AWARD NUMBER: W81XWH1990015

TITLE: Pharmacologic Intervention with CMX-2043 for the Acute Treatment of Neurotrauma and Traumatic Brain Injury (TBI)

PRINCIPAL INVESTIGATOR: Todd J. Kilbaugh MD

PERFORMING ORGANIZATION: Ischemix LLC

REPORT DATE: As of January 25, 2021

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE January 25, 2020	**2. REPORT TYPE** Annual	**3. DATES COVERED 1/1/20 – 12/31/20**

4. TITLE AND SUBTITLE	**5a. CONTRACT NUMBER** W81XWH-15-9-0001
	5b. GRANT NUMBER N/A
	5c. PROGRAM ELEMENT NUMBER (Can be blank if don't
6. AUTHOR(S)	**5d. PROJECT NUMBER** MT19008.61
	5e. TASK NUMBER W81XWH1990015
E-Mail:	**5f. WORK UNIT NUMBER** N/A
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Ischemix LLC, 13 Pullard Rd., Grafton, MA 01519	**8. PERFORMING ORGANIZATION REPORT** [Enter RPA#]
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012	**10. SPONSOR/MONITOR'S ACRONYM(S)**
	11. SPONSOR/MONITOR'S REPORT NUMBER(S) N/A

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER**	**19a. NAME OF RESPONSIBLE PERSON** David DeWahl
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)* 203 561 0806
Unclassified	Unclassified	Unclassified	Unclassified		

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

MTEC Medical Technology Enterprise Consortium

TABLE OF CONTENTS

Annual Technical Status Report for

Pharmacologic Intervention with CMX-2043 for the Acute Treatment of Neurotrauma and Traumatic Brain Injury (TBI) MTEC-19-08-MULTI-0061

EGS#: MT19008.61

Reporting Period: January 1, 2020 – December 31, 2020

MTEC Research Project Awardee

Research Project Lead: David A. DeWahl, Jr.

Other Research Project Team Member(s) Research Project Technical POC:

Alexander Baguisi

Ischemix LLC

13 Pullard Road

Grafton, MA 01519

Cell phone of David DeWahl: 203-561-0806

Email address of David DeWahl: ddewahl@ichemix.com

Submitted: January 25, 2021

1. Project Status

a. Accomplishments

Milestones accomplished

MFR begin GMP mfg; make 2nd pmt.	5-October-2020
MFR finish GMP mfg.; make pmt.	29-October-2020

b. Reportable Outcomes

None.

c. Progress Detail

Objective 1. Manufacture of CMX-2043 drug substance by TCG Lifesciences

TCG began cGMP manufacturing of CMX-2043 on October 5, 2020 and finished the manufacturing on October 29, 2020.

Objective 2. Formulation of drug substance into drug product by Avantgarde Molecular

Avantgarde has formulated a second batch of drug product.

Objective 3. Dose response and PK study in a porcine model at CHOP/Penn laboratory

The initial phases of the study began late in the third quarter, having been delayed by the closing of the Kilbaugh lab for approx. six monthe due to Covid-19 pandemic. However, during the fourth quarter it was decided that the dose levels to be evaluated in this dose response/PK study should be increased on a mg/kg basis.

The reason we have decided to increase the dose level is that earlier in 2020 we requested CRL to perform a single-dose, maximum tolerated dose study (the “MTD” study) to confirm the dose levels we had originally envisioned for the repeat-dose tox study. (This MTD study was not originally thought to be necessary, was not planned as a part of the Award, and, consistent with the fixed-price nature of the Award, was paid for 100% by Ischemix.) The result of the MTD study was that no toxicity was seen at levels up to and including 320 mg/kg. Therefore we have decided to increase the amount of drug to be administered in higher dose groups of the dose response/PK study to accommodate a potentially higher efficacious dose in later human studies than was originally anticpated.

This change requires that an amended protocol be submitted to the CHOP IACUC for review. Following the CHOP IACUC approval, the amended protocol will be submitted to ACURO for approval. ACURO approval is expected in the first quarter of 2021, at which time this study will be commenced at CHOP. This change will not result in any change to the costs of the dose response/PK study.

Objective 4. Efficacy study in a porcine model of diffuse TBI at CHOP

This study is expected to be started after the completion of Objective 3.

Objective 5. Repeat-dose toxicology study in a porcine model

During the fourth quarter it was decided that we need to add an additional dose arm to the tox study and increase the dose levels in each active arm on a mg/kg basis. The reason we have decided to increase the dose level is that, as described in Objective 3 above, earlier in 2020 we requested CRL to perform a single-dose, maximum tolerated dose study (the "MTD" study) to confirm the dose levels we had originally envisioned for the repeat-dose tox study. (This MTD study was not originally thought to be necessary, was not planned as a part of the Award, and, consistent with the fixed-price nature of the Award, was paid for 100% by Ischemix.) The result of the MTD study was that no toxicity was seen at levels up to and including 320 mg/kg. Therefore, because the FDA likes to see a dose level at which toxicity is evidenced in preclinical development, we have altered the dose levels as described.

