chemistry (including eGFR)<br>o BNP and NT-proBNP<br>o Hematology<br>o Urinalysis and microscopy / Urine collection for ACR<br>o Urine pregnancy test for WOCBP<br>• Vital signs<br>• Weight<br>• Adverse event assessment<br>• Prior and concomitant medication assessment<br><br>IP may be resumed if there are no changes in clinical status that would preclude restarting IP. A follow-up telephone call should be conducted 2 weeks after the unscheduled visit to collect adverse events and concomitant medications. Four weeks after the unscheduled visit, the patient should return to the clinic for repeat assessments as outlined in the Week 1 visit. The patient's visit schedule, as outlined in the protocol, may resume thereafter. |
| | **REASON FOR CHANGE:** | Mitigation measures taken by the Sponsor to ensure safety of subjects and trial's integrity during the COVID outbreak. |

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| | **SECTION NO., SECTION TITLE, PAGE NO.(S):** | **9.10.12. Pregnancy Test** page 55 |
| | **OLD TEXT:** | No changes |
| **3.** | **NEW TEXT:** | Added new sub-paragraph **9.10.12.1** ***Self Reading Pregnancy Test***<br>Urinary pregnancy tests for self-reading will be provided by the home health nurse/professional coming to the patient's home. Results will be documented and provided to the site investigators. |
| | **REASON FOR CHANGE:** | Mitigation measures taken by the Sponsor to ensure safety of subjects during the COVID outbreak. |

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| **4.** | **SECTION NO., SECTION TITLE, PAGE NO.(S):** | **9.10.14. Study Drug Dispensation and Collection** page 56 |
| | **OLD TEXT:** | No changes |
| | **NEW TEXT:** | Added subparagraph **9.10.14.1** ***Study drug distribution during the COVID-19 pandemic***<br><br>Prior to the COVID-19 pandemic, trial participants were assigned and dispensed IP during study site visits. During the study site visits, trial participants are sent home with IP and instructed to self-administer the IP each day until their next onsite study visit, at which they would return any unused IP. As the trial participants have been responsible for IP storage within their homes, as well as self-administration of the IP throughout the study, they are properly acquainted with these facets of the study. For those trial participants who discontinue physical site visits during COVID-19, distribution of IP may be made directly to the trial participants' homes by shipment from investigator, through the Hospital pharmacy. IP distributed in this manner will be shipped via traceable courier as an expedited shipment. Given the stability profile of bardoxolone methyl capsules under multiple temperatures and relative humidity conditions, short term temperature excursions above 30°C and as low as 15°C during storage are acceptable. For IP shipments to trial participants' homes, investigators will monitor the time from shipment to receipt of the IP by the trial participant. In the absence of temperature monitoring, and if shipping time exceeds 48 hours, the investigator will immediately instruct the patient not to use the IP until further guidance is provided. The investigator site will then contact Reata (the sponsor) to determine whether the shipment may be used or must be replaced. The investigator site will contact the patient as to the disposition of the IP. Investigators will remain in close contact with trial participants receiving IP at their home and, if necessary, will provide any instructions needed on the use of the IP. Accountability of the IP for these trial participants will be conducted by home health nurses during home visits. After accountability is complete, the home health nurse will secure the kits in a bag that will be returned to the site when the trial participant is able to return to the site for their next visit. The trial participant will be instructed not to take any additional IP from the kits that have been placed in the plastic bag. |
| | **REASON FOR CHANGE:** | Mitigation measures taken by the sponsor to ensure safety of subjects during the COVID outbreak. |

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| **5.** | **SECTION NO., SECTION TITLE, PAGE NO.(S):** | **10.4 Study Drug Administration** page 60 |
| | **OLD TEXT:** | No changes |
| | **NEW TEXT:** | Added subparagraph **10.4.1.** ***Intake of IP Beyond Week 100 During the COVID-19 Outbreak***<br><br>The Week 100 visit (Day 700 +/- 3 days) serves to collect the final "on treatment" lab values from patients. To minimize any days off drug prior to the Week 100 visit, and given the evolving situation of COVID-19, sites may extend dosing by 1 week beyond the protocol window for the Week 100 visit. The maximum extension in dosing is to study Day 710 (Day 707 +/- 3 days), unless otherwise approved by Reata and the IRB. The Week 104 visit must be adjusted accordingly to ensure the Week 104 labs are collected 4 weeks after completing the end of treatment (last dose). |
| | **REASON FOR CHANGE:** | Mitigation measures taken by the sponsor to ensure safety of subjects. |
| **6.** | **SECTION NO., SECTION TITLE, PAGE NO.(S):** | **15.6. Protocol Deviations** page 65 |
| | **OLD TEXT:** | No changes |
| | **NEW TEXT:** | Added new subparagraph **15.6.1.** ***Deviation during the COVID-19 Outbreak***<br><br>Any data that cannot be assessed remotely will be noted as missing. All deviations due to the impacts of COVID-19 will be identified and documented accordingly by the site and the Sponsor. The failure to complete an in-clinic protocol visit will not be considered as a reason for study discontinuation and, beyond the necessary documentation (e.g., duly documented in patient's note by the Investigator), will not be considered as a major deviation. Deviations will be reported, evaluated, and discussed according to the study plan and in the final study report. Sites will continue to document and report protocol deviations according to their usual procedure and institutional requirements. |
| | **REASON FOR CHANGE:** | As allowed by FDA and local guidelines for management of clinical trials during the COVID-19 outbreak. |

