

AMENDMENT NO. 3 TO CLINICAL TRIAL AGREEMENT

Between

CardioPharm International, Inc. ("Sponsor")

and

Memorial Medical Center ("Institution")

Original Agreement Date: January 15, 2022

Amendment No. 3 Effective Date: August 17, 2023

RECITALS

WHEREAS, Sponsor and Institution entered into a Clinical Trial Agreement dated January 15, 2022, as amended by Amendment No. 1 dated June 22, 2022, and Amendment No. 2 dated February 3, 2023 (collectively, the "Agreement"), for the conduct of Study Protocol No. CP-2847-301 (HEARTBEAT-3);

WHEREAS, the COVID-19 pandemic and subsequent regulatory guidance have necessitated updates to clinical trial conduct provisions to accommodate remote/virtual visits, telehealth assessments, and direct-to-patient investigational product shipment;

WHEREAS, FDA and ICH have issued guidance on conduct of clinical trials during public health emergencies, including management of protocol deviations necessitated by pandemic-related restrictions;

WHEREAS, the parties desire to update the Agreement to incorporate pandemic-related provisions and clarify force majeure protections;

NOW, THEREFORE, in consideration of the mutual covenants herein, the parties agree as follows:

AMENDMENTS

1. Addition of Pandemic-Related Provisions

A new **Section 21.7** is hereby added to Article 21 (General Provisions) of the Agreement as follows:

"21.7 Pandemic and Public Health Emergency Provisions.

(a) Scope. In the event of a pandemic, epidemic, public health emergency, or government-mandated restrictions affecting Study conduct, including but not limited to COVID-19 and any variants thereof (collectively, a "Public Health Emergency"), the parties shall cooperate in good faith to implement Protocol modifications necessary to protect Study Subject safety and maintain data integrity while complying with applicable public health directives.

(b) Remote Visits. During a Public Health Emergency, Institution and PI may conduct study visits remotely via telehealth platforms, subject to the following conditions:

- IRB approval of remote visit procedures*
- Documentation of the reason remote visits are necessary*
- Use of secure, HIPAA-compliant telehealth platforms*
- Collection of vital signs and other assessments via home health nurses or mobile health units where feasible*
- Documentation of all remote visit procedures in source documents*

(c) Direct-to-Patient Shipment. Sponsor may authorize direct shipment of Investigational Product to Study Subjects' homes during a Public Health Emergency, provided:

- IRB approval is obtained*
- Appropriate temperature monitoring and chain of custody documentation is maintained*
- Study Subjects or caregivers are trained on storage, handling, and administration*
- PI maintains accountability for all shipped product*

(d) Protocol Deviations. Protocol deviations necessitated by Public Health Emergency circumstances (e.g., missed visits, visit windows exceeded, remote procedures) shall be documented with explanation of the emergency circumstances. Sponsor agrees not to treat such deviations as per-protocol violations for

purposes of payment or site performance evaluation, provided Institution made reasonable efforts to maintain Study Subject safety and data quality.

(e) Visit Payment. Remote visits conducted in compliance with this Section 21.7(b) shall be compensated at the same rate as in-person visits specified in the Budget, provided all required assessments are completed to the extent feasible under the circumstances."

2. Enhanced Force Majeure Provisions

Section 21.7 of the Agreement (previously addressing general force majeure, now renumbered as Section 21.8) is hereby amended to read as follows:

"21.8 Force Majeure.

Neither party shall be liable for delay or failure in performance caused by circumstances beyond such party's reasonable control, including: (a) acts of God, fire, flood, earthquake; (b) epidemic, pandemic, or public health emergency, including COVID-19 and any variant thereof, and any governmental orders issued in response thereto; (c) quarantine, shelter-in-place orders, travel restrictions; (d) supply chain disruptions affecting availability of Investigational Product or study supplies; (e) war, terrorism, civil unrest; or (f) labor disputes not involving the claiming party's employees (each, a "Force Majeure Event").