This decision necessitated the manufacture of additional drug substance and the formulation of additional investigational drug product. This manufacturing process, which was intiated in November 2020, will take approx. 13 weeks. Therefore, the in-life portion of the pig repeat-dose toxicology study will be postponed until March 2021. Under the fixed-price reimbursement procedure in the Award, the costs of manufacturing and formulating this additional drug supply will be borne 100% by Ischemix.

Objective 6.

This objective will commence after all of the prior Objectives have been accomplished.

2. Future Plans

Objective 1. Manufacture of CMX-2043 drug substance by TCG Lifesciences

This objective has been completed.

Objective 2. Formulation of drug substance into drug product by Avantgarde Molecular

Avantgarde formulated a second batch of drug product in December 2020.

Objective 3. Dose response and PK study in a porcine model at CHOP/Penn laboratory

The in-life portion of this objective is estimated to begin in the first quarter of 2021.

Objective 4. Efficacy study in a porcine model of diffuse TBI at CHOP

This study is expected to be started after the completion of Objective 3.

Objective 5. Repeat-dose toxicology study in a porcine model

It is estimated that the in-life portion of the CRL tox study will commence in the first quarter of 2021.

Objective 6.

This objective will commence after all of the prior Objectives have been accomplished.

3. Problems / Issues
   a. Current Problems / Issues
      In section 1(c) above we described the issues that arose in the fourth quarter and the corrective actions we are taking with respect to these issues.

   b. Anticipated Problems / Issues
      None at this time.

4. Financial Health

Despite certain issues that arose during the quarter, the financial health of the research program under the Award is still good. The changes to the Objectives of Award program, as described in section 1(c) above and further described below, will result in additional costs to the program of approximately $305,000, all of which, because this is a fixed-cost award, will be borne by Ischemix. We continue to monitor whether the work under the Award will be able to be completed by the currently agreed final completion date of the Award. If this is not the case and the Award completion date needs to be extended, Ischemix will incur additional direct and indirect overhead expenses, all of which will be paid for by the Company.

Here is a summary of the major components of the Award and the financial status of each:

Objective 1. Manufacture of CMX-2043 drug substance by TCG Lifesciences

This objective has been completed and was on budget.

Objective 2. Formulation of drug substance into drug product by Avantgarde Molecular

This objective has been completed and was on budget.

Objective 3. Dose response and PK study in a porcine model at CHOP/Penn laboratory

This objective was delayed due to the closure of the Kilbaugh Lab at CHOP in response to the Covid-19 pandemic and further delayed by the need to change the dosing regimen of the study. However, there has been no change to the budget for the completion of this Objective.

Objective 4. Efficacy study in a porcine model of diffuse TBI at CHOP

This study is expected to be started after the completion of Objective 3. There has been no change to the budget for the completion of this Objective.

Objective 5. Repeat-dose toxicology study in a porcine model

As described in section 1(c) above, the protocol for this study has been modified. The incremental cost of this revision of the protocol is estimated to cost $305,000, all of which will be paid for by Ischemix.

Objective 6.

This objective will commence after all of the prior Objectives have been accomplished and is still expected to be on budget.

In addition to the changes to the Objectives under the Award, there are two studies we have decided to undertake to complement and further the successful completion of the research program. These two studies have an estimated cost of $280,000, all of which will be paid for by Ischemix.

Additional study #1 – Porcine single-dose maximum tolerated dose (MTD) study

This study was initiated to confirm the dose levels we had originally envisioned for the repeat-dose tox study. The results of this study provided valuable information that caused us to revise the number of dose groups and the dose levels in the porcine repeat-dose toxicology sudy planned under Objective 5. The cost of this MTD study is $40,000.

Additional study #2 – Rodent repeat-dose toxicology study

We originally believed that a rodent repeat-dose study we performed a number of years ago would be sufficient for the purposes of filing an IND for the treatment of acute TBI. Upon further review of the study, we have concluded that is it not sufficient for use in the IND filing. We intend to complete a new rodent repeat-dose tox study prior to the completion of the porcine repeat-dose study referred to above. The cost of this study is $240,000.

Note: In response to the instruction for this section “Provide amount expended this quarter and cumulatively”, please refer to Section 2A of the Annual Business Report below.

There was no major equipment procured, no sub-awards implemented and no travel conducted.

