AWARD NUMBER: W81XWH-16-C-0188

TITLE: Tesamorelin Therapy to Enhance Axonal Regeneration, Minimize Muscle Atrophy and Improve Functional Outcomes Following Peripheral Nerve Injury and Repair

PRINCIPAL INVESTIGATOR: Jaimie T. Shores, MD

CONTRACTING ORGANIZATION: Johns Hopkins University

REPORT DATE: October 2019

TYPE OF REPORT: Annual

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

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6. AUTHOR(S)
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5e. TASK NUMBER

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Johns Hopkins University
Baltimore, MD 21224

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U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study is a randomized, double-blinded, placebo-controlled clinical trial with the primary aim of assessing the efficacy of tesamorelin for peripheral nerve injuries. Patients with ulnar nerve lacerations at the wrist, repaired in a primary fashion, will be eligible for enrolment. Subject recruitment will take place primarily at Johns Hopkins Hospital, Union Memorial Hospital (Curtis National Hand Center), University of Maryland Medical Center/Shock Trauma, and Walter Reed National Military Medical Center. Subject follow up and outcome measurements will take place at Johns Hopkin Hospital. We plan to enroll 36 subjects over 4 years. At the end of the study, if tesamorelin is found to be efficacious, limited off-label use may be justified. Theratechnologies will then pursue a larger Phase 3 clinical trial.

15. SUBJECT TERMS
IRB, FDA IND exemption, HRPO, study set-up phase, patient recruitment

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

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1. **INTRODUCTION**:

This study is a randomized, double-blinded, placebo-controlled clinical trial with the primary aim of assessing the efficacy of tesamorelin for peripheral nerve injuries. Patients with ulnar nerve lacerations at the wrist, repaired in a primary fashion, will be eligible for enrolment. Subject recruitment will take place primarily at Johns Hopkins Hospital, Union Memorial Hospital (Curtis National Hand Center), University of Maryland Medical Center/Shock Trauma, and Walter Reed National Military Medical Center. Subject follow up and outcome measurements will take place at Johns Hopkin Hospital. We plan to enroll 36 subjects over 4 years. At the end of the study, if tesamorelin is found to be efficacious, limited off-label use may be justified. Theratechnologies will then pursue a larger Phase 3 clinical trial aimed at achieving FDA-approval for tesamorelin to become the first drug indicated for treatment of peripheral nerve injuries.

2. **KEYWORDS:**

Tesamorelin, peripheral nerve injury, peripheral nerve regeneration, Phase 2 clinical trial, motor recovery, sensory recovery.

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Below is a table listing the goals of the study as listed in the statement of work for Year 2, including the timeline as initially anticipated. We had initially anticipated beginning patient recruitment in Year 1, however, initiation of patient recruitment was been delayed by the need for more time than anticipated for study set-up, which included contract agreement between JHU and Theratechnologies and HRPO approval. Because of this delay, patient recruitment began in the second half of Year 2.

	Timeline	**Completed**
Major Task 1: Study Set Up	Months	
Coordinate with Theratechnologies for material transfer agreements	1-3	Yes
Complete Investigational New Drug (IND) application to the	1-3	Yes

U.S. Food and Drug Administration		
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	Yes
Finalize consent form & human subjects protocol	1-3	Yes
Finalize assessment measurements	1-4	Yes
Coordinate with Sites for IRB** protocol submission	1-3	Yes
Coordinate with Sites for UMH (Means) and UMMC (Pensy) IRB** review	1-6	Yes
Coordinate with Sites for WR IRB** review (ORP/HRPO)	1-6	Yes
Submit amendments, adverse events and protocol deviations as needed	As needed	Yes
Coordinate with Sites for annual IRB report for continuing review	Annually	Yes
Coordinate with Sites for UMH (Means) and UMMC (Pensy) IRB** review	1-6	Yes
Coordinate with Sites for WR IRB** review (ORP/HRPO)	1-6	Yes
Milestone Achieved: FDA IND approval	3	Yes
*Milestone Achieved: Local IRB** approval at JHH, CNHC, UMMC/ST*	3, 4	Yes (waived at CNHC and UMMC/STC
*Milestone Achieved: HRPO*** approval for all protocols and local IRB**	6	Yes
Major Task 2: Coordinate Study Staff for Clinical Trials		
Coordinate for space allocation for new staff	1-3	Yes
Milestone Achieved: Study space allocated	2-3	Yes
Coordinate with Sites for job descriptions design	1-4	Yes
Advertise and interview for project related staff	1-4	Yes
Train/orient newly hired staff	4-6	Yes
Milestone Achieved: Research staff hired/trained	3-6	Yes
Major Task 3: Randomized Controlled Trial		
Active participant recruitment efforts	4-36	Yes