# 5. CHANGES IN OTHER STUDY-RELATED DOCUMENTS

## 5.1. Informed Consent

A home health service provider has been appointed by the Sponsor to support visit conduct and patient safety management during this period. To further ensure and maintain the protection of patients' rights, the master ICF document will be revised to incorporate this mitigation strategy as an alternate option to support continuity in care and participation.

# 6. APPENDICES

List of memos provided to study sites:

1. Initial COVID-19 Guidance dated 10 March 2020
2. IP shipping instructions dated 17 March 2020
3. Lab Kit Shipping Instructions dated 19 March 2020
4. Guidance for Direct-to-Patient Shipping of RTA-402 Drug Product Capsules During the Coronavirus (COVID-19) Pandemic dated 25 March 2020
5. COVID-19 Update Memo- Q&A dated 26 March 2020
6. IP Kits Round Two dated 06 April 2020

CARDINAL

FOR PATIENTS WITH ALPORT SYNDROME

**Date: 10 March 2020**

Dear CARDINAL Investigators and Site Personnel,

In response to the ongoing COVID-19 (Coronavirus) outbreak, Reata is taking measures to minimize any impact on the trial's integrity while protecting the health of its employees, patients, customers, partners and broader community. Please note, this overview was produced on 10 March 2020. Since the nature and scope of this outbreak is rapidly changing, we will continue to monitor the situation and adjust our response as appropriate.

INVESTIGATIONAL PRODUCT:

We are triggering shipment of additional IP to sites that have remaining dispensation visits in CARDINAL. In a separate communication, we will provide the formal request and instructions for one kit of IP to be shipped, imminently, to all patients who have not yet completed Week 88 visit. For sites impacted by this request, a site-specific communication will be provided within the next several days.

UPCOMING PATIENT VISITS:

While we all aim to have study visits and assessments conducted as outlined in the protocol, we anticipate the virus may result in some disruption to visit schedules. We recognize your site is putting very specific actions into place in a focused manner and aligned with the local environment and business culture. With reference to the CARDINAL study, we offer the following mitigations:

**Week 76 or 88 visits – where the patient is <u>unable/unwilling to conduct an in-person visit</u>:**

- We are procuring services from a home health company to allow collection of central labs in-home for patients and to assist with IP accountability. This will be in place by late March.
    - Please contact the study team for instructions and guidance.
    - If your site already has a preferred/contracted home health nurse, please let us know.
- If you need to perform one of these study visits and assessments prior to the home health agency being contracted, please contact the study team for instruction and guidance on the following:
    - Study drug may be assigned and shipped to the patient via traceable courier
    - Lab samples for these visits can be obtained at a laboratory (i.e. [redacted] or other lab) that is local for the patient; however, patients MUST use the [redacted] Central Lab kit.
        - The study team will assist you in identifying a laboratory and provide guidance to ensure the laboratory kit and necessary documentation is provided to the patient.
        - [redacted] will be providing additional kits to your site in March, to allow shipment to patients.

**Week 100 and 104 visit – where the patient is <u>unable/unwilling to conduct an in-person visit</u>:**

- These visits are **critical** to the study, and every effort should be made to collect these lab samples
- The Week 100 visit is the last on-treatment eGFR value obtained in the trial. If a patient's visit will be delayed, and there is uncertainty around the visit date, please work closely with Reata to discuss timing for discontinuation of IP. If the patient will require an extended treatment duration, we must work closely with your site and the *IRB/IEC* to obtain the necessary approvals.
- The Week 104 visit is targeted to occur 4 weeks after discontinuation of study drug.
    - The analysis plan allows inclusion of eGFR values obtained **14 - 35 days after the last dose of IP.** As you manage scheduling and patient availability, please adhere to the protocol, and where this is not possible, please take every measure necessary to ensure the 14 – 35 day window is followed.
    - Local labs (using the [redacted] Central Lab kit) or a home health visit should be considered. The study team will provide guidance on logistics.

REIMBURSEMENT FOR PATIENT TRAVEL:

For any visit, please remember patients may be reimbursed for travel. If patients who usually travel by air would prefer to drive to the study site, car rental and mileage is reimbursable, along with meals and accommodation.

UPCOMING MONITORING VISITS:

Monitoring visits will be evaluated on a case by case basis; however many visits planned for March will be cancelled. Where possible, CRAs that are within driving distance may attempt to schedule a visit. If your institution cannot accommodate monitoring visits, please let the study team know.