5. Personnel Effort

Personnel	Role	Percent Effort
David DeWahl	Program manager	46%
Alexander Baguisi	Deputy program manager	83
Jacqueline Pooler	Administrative support	4

6. Protocol and Activity Status

a. Human Use Regulatory Protocols

Not applicable

b. Use of Human Cadavers for RDT&E, Education or Training

Not applicable.

c. Animal Use Regulatory Protocols

TOTAL PROTOCOLS:

Two animal protocols are required to complete the Award SOW. Objectives 3. and 4. are considered to be one animal protocol, and Objective 5 is the second protocol.

PROTOCOLS:
Objectives 3 and 4. CHOP/Penn

Protocol: ACURO Log Number MT19008.61.e001
Title: Determining Proof of Concept efficacy of CMX-2043 for future translational and clinical trial development
Target required for statistical significance: 74 pigs **Target**

approved for statistical significance: 74 pigs **Submitted to and**

Approved by:

1. Protocol amendment (806420) submitted to IACUC committee for approval (12/20/2019)
    - Received approval of protocol from IACUC committee: 01/24/20
2. Submitted ACURO Long Application to ACURO for approval: 01/31/2020
    - Received reviewer's comments from ACURO: 03/26/20
    - Responded to reviewer's comments & resubmitted: 03/30/20
    - Responded to reviewer's comments & resubmitted: 04/6/20

3. Initial IACUC approval dated January 9, 2018. PI: Todd J. Kilbaugh
4. Amended IACUC approval dated January 24, 2020. PI: Todd J. Kilbaugh
5. ACURO Long Application approved on April 15, 2020 PI: Todd J. Kilbaugh
6. ACURO approval – renewed on December 3, 2020 PI: Todd J. Kilbaugh

Objective 5. Charles River Laboratories (CRL)

Protocol: ACURO Number MT19008.61.e002
Title: A 14-Day Study of CMX-2043 by Intravenous Infusion in Mini-pigs with a 14- Day Recovery Period

Target required for statistical significance: 34 pigs
Target approved for statistical significance: 34 pigs
Submitted to and Approved by:

1. Protocol submitted to IACUC for approval: July 5, 2020 PI: John Ciallella
2. IACUC approval received: July 6, 2020 PI: John Ciallella
3. Submitted ACURO long application to ACURO for approval: July 30, 2020 PI: John Ciallella
    - Received reviewer's comments from ACURO: August 28, 2020
    - Responded to reviewer's comments and resubmitted: August 31, 2020
4. ACURO long application approved: September 3, 2020 PI: John Ciallella

Annual Business Status Report for

Pharmacologic Intervention with CMX-2043 for the Acute Treatment of Neurotrauma and Traumatic Brain Injury (TBI) MTEC-19-08-MULTI-0061

EGS#: MT19008.61

Reporting Period: January 1, 2020 – December 31, 2020

MTEC Research Project Awardee

Research Project Lead: David A. DeWahl, Jr.

Other Research Project Team Member(s) Research Project Technical POC:

Alexander Baguisi

Ischemix LLC

13 Pullard Road

Grafton, MA 01519

Cell phone of David DeWahl: 203-561-0806

Email address of David DeWahl: ddewahl@ichemix.com

Submitted: January 25, 2021

MTEC
Medical Technology Enterprise Consortium

1. CURRENT STAFF

Personnel	*% of Effort on project*
Program Manager (David DeWahl)	46%
Principal Investigator	
Project Manager (Alex Baguisi)	83
Project Management Officer	
Contracting	
Management Assistant (Jacqueline Pooler)	4

2. CURRENT EXPENDITURES

A. Fixed Priced Contract

MTEC Milestone Number	Milestone Description	Due Date	Government Funds
25	MFR begin GMP mfg.; make 2nd pmt.	8/15/20	$50,921.00
27	MFR finish GMP mfg.; make pmt.	9/30/20	$50,921.00
	Total expenditures for the period		$101,842

B. Cost Share Contributions:

Funding Source (Cash)	This Period (October 1 to December 31, 2020)	Cumulative to Date
Cash	$25,460.00	$203,207.00
Labor Dollars	$0.00	$220.00
Indirect Labor Rates (Overhead/Fringe Benefits)	$0.00	$0.00
Travel	$0.00	$0.00
General & Administrative Services	$0.00	$0.00
Equipment (New)	$0.00	$0.00
Material	$0.00	$0.00
Other Direct Costs	$0.00	$0.00
Other	$0.00	$0.00

Sub-Total	$25,460.00	$203,427.00
Funding Source (In-Kind)	**This Period**	**Cumulative to Date**
Use of Existing Equipment (Estimated fair market value)	$0.00	$0.00
Use of Existing Software (Estimated fair market value)	$0.00	$0.00
Intellectual Property (Estimated fair market Value)	$0.00	$0.00
Space (Land or buildings)	$0.00	$0.00
Sub-Total	$0.00	$0.00
Cost Share Total	$25,460.00	$203,427.00