Milestone Achieved: 1st participant consented, screened and enrolled	6-9	Yes
Participants randomized to study drug or placebo groups	6-36	Yes
Participant follow-up visits from assessments	6-46	Yes
Milestone Achieved: 18 participants consented, screened and enrolled	20-24	Pending
Milestone Achieved: 36 participants consented, screened and enrolled	32-36	Pending
Milestone Achieved: Final patient completed final follow-up vis	46-48	Pending

- **What was accomplished under these goals?**

  All of the aims pertaining to study set-up major task 1 and 2 have been achieved (see above table). The primary goal for Year 3 was participant recruitment and enrollment.

  Subject enrollment is dependent upon identifying patients who match our inclusion criteria and are willing and able to participate in the study. We have multiple centers attempting to identify such patients, but recruitment has been slower than expected.

- **What opportunities for training and professional development has the project provided?**

  Nothing to report.

- **How were the results disseminated to communities of interest?**

  There are no results to report during this reporting period. The results of this study will remain blinded until the end of the study.

- **What do you plan to do during the next reporting period to accomplish the goals?**

During the next reporting period, we plan to continue actively recruiting and enrolling participants to the trial.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing to report.

- **What was the impact on other disciplines?**

  Nothing to report.

- **What was the impact on technology transfer?**

  Nothing to report.

- **What was the impact on society beyond science and technology?**

  Nothing to report.

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

There were no significant changes in approach other than some changes to personnel, which are detailed below under 'changes that had a significant impact on expenditures.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

Recruitment has been slower than expected. This is in part due to there being fewer than expected patients referred to us with the appropriate injury pattern and surgical repair. The percentage of patients who meet our inclusion criteria who have consented to participate is also lower than expected (approximately 29 %)

We are now considering a major restructuring of the clinical trial in which we will open additional distant sites for recruitment, enrollment, and collection of outcome measure. We have discussed these potential changes with our DOD study advisors and we are currently in the process of investigating logistics and feasibility.

- **Changes that had a significant impact on expenditures**

  Nothing to report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  The study protocol was updated to reflect changes to include a future change in the study drug. We have received confirmation that our FDA IND exemption (number 144372) is still valid with this change. No revision to the informed consent form was made as the formulation currently being used and the new formulation requested to be used are the same drug – Tesamorelin. JHU IRB and HRPO have approved this change over in study drug.

- **Significant changes in use or care of human subjects**

  Protocol: 9 of 9

  Target required for clinical significance: 36

  Target approved for clinical significance: 36

  Submitted to and Approved by: JHM IRB and USAMRMC HRPO

  Provide bullet point list of protocol development, submission, amendments, and approvals (include IRB in addition to HRPO). Status:

  (i) Progress on subject recruitment:

  (a) Two participants are currently enrolled in the study. Subject 2 has completed their 10-month follow-up and subject 3 has reached their 4-month follow-up. We are currently evaluating other potential clinical sites to add to this protocol in an effort to increase enrollment as we are substantially behind in recruitment.

(ii) Screening:

(a)Five patients were screened for potential inclusion in to the trial.

(iii) Enrollment:

(a) In total four patients were enrolled in the study. Two cases were subsequently withdrawn. One participant was withdrawn from the study. It took longer than expected to receive the study medication and as a result, the participant was withdrawn. A second participant was enrolled in to the study but subsequently decided to drop out of the study prior to taking the study drug or having any study related tests done. Other patients have been screened and declined due to the nature of the intervention (daily injection).