**If your site has any concerns or patient notifications of a visit impacted by the coronavirus, please immediately inform Reata** [redacted] so we may provide ongoing support. Reata will be monitoring and addressing clinical trial activities from an employee safety and business continuity perspective.

Please submit this letter to your IRB/IEC and file a copy in your regulatory binder.

As always, the health and safety of our study participants and site personnel is our primary concern. As preparations for COVID-19 are underway at many institutions and sites, we are sensitive to the complexities of managing the uncertainty and variables. We appreciate your continued dedication to CARDINAL. If you have any questions regarding the contents of this correspondence, please contact your assigned CRA.

Note: This overview was produced on 10 March 2020. Since the nature and scope of this outbreak is rapidly changing, we will continue to monitor the situation and adjust our response as appropriate.

Sincerely,

[redacted]

CARDINAL

FOR PATIENTS WITH ALPORT SYNDROME

**Date: 17 March 2020**

Dear CARDINAL Investigators and Site Personnel,

In response to the ongoing coronavirus disease (COVID-19), Reata is taking measures to minimize any impact on the trial's integrity while protecting the health of its employees, patients, customers, partners and broader community. This memo is to provide additional guidelines for IP dispensation following the initial memo released on 10 March 2020. Please note, this guideline was produced on 17 March 2020. Since the nature and scope of this outbreak is rapidly changing, we will continue to monitor the situation and adjust our response as appropriate.

**Summary of This Memo**

1. **For subjects on IP treatment but not yet completed Week 88 visit, an additional IP kit will be provided. The kit ID can be found in the subject's Unscheduled Visit folder in EDC and the kit should be shipped from the site to the subject.**
2. **All subjects who receive additional one IP kit for the purpose outlined in this memo are instructed NOT to open this specific IP kit until receiving instruction from the investigator and/or the study coordinator.**
3. **Cost incurred from shipping and dispensing the additional kit should be submitted to eGPS as an invoiceable item.**

ADDITIONAL IP KITS TO ARRIVE

Manual IP shipments have been triggered to provide additional IP kits to sites. You/ your pharmacy will receive additional IP kits, regardless of the amount of IP you currently have in inventory.

ADDITIONAL IP KITS TO BE DISPENSED TO STUDY SUBJECTS

**It is critical that your site continue to closely follow study subjects via telephone to address any queries regarding additional IP kit dispensing as described in the section below:** GUIDELINES FOR SUBJECTS WHO RECEIVE THE ADDITIONAL ONE IP KIT. **Documentation of phone follow up should be documented in your source documents.**

Please follow the steps below to designate and ship one additional IP kit to subjects who have not yet completed the Week 88 visit but remain on IP treatment.

1. For every subject who is still on IP treatment and have not completed Week 88 visits, an Unscheduled Visit folder with only Study Drug Dispensation page has been generated in EDC by Reata. On that page, you will find the ID of the IP kit that you should send or provide to the study subject. The purpose of providing an additional IP kit is to provide flexibility, due to the potential for COVID-19 to disrupt the current dosing schedule. All subjects should continue their current IP dosing schedule and strictly comply with the investigator's direction.
2. The dose of the additional IP kit aligns with the subject's current dose.
3. Please locate the IP kit from your inventory, ship the IP kit to the subject, and prepare your package as described in steps "a" through "d" below:
   a. Your package should be shipped via a traceable courier, such as FedEx and UPS, using overnight delivery services. Please prepare your package based on the courier's guidance. The IP kit can be shipped under ambient temperature.
   b. Appendix I is a label to inform subjects that the IP kit should not be opened or used until directed by the study physician or study coordinator. Please ensure this label is affixed to the outside of the IP kit before shipping to the research subject.
   c. If the subject does not have the Drug Diary for the next IP treatment period, please send the diary with the additional IP kit. For example, if a subject has completed Week 76 but does not have drug diary for Week 88-100 in hand, the diary for Week 88-100 should be sent with the additional IP kit.
   d. **We encourage shipment to the subject as soon as possible as the situation of COVID-19 is evolving rapidly.** If the subject is expected to visit your site in the next few days, you may hand over this additional kit along

with the diary to the subject when s/he is on site. Please note, the IP kit noted in the Unscheduled Visit folder should be provided *in addition* to the IP assigned during the protocol defined study visit.

4. For eCRF completion- please enter 'Yes' to the question 'Will study drug be dispensed to the patient', the date the additional kit is being shipped or provided to the patient in the 'Date dispensed' field, and manually enter the kit number being shipped/provided to the subject as identified in the system auto-populated field. Please also document accordingly in the subject source binder.

