AMENDMENT NO. 4 TO CLINICAL TRIAL AGREEMENT

Between

CardioPharm International, Inc. ("Sponsor")

and

Memorial Medical Center ("Institution")

Original Agreement Date: January 15, 2022
Amendment No. 4 Effective Date: March 15, 2024

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, Amendment No. 2 dated February 3, 2023, and Amendment No. 3 dated August 17, 2023 (collectively, the "Agreement"), for the conduct of Study Protocol No. CP-2847-301 (HEARTBEAT-3);

WHEREAS, Sponsor has issued Protocol Amendment No. 2 dated February 1, 2024, which removes the Week 56 and Week 64 follow-up visits (previously added in Protocol Amendment No. 1) based on interim safety data demonstrating no safety signals requiring extended follow-up;

WHEREAS, Protocol Amendment No. 2 adds biomarker blood sample collection (NT-proBNP, troponin-I, and inflammatory markers) at Weeks 12, 24, 36, and 48 to support secondary endpoint analyses;

WHEREAS, the parties desire to amend the Agreement to reflect Protocol Amendment No. 2 and associated budget adjustments;

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

AMENDMENTS

1. Protocol Update

Section 2.1 of the Agreement is hereby amended to reference **Protocol No. CP-2847-301, Version 3.0 dated February 1, 2024 (Protocol Amendment No. 2)**, which is attached hereto as Exhibit A-2 and incorporated by reference.

The Protocol as amended supersedes all prior Protocol versions, including Version 1.0 (original), Version 1.1 (if any administrative updates), and Version 2.0 (Protocol Amendment No. 1).

2. Scope of Work Modification

Section 2.1 of the Agreement is hereby further amended by adding the following language:

"Institution and PI shall collect and process biomarker blood samples (NT-proBNP, troponin-I, CRP, IL-6, and TNF-alpha) at Weeks 12, 24, 36, and 48 per the Protocol. Samples shall be processed according to the Laboratory Manual (Version 2.0) and shipped to the central laboratory (LabCorp, Burlington, NC) within 4 hours of collection on dry ice per shipping instructions."

3. Study Timeline Reduction

Section 2.3 of the Agreement is hereby amended to read as follows:

"2.3 Study Timeline. The Study is anticipated to be completed within eighteen (18) months from Site Activation, including a twelve (12) month enrollment period and six (6) month follow-up period, consistent with the Protocol as amended."

Note: This reverts the timeline to the original duration, as the extended follow-up visits added in Amendment No. 1 have been removed by Protocol Amendment No. 2.

4. Budget Revision

Exhibit B-1 (Budget and Payment Schedule) is hereby deleted in its entirety and replaced with the revised Exhibit B-2 attached hereto as Attachment 1 to this Amendment No. 4.

The revised budget reflects the following changes:

- **Removal** of Week 56 and Week 64 follow-up visits (-$2,400 per patient)
- **Addition** of biomarker blood collection and processing at Weeks 12, 24, 36, and 48 (+$200 per patient per visit = +$800 per patient)
- **Net decrease** in per-patient total from $21,200 to $19,800

5. Pass-Through Cost Adjustment

Pass-through costs for central laboratory biomarker analysis are estimated at $300 per patient ($75 per biomarker visit × 4 visits), to be invoiced at actual cost with documentation from the central laboratory.

6. Study Subject Follow-Up Adjustment

As of the effective date of this Amendment:

- **Enrolled Study Subjects who have not yet reached Week 56:** Will NOT complete Week 56 or Week 64 visits. Their follow-up will conclude at Week 52 (the final visit under the revised Protocol).
- **Enrolled Study Subjects who have already completed Week 56 or Week 64:** These visits will be compensated as completed per the prior budget (Exhibit B-1), as the visits were conducted per the Protocol in effect at the time. Sponsor acknowledges that approximately 3 patients have completed Week 56 visits prior to this Amendment.
- **All Study Subjects:** Will have biomarker blood samples collected at their remaining Weeks 12, 24, 36, and 48 visits (if not yet completed). For subjects who have already completed these visits without biomarker collection, Sponsor will not require retroactive sample collection.

7. IRB Amendment

Institution confirms that Protocol Amendment No. 2 has been submitted to the IRB and approval was received on February 28, 2024. Study Subjects have been re-consented as necessary to reflect the Protocol changes.

GENERAL PROVISIONS

8. Cross-Reference Clarification

The parties acknowledge that this Amendment modifies provisions previously established in Amendment No. 1 (which added the Week 56 and Week 64 visits now being removed). For clarity:

- **Amendment No. 1** added cardiac MRI at Week 24 and extended follow-up to Week 64 → Cardiac MRI at Week 24 **REMAINS** per current Protocol Version 3.0; extended follow-up visits **REMOVED** per current Protocol Version 3.0.
- **Budget Exhibit B-2** (attached to this Amendment No. 4) supersedes Budget Exhibit B-1 (attached to Amendment No. 1), which superseded original Budget Exhibit B.

9. Ratification

Except as specifically modified by this Amendment No. 4, all terms, conditions, and provisions of the Agreement, as previously amended by Amendment No. 1, Amendment No. 2, and Amendment No. 3, shall remain in full force and effect and are hereby ratified and confirmed.