(iv) Completion:

(a) No participants have reached 12-month follow-up.

(v) Numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed:

(a) We have consented and enrolled two cases. Our target enrollment number is 36 cases.

(vi) Amendments submitted to the IRB and USAMRMC HRPO for review:

(a) The protocol and informed consent form were updated to include reimbursement of travel and food. In addition, the payment method was changed from check to BOA prepaid credit cards.

(b) A protocol deviation was noted on January 26th 2019. The study participant and their caregiver were thought how to prepare and inject the study drug by

study PI instead of the research nurse as reported in the consent form and protocol. Because of this protocol deviation, it was necessary for us to revise and submit a change in research. We have updated our drug administration teaching protocol to include teaching provided by a nurse, study physician, or study affiliated nurse practitioner or physician assistant. Adjustments were made to the protocol and consent form. This event was acknowledge by JHM IRB on February 21, 2019 and approved by HRPO 0ctober 22, 2019. Please see protocol deviation report attached to this report under Appendices.

(c) The inclusion criteria was changed in the protocol and patient advertisement flyer to extend the recruitment window from 3 weeks to 6 weeks. This change was approved by JHM IRB on January 7, 2019 and approved by HRPO February 11, 2019.

(d) The protocol was updated to include a future change in the study drug. We have been granted a FDA IND exemption, IND number 144372. No revision to the informed consent form is being made because both the formulation currently being used and the new formulation requested to be used are the same drug- Tesamorelin. JHM IRB approved this change on July 30, 2019 and HRPO approved this change on October 22, 2019.

(e) Changes were made to the study co-investigators during the last approval period. Dr. Allan Belzberg was added as a co-investigator. Dr. WP Andrew Lee was removed as a co-investigator as he is the new Executive Vice President for Academic Affairs, Provost, and Dean, UT Southwestern Medical School. Dr. Lance Nowell at USAMRC HRPO, has been notified by Ms Ashley Evans, Sr. Grants Associate at Johns Hopkins University School of Medicine Office of Research of the addition of Dr. Belzberg to the study as a co-investigator. JHM IRB have approved this change in study personnel on September 6 2019.

(f) The Spanish informed consent form was updated to include changes to the study personnel provide study drug teaching. The following documents have

been translated to Spanish and submitted and approved by JHM IRB on September 6, 2019 and by HRPO on October 22, 2019:

(i) Michigan hand score,

(ii) patient study diary

(iii)Participant financial responsibility leaflet.

(g) Theratechnologies have extended the shelf life of the study drug currently in stock in JHH IDS pharmacy to the end of November 2019. This memo was submitted and approved by JHM IRB (09/06/2019) and HRPO (10/14/2019). Please see memo attached to this report under Appendices.

(h) Theratechnologies have extended the shelf life of the study drug currently in stock in JHH IDS pharmacy to the end of February 2020. This memo was submitted and approved by the JHM IRB October 17, 2019 and submitted to HRPO December 6, 2019. Please see memo attached to this report under Appendices.

(vii) Any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation.

(a) Two adverse events were identified during the last reporting period. These events have been submitted and approved by JHM IRB (10/14/2019) during the Continuing Review

i. Subject 2 was diagnosed with carpal tunnel syndrome (CTS) of her right hand (uninjured hand) by Dr. Shores during her month 8 visit. The cause of the carpal tunnel syndrome is *possibly* related to the study drug and is a known adverse event related to the use of EGRIFTA® (Tesamorelin). JHM IRB, sponsor and drug company were notified of the adverse event. Please see adverse event summary attached to this report under Appendices.

ii. Subject 3 experienced abdominal pain after administrating study drug, which resolved within 1 to 2 hours. Injection site pain is an adverse event identified in the prescribing information. JHM IRB, sponsor and drug company were notified of the adverse event. Please see adverse

event summary attached to this report under Appendices.