GUIDELINES FOR SUBJECTS WHO RECEIVE THE ADDITIONAL ONE IP KIT

Please communicate with your subject based on the following guideline:

1. The additional IP kit should be stored at room temperature (i.e., 20° - 25°C based on the label).
2. When the next scheduled visit approaches, your study team should determine whether it is necessary to postpone the visit. This decision should also be discussed with the study subject. If rescheduling is confirmed, your site should instruct the subject to open and begin taking IP from the additional kit.
3. The subject should document taking any IP dose in the drug diary for the appropriate study period. For example, if the subject has to postpone Week 88 visit, the information of taking this additional IP kit should be in the diary of Week 88-100.
4. The subject should return all kits that were dispensed or shipped (used and unused) during the very next visit.
5. If the investigator wishes to change the dose of the additional IP kit, please follow protocol section 7.3.2 and inform your assigned CRA and CTA.

SITE PAYMENT

All costs incurred from shipping and dispensing the one additional kit (including shipping cost, drug dispensation, study coordinator time and other applicable items on the budget) should be submitted to [redacted].

- Payment Description = the exact name of the Unscheduled Visit folder where the additional kit information resides. For instance, if the name of the folder is 'Unscheduled Visit (3)', Payment Description is 'Unscheduled Visit (3)'.
- Activity Date = 'Date dispensed' on the corresponding eCRF.
- Please merge all costs into one item.

As always, we appreciate your continued dedication to CARDINAL. If you have any questions regarding the contents of this correspondence, please contact your assigned CRA.

Note: This guideline was produced on 17 March 2020. Since the nature and scope of this outbreak is rapidly changing, we will continue to monitor the situation and adjust our response, as appropriate.

Sincerely

[redacted]

APPENDIX I

Cut and affix to the outside of the IP kit

# ! STOP !

CARDINAL

## DO NOT OPEN UNTIL INSTRUCTED BY YOUR STUDY PHYSICIAN OR STUDY COORDINATOR!

This is the investigational drug for the study "CARDINAL", in which you are currently participating. Please bring all used and unused drug/kits to your next study visit. If you have any questions, contact your study physician, study coordinator or the contact on the first page of the informed consent form.

CARDINAL
FOR PATIENTS WITH ALPORT SYNDROME

**Date: 19 March 2020**
**Subject: Supplying lab kits to research subjects; supplements initial memo issued 10 Mar 2020**

Dear CARDINAL Investigators and Site Personnel,

The purpose of this memo is to provide additional guidance for supplying lab kits to research subjects participating in 402-C-1603 (CARDINAL) following the initial memo released on 10 March 2020.

In response to the ongoing coronavirus disease 2019 (COVID-19) outbreak, Reata is taking measures to minimize any impact on the trial's integrity while protecting the health of patients, employees, customers, partners and the broader community.

While we all aim to have study visits and assessments conducted as outlined in the protocol, we anticipate the current pandemic may result in some disruption to visit schedules. We recognize that your site is putting very specific actions into place in a focused manner and aligned with the local environment and business culture.

The Reata team has identified the study visits that are expected to occur over the next 6 weeks and have requested that lab kits for these visits be shipped to sites. Lab kits should arrive on site by end of day on Friday, 20 March 2020. As a reminder, while the collection of study required laboratory data is important, the lab samples obtained at the Week 100 and Week 104 visits are **critical** to the study and every effort should be made to collect these samples. Please contact us immediately if you think this will be a problem.

**Providing Lab kits to patients during an upcoming office visit**

If an in-person office visit is expected **within one week** from the date of this memo, please dispense to the patient the lab kit for the next per-protocol-visit. Please ensure you provide the research patient with all the essential lab kit components before they depart your site, including:

- ☐ the lab kit for the next study visit,
- ☐ the requisition form,
- ☐ the shipper,
- ☐ Styrofoam container,
- ☐ Specimen collection bag,
- ☐ Urine specimen collection cup,
- ☐ Gel Pak,
- ☐ lab collection instructions,
- ☐ instructions for shipping, and the
- ☐ [redacted] airway bill.

Inform the patient that the kit will only be used if an in- person office visit will not be performed due to Coronavirus restrictions and instruct the patient to not open the laboratory kit until instructed by the study physician or coordinator.

The lab kit will be used if the home health care service cannot supply a complete kit, or if the blood sample will be collected at a location that is local to the subject (i.e. [redacted] or other lab). In the event a

local laboratory facility is utilized, any fees incurred by the research patient for collection of the lab samples will be submitted through [redacted] for reimbursement.

**Providing Lab kits to patients who do not have an upcoming office visit (in the next 6 weeks):**

For research patients whose next protocol defined study visit should occur within the following 6 weeks, a lab kit for the defined visit should be shipped to the patient using a traceable courier, such as FedEx and UPS. Ensure the following essential lab kit components are included in the shipment:

- ☐ the lab kit for the next study visit,
- ☐ the requisition form,
- ☐ the shipper (may be used as your box to ship the supplies to the research subject),
- ☐ the Styrofoam container,
- ☐ Specimen collection bag,
- ☐ Urine specimen collection cup,
- ☐ Gel Pak,
- ☐ lab collection instructions,
- ☐ instructions for shipping, and
- ☐ the [redacted] airway bill.

Inform the patient that the kit will only be used if an in- person office visit will not be performed due to Coronavirus restrictions. Instruct the patient to not open the laboratory kit until instructed by the study physician or coordinator.