3. STATUS OF MILESTONES

MTEC Milestone Number	Task #	Significant Event/ Accomplishments	Due Date	% Completed This Reporting Period	Cum. % Complete
1	N/A	Receive Project Award	1/20/20	0	100
2	N/A	Kick off call with government sponsor	1/24/20	0	100
3	1A	Submit ACURO app for CHOP studies	1/31/20	0	100
4	2A	Sign contract w/ AvantGarde; make first batch of formulation; make payment	3/15/20	0	100
5	5A	Sign contract w/ MFR re mfg of drug powder; make 1st pmt	4/22/20	0	100
6	3A	Sign contract w/ CHOP re DR/PK and efficacy studies; make payment	4/22/20	0	100
7	4A	Sign contract w/CRL and make payment re toxicology study	4/22/20	0	100
8	N/A	Quarterly Report 1 (January - March, Technical and Business Reports)	4/25/20		
9	5B	Start MFR Proc Development	5/1/20	0	100
10	5C	Receive MFR mfg. materials; begin Analyt. Meth. Development	5/1/20	0	100
11	4B	Submit app to CRL IACUC	5/6/20	0	100
12	4C	Receive CRL IACUC approval	5/13/20	0	100

13	2B	AvantGarde second batch; make payment; deliver to CHOP	5/15/20	0	0
14	1B	Submit ACURO application for CRL study	5/20/20	10	100
15	5D	MFR make 1st payment for process dev	5/31/20	0	100
16	1C	Receive ACURO approval for CHOP DR/PK study	6/15/20	0	100
17	5E	Make 2nd pmt and finish MFR Analyt. Meth Dev; start Meth. Dev - Impurities	6/15/20	0	100
18	5F	Start MFR non-GMP mfg. and make payment	6/30/20	0	100
19	5G	Make 2nd payment MFR Process Development and finish Proc Devel	6/30/20	0	100
20	3B	CHOP start DR/PK study; make payment	7/1/20	20	100
21	N/A	Quarterly Report 2 (April - June, Technical and Business Reports)	7/25/20	100	100
22	5H	MFR Complete analytical assays and make payment	7/31/20	50	100
23	5I	MFR start Development Report	7/31/20	100	100
24	5J	Finish MFR Dev Rept and make payment	7/31/20	100	100
25	5K	MFR Begin GMP mfg of powder; make 2nd payment re GMP mfg.	8/15/20	100	100
26	1D	Receive ACURO approval for TOX study	9/30/20	100	100
27	5L	MFR Finish mfg of GMP drug and make payment	9/30/20	100	100
28	3C	CHOP Receive preliminary DR/PK data; make payment	10/1/20	0	0
29	N/A	Quarterly Report 3 (July - Sept, Technical and Business Reports)	10/25/20	100	100
30	4D	CRL Begin toxicology study; make payment	12/15/20	100	100
31	N/A	Annual Report 1	1/25/21	0	0
32	6A	Reimbursement of consultant expenses	2/28/21	0	0
33	4E	CRL Complete in-life portion of toxicology study; make payment	3/15/21	0	0
34	3D	CHOP Dose first pig in efficacy study and make payment	3/31/21	0	0
35	N/A	Quarterly Report 4 (January - March, Technical and Business Reports)	4/25/21	0	0
36	4F	CRL Finish toxicology study; make payment	5/15/21	0	0
37	N/A	Quarterly Report 5 (April - June, Technical and Business Reports)	7/25/21	0	0
38	7A	Sign IND electronic filing vendor contract	8/1/21	0	0

39	8A	Sign brain biomarkers study contract and make payment	8/1/21	0	0
40	3E	CHOP Receive efficacy study preliminary report and make payment	10/1/21	0	0
41	3F	Deliver efficacy study samples to biomarker lab for analysis	10/1/21	0	0
42	N/A	Quarterly Report 6 (July - Sept, Technical and Business Reports)	10/25/20	0	0
43	8B	Receive brain biomarkers study results; make payment	12/1/21	0	0
44	3G	CHOP Receive final efficacy study report; make payment	12/31/21	0	0
45	7B	Make IND filing and make payment to electronic filing company	2/1/22	0	0
46	6B	Reimbursement of consultant expenses	2/1/22	0	0
47	N/A	Final reports	2/1/22	0	0
		TOTAL			

4. DEVIATION FROM PROJECT PLAN

Please see sections 1 and 3 of the Annual Technical Status Report above, in which the deviations and remedial steps are described in detail.

Please name this annual report file as EGS#_Annual Report_Y# (For example MT160001.01_Annual Report_Y2)
Please submit as a PDF file.
Please make sure to fill in the page number on page 3 Table of Contents.
Don't forget to submit an updated Quad Chart as well. Please name the Quad chart file as EGS#_Quad Chart_Y#.