- **Significant changes in use or care of vertebrate animals**

  Nothing to report

- **Significant changes in use of biohazards and/or select agents**

  We have been granted a FDA IND exemption, IND number 144372 for a change in the study drug. JHM IRB approved this change on July 30, 2019 and HRPO approved this change on October 22, 2019.

  Based on comparative review of the approved prescribing information for the new 2mg/vial (Revised 11/2018) and 1 mg/vial formulations (Revised 7/2018), it was determined that for both:

  1. The approved indication remains "the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy." The active ingredient remains tesamorelin as the acetate salt

  2. The route of administration is still by a once daily subcutaneous injection.

  Furthermore, the safety and effectiveness of the EGRIFTA 2 mg/vial formulation has been established based on adequate and well controlled studies with the EGRIFTA 1 mg/vial formulation as well as a demonstration of comparable bioavailability between the 1.4 mg EGRIFTA dose (2 mg/vial formulation) and the 2 mg EGRIFTA dose (1 mg/vial formulation). After confirming the bioavailability of the new formulation, it appears that when used for its labeled indication in lipodystrophy, there were no concerns that the changes made to develop the more concentrated product, created any additional risks which were not already known based on previous studies with the original 1mg/vial drug.

  The only differences that was identified between the 1 mg/vial and 2 mg/vial formulations are:

1. The approved tesamorelin dose for the 2 mg/vial formulation was lowered to 1.4 mg /injection, but as stated above, a bioavailability was achieved that was comparable to what was obtained after a 2 mg/injection dose using the 1mg/vial formulation.

2. The inactive ingredients as follows :

1 mg/vial Formulation	2 mg/vial Formulation
50 mg mannitol	20 mg mannitol 10 mg sucrose 0.78 mg histidine 0.05 mg polysorbate 20

The 1mg/vial formulation is marketed in the U.S. by Theratechnologies (Montreal, Quebec). Both the 1mg/vial and 2mg/vial are currently approved by the FDA for treatment of HIV lipodystrophy. In our study, we will use the same dose and route of administration (2mg daily, subcutaneously) as is indicated for treatment of HIV lipodystrophy and has been shown to be safe in this patient population. The 2 mg/vial product did not introduce any additional safety risks for the approved population of HIV patients with lipodystrophy, the standard safety profile by which the level of relative risk was compared for our original IND exemption, it does not appear that any of the parameters affecting the relative risk of using tesamorelin "off label" in our study have changed. Since the 1mg/vial and the 2mg/vial formulations are interchangeable, the pharmacist can issue either when prescribed and switching participants from the 1mg/vial formula to the 2mg/vial formula, should not have any serious adverse effects on our study participants or affect the integrity of the study data.

While the drug is indicated for use in HIV patients who develop lipodystrophy as a result of HIV treatment, the patient population in our study will include healthy adults. Tesamorelin has been shown to be safe in patients with HIV, with minimal side effects observed other than injection site reactions, and there is no reason to believe that the drugs will be any less safe in our study population of healthy adults. While the 1mg/vial and 2mg/vial drugs are approved for indefinite duration of treatment, our study subjects will receive the drug for duration of 12 months.

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**

  Nothing to Report

- **Journal publications.**

  Nothing to Report

- **Books or other non-periodical, one-time publications.**

  Nothing to Report

- **Other publications, conference papers, and presentations.**

  Nothing to Report

- **Website(s) or other Internet site(s)**

  Nothing to Report

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**

  Nothing to Report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	*Jaimie Shores*
Project Role:	*PI*

Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Shores has worked on all aspects of study set up, regulatory set up and patient recruitment, enrollment and follow-up visits.* *Dr. Shores will lead and oversee the rest of the study team in the execution of the study. Dr. Shores will maintain open communication with all co-investigators and collaborators. He will schedule regular group meetings to give progress updates and provide a forum to trouble shoot problems. He will also maintain close communication with and oversight of the study coordinator. Dr. Shores will schedule regular meetings with Dr. Brown, the study monitor to discuss reports regarding study safety, hear continuation recommendations, and ensure timely submission of required documentation. He will also closely monitor accrual rates and make adjustments to the recruitment plan accordingly.*
Funding Support:	