The lab kit will be used if the home health care service cannot provide a complete kit, or if the blood sample will be collected at a location that is local to the subject (i.e. [redacted] or another lab). In the event a local laboratory facility is utilized, any fees incurred by the research patient for collection of the lab samples will be submitted through [redacted] for reimbursement.
All shipping costs incurred by your site for shipment of the kit to the patient's home should be submitted through [redacted], as well.

Since the nature and scope of this outbreak is rapidly changing, we will continue to monitor the situation and adjust our response as appropriate.
The health and safety of our study participants and site personnel will continue to be our primary concern. We are sensitive to the complexities of managing the uncertainty and variables and appreciate your continued dedication to CARDINAL. If you have any questions regarding the contents of this correspondence, please contact your assigned CRA.

Sincerely,

[redacted]

March 25, 2020

To: Clinical Program Operations
Reata Pharmaceuticals, Inc.

From: Chemistry, Manufacturing & Controls / Quality Assurance
Reata Pharmaceuticals, Inc.

Via E-mail Transmission

RE: Guidance for Direct-to-Patient Shipping of RTA 402 Drug Product Capsules during the Coronavirus (COVID-19) Pandemic

As a result of the coronavirus (COVID-19), certain adjustments have been made to ensure study patients receive their investigational product, on time, and consistently.

For clinical investigators, where patients are unable to travel outside of their home to the site, one adjustment being implemented is the shipping of investigational product directly to the patient, from the clinical investigator site.

As background, RTA 402 drug product capsule kits (30ct, 1g desiccant, 60 mL bottle) have been assessed for stability following ICH guidelines for long term and accelerated conditions. The results support the current labeled storage conditions of controlled room temperature, which is defined as 20°C to 25°C (68°F to 77°F), with brief excursions allowed to 15°C to 30°C (59°F to 86°F).

The stability results also provide supporting data to assess potential impact of short-term temperature excursions outside the labeled storage conditions. More specifically, for drug product capsule stored as a 30ct supply in 60 ml bottle with 1g desiccant, no significant changes in drug product quality were observed for 6 months for accelerated (40°C/75% RH) and 36 months for long term (25°C/60%RH) conditions.

Given the stability of the product under multiple temperatures and relative humidity conditions, it can be concluded that short term temperature excursions above 30°C and low as 15°C during storage are acceptable. For those excursions to non-freezing temperatures below 15°C but at or above 1°C, no additional risk to drug product quality is presented based on the well-established principal of Arrhenius degradation kinetics (i.e., degradation reaction rates are temperature-dependent and occur faster at higher temperatures and slower at lower temperatures).

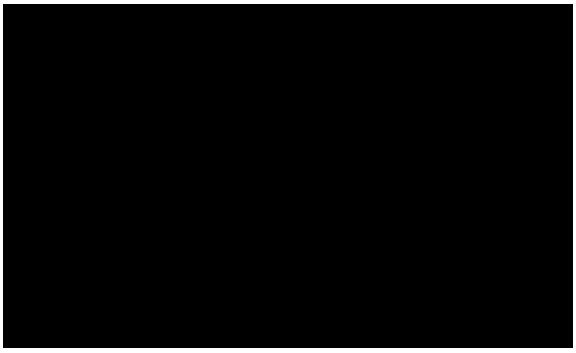
In consideration of the product stability information, the following direct-to-patient guidance is provided during this coronavirus (COVID-19) pandemic period:

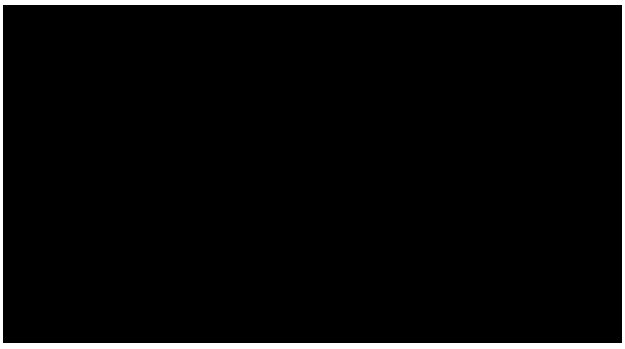
1. To mitigate any unforeseen issues impacting the shipment (i.e., lengthy delays, extreme temperatures, etc.), shipping only the minimum number of product required for patient dosing administration and priority overnight shipment is advised.

2. While the data provides assurance that RTA 402 Drug Product Capsules are stable, additional shipping and storage studies are either planned or currently being conducted. As such, certain limitations have been placed on the product until these results are reported. Accordingly, shipment durations during this period lasting longer than 48 hours, without a temperature monitor, are not advised. If shipment exceeds this duration due to unforeseen shipping delays, the site should contact Reata for further guidance.

Additional guidance will be provided when data is available.