10. Study Status

As of the effective date of this Amendment:

- Enrollment is **COMPLETE** at 20 patients (target achieved December 2023)
- **17 patients** are in active follow-up
- **3 patients** have completed the study under the prior Protocol version (including Week 56/64 visits)
- Anticipated Last Patient Last Visit: **September 2024**

11. Payment Terms

Payment terms remain Net 45 as established in Amendment No. 3. The 10% holdback provision remains in effect.

12. 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.

13. 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: David Patel
Title: Associate Director, Clinical Operations
Date: March 15, 2024

MEMORIAL MEDICAL CENTER

By: _____
Name: Lisa Anderson
Title: Manager, Clinical Research Contracts
Date: March 15, 2024

ATTACHMENT 1 TO AMENDMENT NO. 4: REVISED EXHIBIT B-2

BUDGET AND PAYMENT SCHEDULE (REVISED)

Study: HEARTBEAT-3 (Protocol CP-2847-301, Version 3.0)
Site: Memorial Medical Center
PI: Dr. James Martinez
Enrollment Target: 20 patients (ENROLLMENT COMPLETE)
Budget Version: 1.2
Date: March 15, 2024

SITE STARTUP COSTS (No Change)

Item	Amount
IRB Submission & Approval	$3,500
Regulatory Document Preparation	$2,000
Site Initiation Visit	$4,000
Site Activation Payment	$5,000
TOTAL STARTUP	**$14,500**

PER-PATIENT COSTS (REVISED)

Enrollment: 20 patients (complete)
Per-Patient Total: $19,800 (decreased from $21,200)

Visit	Procedures	Payment per Patient
Screening	Consent, vitals, ECG, echo, labs, medical history	$2,200
Baseline/Randomization	Vitals, ECG, labs, drug dispensing	$1,100
Week 4	Vitals, ECG, labs, drug dispensing	$900
Week 8	Vitals, ECG, labs, drug dispensing	$900
Week 12	Vitals, ECG, echo, **biomarker labs**, drug dispensing	**$1,800** *(+$200)*
Week 16	Vitals, ECG, labs, drug dispensing	$900
Week 20	Vitals, ECG, labs, drug dispensing	$900
Week 24	Vitals, ECG, echo, cardiac MRI, **biomarker labs**, drug dispensing	**$2,600** *(+$200)*
Week 28	Vitals, ECG, labs, drug dispensing	$900
Week 32	Vitals, ECG, labs, drug dispensing	$900
Week 36	Vitals, ECG, echo, **biomarker labs**, drug dispensing	**$1,800** *(+$200)*
Week 40	Vitals, ECG, labs, drug dispensing	$900
Week 44	Vitals, ECG, labs, drug dispensing	$900
Week 48 (End of Treatment)	Vitals, ECG, echo, **biomarker labs**, safety follow-up	**$1,800** *(+$200)*
Week 52 (Final Follow-up)	Vitals, ECG, labs, safety follow-up	$800
~~Week 56 (Follow-up)~~	~~REMOVED~~	~~$0~~

Visit	Procedures	Payment per Patient
~~Week 64 (Final Follow-up)~~	~~REMOVED~~	~~$0~~
TOTAL PER PATIENT		**$19,800**

Changes from Budget Version 1.1 (Exhibit B-1):

- Added $200/visit for biomarker collection at Weeks 12, 24, 36, 48 = **+$800**
- Removed Week 56 visit = **-$800**
- Removed Week 64 visit = **-$1,600**
- **Net change:** -$1,400 per patient

Total for 20 Patients: $396,000 (decreased from $424,000)

SCREEN FAILURE PAYMENT (No Change)

Per Screen Failure: $1,200
Actual Screen Failures: 7 patients (final count)
Screen Failure Total: $8,400

SITE CLOSEOUT (No Change)

Item	Amount
Close-Out Visit	$3,000
Final Query Resolution	$1,500
Drug Accountability & Return	$500
Document Archival	$1,000

Item	Amount
TOTAL CLOSEOUT	**$6,000**

PASS-THROUGH COSTS (Revised)

Institution may invoice for the following at actual cost with documentation:

- Central laboratory costs (pre-approved vendor)
- **Biomarker assay costs (central laboratory) - NEW**
- ECG reading fees (central ECG lab)
- Echocardiogram reading fees (core lab)
- Cardiac MRI reading fees (core imaging lab)
- Unscheduled visits required for safety monitoring

Estimated Pass-Through Costs: $18,000 (increased from $12,000 due to biomarker assays)

Breakdown:

- Biomarker assays: ~$6,000 (20 patients × $300)
- Other pass-through: ~$12,000

TOTAL SITE BUDGET (REVISED)

Category	Amount	Change from B-1
Site Startup	$14,500	No change
Per-Patient Costs (20 patients)	$396,000	-$28,000
Screen Failures (actual 7)	$8,400	-$1,200

Category	Amount	Change from B-1
Site Closeout	$6,000	No change
Pass-Through Costs (estimated)	$18,000	+$6,000
TOTAL BUDGET	**$442,900**	**-$23,200**

PAYMENT TERMS (Updated from Amendment No. 3)

- **Holdback:** 10% of per-patient payments retained until LPLV + query resolution + closeout
- **Payment Schedule:** Net 45 from invoice receipt (per Amendment No. 3)
- **Invoicing:** Monthly invoicing permitted for completed visits
- **Holdback Release:** Within 60 days of closeout completion