Name:	*Sami Tuffaha*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0003-2921-0928*
Nearest person month worked:	*1*
Contribution to	*Dr. Tuffaha has worked on all aspects of study set up, regulatory set up*

Project:	*and patient recruitment, enrollment and follow-up visits.* Dr. Tuffaha will provide input with regards to study design and data interpretation. He will dedicate his protected research time to ensuring that all regulatory hurdles are cleared in a timely manner. This will be done in conjunction with the Johns Hopkins Clinical Trials Unit, which offers fee-for-service assistance with IRB and IND preparation.
Funding Support:	

Name:	*Roberto Salvatori*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0001-6495-2244*
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Salvatori* will have an integral role in the study, particularly with regards to dosing and safety monitoring guidelines. He will be present for all meeting with the Safety Monitor and the Principal Investigator to help interpret safety data and implement necessary changes.
Funding Support:	

Name:	*Shivani Ahlawat*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0003-4437-5237*

Nearest person month worked:	*1*
Contribution to Project:	*Dr. Ahlawat will be responsible for performing the MRI imaging on all study participants. She will work with Dr. Carrino to ensure optimal implementation of standardized imaging protocols. She will also be responsible for ensuring appropriate MRI data management according to protocol and will also work with Dr. Shores and the biostatistician in analysis of data.*
Funding Support:	

Name:	*Ahmet Hoke*
Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	*https://orcid.org/0000-0003-1215-3373*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Hoke will perform the electromyography (EMG) and oversee performance of the nerve conduction studies (NCS) on study participants. He helped design the protocols for these assessments. He will be intimately involved in troubleshooting any issues that arise and in data analysis and interpretation.*
Funding Support:	

Name:	*W.P. Andrew Lee*

Project Role:	*Co-Investigator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Lee has worked on all aspects of study set up. Dr. Lee is heavily invested in this study and has been involved in conception and design. He will ensure complete institutional support for all aspects of the study. As a prominent hand surgeon and recent President of the American Society for Surgery of the Hand, he will leverage his clout among his colleagues to facilitate patient recruitment.* *Update: Dr Lee left JHU in 2/2019 to become Dean of the school of Medicine at the University of Texas at Southwestern. He is no longer involved with this project.*
Funding Support:	

Name:	*Todd Brown*
Project Role:	*Study Monitor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Brown will serve as the study medical monitor. He has ample biostatistical expertise to allow effective analysis of safety data. He has no stake in the outcome of this study and has no financial or fiduciary*

	interests related to the study. He is in no way a member of the study team and will not receive compensation. He has no incentives, financial or otherwise, related to this study.
Funding Support:	

Name:	*Ala Elhelali*
Project Role:	*Clinical Study Coordinator*
Researcher Identifier (e.g. ORCID ID):	0000-0002-7147-3564
Nearest person month worked:	*12*
Contribution to Project:	*Dr. Elhelali has worked on all aspects of study set up and patient recruitment, enrollment, follow-up visits*
Funding Support:	

Name:	*Chia Na Min*
Project Role:	*Sr. Research Technician*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*6*
Contribution to Project:	*Ms Min has worked on the regulatory paperwork*
Funding Support:	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Dr. WP Andrew Lee left Johns Hopkins University and is now the new Executive Vice President, Provost, and Dean of UT Southwestern School of Medicine.

Ms Chia Na Min official finished working on the study in July 2019.

Dr. Allan Belzberg was added to the study as a co-investigator. Dr. Belzberg is a neurosurgeon specializing in surgery of the peripheral nervous system. Dr. Belzberg is Director of peripheral nerve surgery at Johns Hopkins Hospital. Dr. Belzberg will have an integral role in the study, particularly in identifying and recruiting patients to the study and will provide input regarding data interpretation. He will also work to inform his colleagues about the study to aid in recruitment effects.