Best regards,





REATA

MEMORANDUM: COVID-19 UPDATE
Date: 26 March 2020

Dear CARDINAL Investigators and Site Personnel,

In further response to the ongoing COVID-19 (Coronavirus) outbreak, Reata continues to take measures to minimize any impact on the trial's integrity while protecting the health of its employees, patients, customers, partners and broader community. Please note, this update, formatted as a Question & Answer document, was produced on 26 March 2020. Since the nature and scope of this outbreak is rapidly changing, we will continue to monitor the situation and adjust our response as appropriate.

We have seen disruption in patient visits across many states and countries. We recognize your site is putting very specific actions into place in a focused manner and aligned with the local environment and business culture. The follow Q&A is being provided in an effort to provide COVID-19 related guidance for the conduct of CARDINAL.

1. **May I ship study drug to a patient who cannot complete a study visit?**
   YES. FDA and EMA have released guidance supporting the shipment of IP directly to patients, where appropriate and where patient safety can be ensured/monitored. All sites have been asked to ship IP to patients who have not yet had a Week 100 visit, to avoid a disruption in study drug administration. Please ship drug to patients as soon as possible.

2. **Do I need to include a temperature monitoring device when I ship drug to a patient?**
   NO. In the US, EU, and Australia - IP may be shipped priority overnight without use of a temperature monitoring device. (Bardoxolone methyl stability data are robust with regard to temperatures within normal [non-extreme cold or hot] short-term fluctuations, as would be expected during overnight shipment.) See attached Guidance for Direct-to-Patient Shipping.

3. **If I shipped study drug to a patient outside of a normal visit, when should I dispense additional drug to the patient?**
   NOT UNTIL LATE MAY. All patients have been manually dispensed study drug to avoid a disruption in dosing. If you have shipped this drug to patients, no additional study drug needs to be dispensed until approximately late May 2020. Reata will work closely with you regarding drug dispensation.

4. **When will home health services be available for CARDINAL patients and will my site contract need to be amended?**
   FOR US PATIENTS: ~31 MAR 2020. FOR EU/AUS PATIENTS: ~MID-APRIL 2020. We are working to employ one, or more, agency(ies) to facilitate home health service needs. Currently [redacted] is being set up to provide home health services to sites and has been procured directly by Reata. Site contracts are not required to be amended for use of these services. Sites should determine use of home health services are aligned with institutional policy and will be required to complete a [redacted] request form for each patient visit requested.

5. **Should I obtain a patient's verbal agreement to share his/her contact information with the home health agency?**
   YES. The current ICF does not specifically cover the patient's information being shared with a home health company. In line with FDA and EMA guidance, and due to COVID-19, we are expediting the set-up of home health services. IRBs/IECs are being notified accordingly. Due to the urgent situation ICF revisions will be considered at a later date.

6. **If a patient cannot complete an in-person visit, what options exist to follow my patient for safety and data collection purposes?**
   Sites should maintain phone contact with patients and should document all phone conversations. In addition, the following options exist for assessing the patient:
   a. Home health nurses (e.g. [redacted] etc.)
   b. In accordance with institutional policy and allowances, the research coordinator or a member of the study team, may travel to the patient's home when possible and appropriate. Reata will compensate site staff for time.
   c. Mobile phlebotomist – for lab collection only, using the [redacted] central lab kit
   d. Local lab – using a [redacted] central lab kit
   e. Local lab – using the lab's standard methods

7. **What documents will I receive from [redacted] to be filed in my regulatory binder?**
   Documentation for each Certified Mobile Research Nurse (CMRN) is provided to the site, accordingly:
   - Signed and Dated Resume
   - Nursing License Verification
   - GCP Training Certificate
   - Protocol Training Certificate
   - Signed Delegation of Authority Log

8. **What assessments will the home health service perform? Are staff properly trained?**
   The home health agency will only perform assessments critical to safety monitoring (see below) and staff will be trained on all applicable protocol specific visit procedures.
   - Vital sign measurement
   - Adverse Event/Concomitant Medication collection
   - Weight
   - Laboratory sample collection (blood/urine)
   - Pregnancy testing
   - IP accountability (in some cases also IP dispensations)

9. **How should the cost of a local lab be covered?**
   DIRECT BILLING TO SITE OR PATIENT REIMBURSEMENT. A local lab may bill the site directly, and this cost can be invoiced to CARDINAL through [redacted] or to Reata directly. Alternatively, if a patient will incur costs related to a local lab, this may be fully reimbursed through [redacted] or the funds may be pre-loaded for the patient.

10. **If a patient cannot complete a Week 100 Visit within the protocol window, how long can the patient continue on study drug?**
    **1 WEEK, UNLESS OTHERWISE APPROVED BY REATA.** The Week 100 visit (Day 700 +/- 3 days) serves to collect the final "on treatment" lab values. As you manage the scheduling of Week 100 visits, to minimize any days off drug prior to the visit, you may extend dosing by 1 Week beyond the protocol window for the Week 100 visit. The maximum extension in dosing is to study Day 710 (Day 707 +/- 3 days), unless otherwise approved by Reata and the IRB/IEC. The Week 104 visit must be adjusted accordingly, with particular attention to ensuring the Week 104 labs are obtained 14 to 35 days following the last dose of IP.