In the event of a Force Majeure Event materially affecting Study conduct, the parties shall promptly confer to determine appropriate remedial measures, which may include Protocol amendments, temporary suspension of enrollment, or extensions of Study timelines. During a Force Majeure Event, Institution shall continue to provide appropriate medical care and safety monitoring for enrolled Study Subjects to the extent feasible."

3. IRB Amendment Requirements

Section 4.1 of the Agreement is hereby amended by adding the following language at the end of the existing section:

"Institution shall submit amendments to the IRB as necessary to implement pandemic-related Protocol modifications authorized under Section 21.7, including remote visit procedures and direct-to-patient drug

shipment. Sponsor shall provide template IRB submission language upon request."

4. Payment Terms Clarification

Section 7.2 of the Agreement is hereby amended to read as follows:

*"7.2 Payment Terms. Institution shall submit invoices monthly for completed study visits and other compensable activities. Sponsor shall pay undisputed invoices within **forty-five (45) days** of receipt ('Net 45'). In the event of a payment dispute, Sponsor shall pay the undisputed portion within the specified timeframe and shall provide written explanation of any disputed amounts. Disputed amounts shall be resolved through good faith negotiation within thirty (30) days."*

5. Data Management During Remote Visits

A new subsection is added to Section 9.3 (Data Integrity) as follows:

"9.3(d) Remote Visit Data. For study visits conducted remotely pursuant to Section 21.7(b), Institution shall ensure that:

- Source documentation clearly identifies the visit as conducted remotely and documents the reason (e.g., pandemic restrictions, subject quarantine)*
- All data collected remotely (vital signs via home monitoring devices, patient-reported outcomes via electronic platforms) is attributable to the specific device or platform used*
- Chain of custody is maintained for any specimens collected via mobile phlebotomy or home health services*
- Electronic signatures on informed consent documents or other study documents comply with 21 CFR Part 11 where applicable"*

6. Investigational Product Accountability

Section 6.2 of the Agreement is hereby supplemented with the following language:

"For Investigational Product shipped directly to Study Subjects pursuant to Section 21.7(c), Institution and PI shall maintain accountability records including: (a) shipping manifests and tracking numbers; (b) temperature monitoring data from shipment; (c) subject acknowledgment of receipt; (d) subject-reported

administration logs; and (e) records of any unused product returned to site or destroyed by the subject under PI supervision via telemedicine."

GENERAL PROVISIONS

7. No Budget Modification

This Amendment does not modify Exhibit B-1 (Budget and Payment Schedule) except as specifically addressed in Section 4 above regarding payment terms (Net 30 changed to Net 45). Per-patient payment amounts and visit schedules remain unchanged. Remote visits shall be compensated at the same rate as in-person visits as specified in Section 21.7(e) added by this Amendment.

8. Ratification

Except as specifically modified by this Amendment No. 3, all terms, conditions, and provisions of the Agreement, as previously amended by Amendment No. 1 and Amendment No. 2, shall remain in full force and effect and are hereby ratified and confirmed.

9. Study Status

As of the effective date of this Amendment, the Study has enrolled 18 of 20 target patients. Enrollment is anticipated to complete by October 2023. No Study Subjects have required remote visits to date, but this Amendment provides the framework should pandemic conditions or future public health emergencies necessitate such modifications.

10. Regulatory and IRB Status

Sponsor confirms that FDA has not placed the Study on clinical hold and that the Protocol remains under active IND. Institution confirms that IRB approval remains current with no restrictions or suspension.

11. Counterparts

This Amendment may be executed in counterparts, each of which shall be deemed an original and all of which together shall constitute one and the same instrument.

12. Governing Law

This Amendment shall be governed by the laws of the State of Ohio, consistent with the Agreement.

SIGNATURES

CARDIOPHAM INTERNATIONAL, INC.

By: _____

Name: Jennifer Kim

Title: Senior Director, Clinical Operations

Date: August 17, 2023

MEMORIAL MEDICAL CENTER

By: _____

Name: Dr. Robert Johnson

Title: Director, Clinical Research Office

Date: August 17, 2023