- **What other organizations were involved as partners?**

Organization Name: Theratechnologies
Location of Organization: *Quebec, Canada*
Partner's contribution to the project: Material support (future). This company will provide the study drug and placebo, as previously described. During this reporting period, we were able to secure a material transfer agreement with Theratechnologies for this arrangement.

Organization Name: Union Memorial Hospital
Location of Organization: *Baltimore, MD*
Partner's contribution to the project: Collaboration in research, study set-up

Organization Name: University of Maryland/Shock Trauma
Location of Organization: *Baltimore, MD*
Partner's contribution to the project: Collaboration in research, study set-up

Organization Name: Walter Reed NMMC
Location of Organization: *Bethesda, MD*
Partner's contribution to the project: Collaboration in research, study set-up

8. **SPECIAL REPORTING REQUIREMENTS**

QUAD CHARTS: An updated quad chart is attached to this report under Appendices.

9. APPENDICES:

Office of Human Subjects Research
Institutional Review Boards

1620 McElderry Street, Reed Hall, Suite B-130
Baltimore, Maryland 21205-1911
410-955-3008
410-955-4367 Fax
e-mail: jhmeirb@jhmi.edu

Date: October 14, 2019

CONTINUING REVIEW APPROVAL

Review Type:	Convened
Principal Investigator:	Jaimie Shores
Number:	IRB00110936 / CR00028025
Title:	Tesamorelin Therapy to Enhance Axonal Regeneration, Minimize Muscle Atrophy, and Improve Functional Outcomes following Peripheral Nerve Injury
Committee Chair:	B Douglas Smith
IRB Committee:	IRB-2

Date of approval: October 10, 2019

Date of Expiration: October 9, 2020

The JHM IRB approved the above-referenced Continuing Review.

Approval includes progress report, interim analysis, protocol deviation, AEs, and CRMS enrollment summary report.

If this study is a clinical trial and data collection is complete for the perspecified primary outcome, Section 801 of the Food and Drug Administration Amendments Act requires reporting of summary results information at http://www.clinicaltrials.gov. Reporting must be done within 12 months of completing data collection for the prespecified primary outcome, regardless of sponsor or funding source. Failure to comply with this law may result in civil penalties. For more information on results reporting go to http://www.clinicaltrials.gov. If the study is registered with Clinicaltrials.gov and is closed to recruitment and enrollment, the record must be updated within 30 days to reflect the study's enrollment status. See http://clinicaltrials.gov/ct2/manage-recs/how-edit for more information. Questions can be directed to register@clinicaltrials.gov.

Date of Approval and Expiration Date: The approval and expiration date for this research are listed above. If the approval lapses, the research must stop and you must submit a request to the IRB to determine whether it is in the best interests of individual participants to continue with protocol-related procedures.

Changes in Research: All proposed changes to the research must be submitted using a Change in Research application. The changes must be approved by the JHM IRB prior to implementation, with the following exception: changes made to eliminate apparent immediate hazards to participants may be made immediately, and promptly reported to the JHM IRB.

Continuing Review/Progress Report: Continuing Review/Progress Report Applications should be submitted at least 6 weeks prior to the study expiration date. Failure to allow sufficient time for review may result in a lapse of approval. If the Continuing Review/Progress Report Application is not submitted prior to the expiration date, your study will be terminated and a New Application must be submitted to reinitiate the research.

Unanticipated Problems: All unanticipated problems must be submitted using a Protocol Event Report.

If this research has a commercial sponsor, the research may not start until the sponsor and JHU have signed a contract.