11. **What should I do if my patient's labs must be collected through a local laboratory? How will the local lab be identified? Who will facilitate the logistics for lab collection?**
    If you have a patient that will require local lab specimen collection, please contact the Reata study team as soon as possible for further guidance and support. The site will be required to identify the local lab in closest proximity, or preferred, to the patient and provide information to the Reata study team. Reata will facilitate the logistics for lab collection with the site.

Other important reminders:

- Please notify Reata if the operational status of your site changes.
- These Week 100 and Week 104 visits are critical to the study, and every effort should be made to collect these lab samples and assess patient safety at these visits. Reata can provide assistance.
- The Week 104 visit is targeted to occur 4 weeks after discontinuation of study drug. The analysis plan allows inclusion of eGFR values obtained 14 - 35 days after the last dose of IP. Please use home health services and assistance from Reata to ensure the 14 – 35 day window is followed.
- Patients may be reimbursed for travel, and if patients who usually travel by air would prefer to drive to the study site, car rental, mileage, meals, and accommodation are reimbursable, when permissible by the IRB/IEC.
- Monitoring visits remain on hold for most sites; however, your CRA is available and accessible for questions.
- If a patient tests positive for COVID-19, please stop study drug and contact the medical monitor.

If your site has any concerns or patient notifications of a visit impacted by the coronavirus, please immediately inform Reata at [redacted] so we may provide ongoing support. Reata will be monitoring and addressing clinical trial activities from an employee safety and business continuity perspective.

Please submit this letter to your IRB/IEC and file a copy in your regulatory binder.

As always, the health and safety of our study participants and site personnel is our primary concern. As preparations for COVID-19 are underway at many institutions and sites, we are sensitive to the complexities of managing the uncertainty and variables. We appreciate your continued dedication to CARDINAL. If you have any questions regarding the contents of this correspondence, please contact your assigned CRA.

Sincerely,

[redacted]

PREVIOUS COVID-19 RELATED CORRESPONDENCE

| Topic | Date | Overview of Communication |
|---|---|---|
| Initial COVID-19 Guidance | 10 Mach 2020 | Memorandum for submission to IRB/IEC. Initial guidance to CARDINAL site with active participants in the trial, covered various topics |
| IP Shipping Instructions | 17 March 2020 | Instructions related to additional IP kits manually assigned to on-IP study patients who have not reached to Week 88 as an Unscheduled Visit. These kits should be shipped to the study patients with instructions not to open unless instructed by the site. The instruction is only provided to sites with these patients. |
| Lab Kit Shipping Instructions | 19 March 2020 | Instructions related to additional lab kits provided to sites for shipment to study patients who have upcoming study visits, in the event the patient must go to a local lab or have a visit from a home health nurse. The instruction is only provided to sites with these patients. |

CARDINAL
FOR PATIENTS WITH ALPORT SYNDROME

**Date:** 06 April 2020

Dear Investigator and Study Team,

In the continued response to the rapidly evolving situation due to COVID-19, on 20-Mar-2020, Reata manually dispensed additional IP kits to specified subjects to ensure they will have enough IP kits in hand to continue the treatment through Week 100 visit window or July 1, 2020, whichever would present first. You are receiving this instruction because one or more of these subjects are from your site. We would like to request shipment of these additional kits to the subject(s) be made at your earliest convenience. This instruction applies to all manual dispensations made by Reata in March 2020 at your site, including those IP kits described in the memo dated 17-Mar-2020.

**How do I prepare the shipment?**
The process for IP shipments is outlined in the attached memo dated on 17-Mar-2020 ("Round 1"), section 'ADDITIONAL IP KITS TO BE DISPENSED TO STUDY SUBJECTS'.

If there are any discrepancies with the manually dispensed dose amount, or the investigator would like to modify the dose amount for safety reasons, please contact the Reata study team immediately.

1. For every subject who is still on IP treatment and have not completed Week 88 visits before 20-Mar-2020, another Unscheduled Visit folder with Study Drug Dispensation page has been generated in EDC by Reata. On that page, you will find the ID of the IP kit that you should send or provide to the study subject.
2. Please verify that the dose of the additional IP kit aligns with the subject's current dose (i.e., Dose of Round 2 = Dose of Round 1 = Dose dispensed at the most recent scheduled visit).
3. Please locate the IP kit from your inventory, ship the IP kit to the subject, and prepare your package as described in steps "a" through "c" below:
    a. Your package should be shipped via a traceable courier (i.e,FedEx) using overnight delivery services. Please prepare your package based on the courier's guidance. The IP kit can be shipped under ambient temperature.
    b. Appendix I is a label to inform subjects that the IP kits should not be opened or used until directed by the study physician or study coordinator. Please ensure this label is affixed to the outside of the IP kit before shipping to the research subject.
    c. If the subject does not have the Drug Diary for the next IP treatment period, please send the diary with the additional IP kits.

