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

ADDENDUM 1 DATED 21 APRIL 2020
TO
PROTOCOL VERSION 4.0 – 23 MAY 2019
FRANCE, SPAIN, UNITED KINGDOM

[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the addendum to the protocol v4 dated 23 May 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

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3. JUSTIFICATION FOR THE ADDENDUM

Since the OMS 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. 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 Medicinal Products (IMPs).

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, and in 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. Of course, 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 IMP supply for patients
- 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 (FR, SP, UK)	23 May 2019
CHANGES TO THE CURRENT APPROVED PROTOCOL			
1.	**SECTION NO., SECTION TITLE, PAGE NO.(S):**	7. INVESTIGATIONAL PLAN page 33	
	OLD TEXT:	No changes	
	NEW TEXT:	Added: new subparagraph **7.6: *Home Health Provider Use*** Due to the COVID-19 outbreak and the resulting restrictive measures put in place by the different national governments that in many cases resulted in travel restrictions, limited availability of site access and personnel, and local limitation on the movement of individuals delegated, in order to guarantee the rights, safety and wellbeing of participants and of the trial sites' staff, the Sponsor implemented the use of a home health group in the EU to assist with the collection of study required visits and laboratory assessments for the CARDINAL study. 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 EMA and local guidelines about the COVID-19 pandemic management. Different companies have been approached, all of them specialized in providing health professionals (Certified Mobile Research Nurses – CMRN) experienced in supporting investigators in conducting certain activities related to clinical trial conduct. For each hired CMRN, the site will be provided with the following documentation: signed and dated CV, Nursing Licensure, GCP training certificate, and protocol training certificate. The CMRN will also be included in the Delegation of Activities log of the site.	

		The tasks delegated to the CMRN 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 of urinary 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, 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.
2.	**SECTION NO., SECTION TITLE, PAGE NO.(S):**	9.10.11. Physical Examination page 53
	OLD TEXT:	No changes
	NEW TEXT:	Additional sub-paragraph **9.10.11.1*: Short Physical assessment during the COVID-19 outbreak***: The home health agency appointed by the Sponsor to support visit conduct and patient safety management will only perform assessments critical to safety monitoring (see below). Staff will be trained, and training documented, on the following applicable protocol specific visit procedures: o Vital sign measurements (e.g., blood pressure, heart rate, etc.) o Adverse Event/Concomitant Medication collection o Weight measurement o Laboratory sample collection (blood/urine) and processing o Urine Pregnancy testing (for women of childbearing potential)
	REASON FOR CHANGE:	Mitigation measures taken by the Sponsor to ensure safety of subjects and trial's integrity.
3.	**SECTION NO., SECTION TITLE, PAGE NO.(S):**	9.10.12. Pregnancy Test page 53
	OLD TEXT:	No changes
	NEW TEXT:	Added: new subparagraph **9.10.12.1** ***Self reading pregnancy test:*** During the emergency, urinary pregnancy test for self-reading will be

		provided by the CMRN coming to patient's home. Results will be transmitted to the site investigators.
	REASON FOR CHANGE:	Mitigation measures taken by the Sponsor to ensure safety of subjects.
4.	**SECTION NO., SECTION TITLE, PAGE NO.(S):**	9.10.14. Study Drug Dispensation and Collection page 54
	OLD TEXT:	No changes
	NEW TEXT:	Added subparagraph **9.10.14.1** ***Study drug distribution during the COVID-19 pandemic.*** Prior to the COVID-19 pandemic, trial participants were assigned and dispensed IMP during study site visits. During the study site visits, trial participants are sent home with IMP and instructed to self-administer the IMP each day until their next on-site study visit, at which they would return any unused IMP. As the trial participants have been responsible for IMP storage within their homes, as well self-administration of the IMP throughout the study, they are well acquainted with these facets of the study. For those trial participants who discontinue physical site visits during COVID-19, distribution of IMP may be made directly to the trial participants' homes by shipment from investigator, through the Hospital pharmacy. IMP 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 IMP shipments to trial participants' homes, investigators will monitor the time from shipment to receipt of the IMP 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 IMP 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 IMP. Investigators will remain in close contact with trial participants receiving IMP at their home and, if necessary, will provide any instructions needed on the use of the IMP. Accountability of the IMP

		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 IMP 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.
5	**SECTION NO., SECTION TITLE, PAGE NO.(S):**	10.4. Study Drug Administration page 58
	OLD TEXT:	No changes
	NEW TEXT:	Added subparagraph **10.4.1** ***Intake of IMP Beyond Week 100 during the COVID-19 outbreak***. 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 EC. 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):**	15.3. Written Informed Consent page 71
	OLD TEXT:	No changes
	NEW TEXT:	Additional sub-paragraph **15.3.1:** ***Informed Consent for Home Health Services:*** A home health services provider to support visit conduct and patient safety management during this period has been appointed by the Sponsor. An ICF letter has been created and provided to the EC for approval in participating countries. Approval of the revised consent form will allow sites to obtain verbal permission from the study patient to share their contact information with the home health services company and to conduct the study visit.
	REASON FOR CHANGE:	Among mitigation measures taken by the Sponsor to ensure safety of subjects.
7.	**SECTION NO., SECTION TITLE, PAGE NO.(S):**	15.6. Protocol Deviations page 73

	OLD TEXT:	No changes
	NEW TEXT:	Additional subparagraph **15.6.1** ***Deviation during the COVID-19 Outbreak:*** 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 a 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 that must be notified to the Competent Authority according to GCP § 5.20. Deviations will be reported, evaluated, and discussed according to the study plan and in the final study report.
	REASON FOR CHANGE:	As allowed by EMA and local guidelines for management of clinical trials during the COVID-19 outbreak.

5. CHANGES IN OTHER STUDY-RELATED DOCUMENTS

5.1. Informed Consent

An ICF letter has been created and provided to the EC for approval in participating countries. Approval of the revised consent form will allow sites to obtain verbal permission from the study patient to share their contact information with the home health services company and conduct of the study visit. After verbal agreement is obtained, written permission can be obtained at the next on-site study visit.

6. APPENDICES

List of memos provided to the 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