**How do I handle IP dispensation during an upcoming scheduled visit?**

1. For all Week 76 and Week 88 visits in April or May 2020, please do not dispense IP if the subject has already received both Round 1 and Round 2 IP kits and the investigator does not want to change the dose amount. The subject should take Round 1 and Round 2 to continue IP treatment.

2. The next required IP dispensation is projected for approximately June or July 2020. Depending on the situation of COVID-19 and the subject's schedule, the IP kit may be dispensed during a subject's Week 88 or an unscheduled visit.

**How do I handle IP return during an upcoming scheduled visit?**

- For subjects who will have their scheduled visit conducted by home health service provider
  a. IP accountability will be performed during the visit.
  b. Used IP kits will be sealed by the home health service provider and the subject will be instructed to bring the sealed kits to the clinic during the next visit.
  c. If the subject cannot bring the sealed kits to the clinic by Week 104 visit, the subject or the home health service provider should ship the kit to the study site. The shipping cost can be reimbursed through [redacted] for any direct subject costs.
- For subjects who will have scheduled visit labs drawn at a local lab
  a. The subject should keep any used IP kits and bring them to the clinic during the next visit.
  b. IP accountability should be performed as usual, per protocol.
  c. If the subject cannot bring the used kits to the clinic by Week 104 visit, the subject should ship the kits to the study site. The shipping cost can be reimbursed through [redacted].
- For subjects who will have scheduled visit in clinic
  a. IP accountability should be performed as usual per protocol.
  b. For scheduled visits in April or May 2020, where subjects received shipped IP (Round 1/Round 2), subjects should be instructed to begin or continue dosing with the Round 1 and/or Round 2 IP kits.

     Note: if there is any concern with IP quality of Round 1 and/or Round 2 kits, or dose modifications are required, you may dispense new IP kits during the visit.

**How do I communicate with study subjects who received these IP kits?**

With the dispensation of Round 2 kits, subjects should be reminded of the storage requirements. Please communicate the additional kits have been shipped to avoid a disruption to dosing, and are considered the kits that would have otherwise been dispensed during their next regularly scheduled on site visit. Subjects should only return kits that were used during the previous treatment period. If the investigator wishes to change the dose of the additional IP kit, please follow protocol section 7.3.2 and inform your assigned CRA and CTA.

**How do I request site payment?**

All costs incurred from IP shipping and dispensing (including shipping cost, drug dispensation, study coordinator time and other applicable items on the budget) should be submitted to [redacted]. The steps are detailed below.

1. Payment Description: if possible, please enter the exact name of the Unscheduled Visit folder where the Round 2 information resides in EDC. For instance, if the name of the folder is 'Unscheduled Visit (3)', Payment Description should be 'Unscheduled Visit (3)'.

2. Activity Date= 'Date dispensed' on the corresponding eCRF.
3. Please merge all costs into one item.
   For the Notes box, please enter "COVID-19 manual dispensation, Round 2".

**How do I handle EDC data entry and relevant documentation?**
The process of data entry in EDC for Round 2 is very similar with the one with Round 1. Please enter the following data on Study Drug Dispensation form that resides in Round 2 Unscheduled Visit folder.

1. Will study drug be dispensed to the subject – enter yes
2. Date Dispensed – enter the date the drug was shipped or if the subject comes into the office the date the drug was handed to the subject
3. Kit # of the box being handed to the subject – enter the kit number(s) shipped or handed to the subject

For Week 76 and Week 88 visits that will happen in April or May 2020 with no IP dispensation because of sufficient supply from Round 1 and Round 2, Study Drug Dispensation form should be entered as following:

1. Indicate the dosage dispensed at the immediately prior visit – IP Not dispensed
2. Will study drug be dispensed to the subject? – No
3. Date dispensed – left as blank
4. Enter the dosage being dispensed to the subject at this visit. – IP Not dispensed
5. If study drug was not dispensed, select a reason: Other, sufficient supply previously provided due to COVID19

**May a subject continue IP treatment if there is an inability of an in person visit before July?**
Per the IRB submitted memo dated on 26-Mar-2020, a subject may continue IP treatment without an in person visit, where appropriate and where subject safety can be ensured/monitored. This practice is supported by FDA and EMA guidance.

**What should I do if no one from my site can perform IP kit shipments to the subject?**
Please contact your CRA and/or CTA immediately for further guidance and support.

As always, we appreciate your continued dedication to CARDINAL. If you have any questions regarding the contents of this correspondence, please contact your assigned CRA.

Sincerely,

[redacted]

**APPENDIX I**

Cut and affix to the outside of the IP kit

# ! STOP !

CARDINAL

## DO NOT OPEN UNTIL INSTRUCTED BY YOUR STUDY PHYSICIAN OR STUDY COORDINATOR!

This is the investigational drug for the study "CARDINAL", in which you are currently participating. Please bring all used drug/unused kits to your next study visit. If you have any questions, contact your study physician, study coordinator or the contact on the first page of the informed consent form.