Protocol Deviation or Regulatory Noncompliance Reporting Form

Please provide contact information for a representative who can answer any questions that the IRB might have concerning this submission:	
Name:	Dr. Jaimie Shores
Position:	Principal Investigator
E-mail:	Jshores3@jhmi.edu
Phone #:	
Pager #:	
2nd Contact:	Ala Elhelali, CRC, 4439322082, aelhela1@jhmi.edu
Group:	IRB00110936

1. **Date:** 1/26/2019

2. **Principal Investigator:** Dr. Jaimie Shores

3. **IRB Project #:** 00110936

4. **Project Title:** Tesamorelin Therapy to Enhance Axonal Regeneration, Minimize Muscle Atrophy, and Improve Functional Outcomes following Peripheral Nerve Injury

5. **What are you reporting?**

☐ **Regulatory Noncompliance**

☒ **Unplanned Minor Deviation**

☐ **Unplanned Major Deviation** potentially affecting (a) study subject safety, rights, welfare, or willingness to continue participating in the study, or (b) research data integrity.

6. **Subject ID:** 2

7. **Date of occurrence:** 01/24/2019 **Date of discovery:** 01/24/2019

8. **Please describe what occurred:**

A study nurse was unavailable to teach the study subject how to administer the study drug. As a result, Dr. Jaimie Shores, the study PI, provided the teaching to the study participant and their caregivers.

9. **Did this occur in order to eliminate an apparent immediate hazard to subjects?**

☒ **Yes — explain:**

The patient and their caregiver were taught how to draw up diluent and reconstitute the medication and also taught how to self-administer subcutaneous (SQ) injection by the study PI a highly qualified surgeon, in order to prevent any serious effects to the participant and their caregivers.

☐ **No**

10. **Did any study subjects experience adverse effects or unanticipated problems as a result of the occurrence?**

☐ Yes –attach either an *Adverse Event Reporting Form* or *Unanticipated Problem Reporting Form.*

☒ No

☐ Other – describe: ☐

11. **Explain why this occurrence does or does not affect the integrity of the research data:**

This protocol deviation has warranted us to revise and submit a change in research clarifying who will provide teaching to the study participants in order to ensure research integrity of this study.

12. **What corrective action have you taken to directly address this event?**

Because of this protocol deviation, it was necessary for us to revise and submit a change in research. We have updated our drug administration teaching protocol to include teaching provided by a nurse, study physician, or study affiliated nurse practitioner or physician assistant. Adjustments were made to the protocol and consent form.

13. **What have you done to prevent this from reoccurring?**

We have revised our drug administration teaching protocol to include a nurse or study physician or study affiliated nurse practitioner or physician assistant.

Signature of Principal Investigator 04 Feb 2019 **Date**

THERA technologies	**Certificate of Compliance-Extension to Retest Date for Clinical Lot F3-QAS-030**	**# Version 3**

Product: TH9507_Lyophilized Powder for Injection, 1 mg/vial

Clinical Packaging Lot Number: Z000679

Please note that clinical material packaged under lot Z000679 will be attributed an extension to their Retest Date based on acceptable stability results.

An extension to the Retest Date was attributed to lot Z000679.

The new retest date is **November 2019.**

Issued by: _____ Date: 11 July 2019
Quality Assurance Specialist

Approved by: _____ Date: 11 July 2019
Senior Project Manager

Theratechnologies Inc.
2015 Peel Street, 11th Floor
Montreal, Quebec,Canada
H3A 1T8
Tel: 514-336-7800

Product: EGRIFTA (TESAMORELIN) (1 MG/ML) OR PBO VIAL

Clinical Packaging Lot Number: Z000679

Products packaged under this lot number have an extension to their Retest Date.

The new Retest Date is February 2020 (this date may be extended on the basis of stability data).

Issued by: Liliana Perdomo Date: 09-OCT-2019

Title: Quality Assurance Specialist

Approved by: Maria Renella Date: October 8, 2019

Title: Director, Regulatory Affairs, Quality and Compliance

Theratechnologies Inc.
2015 Peel Street, 11th Floor
Montreal, Quebec,Canada
H3A 1T8
Tel: 514-336-7800 Fax: 514-331-9691

FORM R.F.3: ANTICIPATED EVENT REPORT SUMMARY SHEET (for Continuing Review)

Directions:

1. Complete this form only to report anticipated problems/events as described in the protocol, consent form, and/or investigator's brochure.

2. Submit by uploading in the Continuing Review Application where prompted.

Note: To submit either A.) adverse events for which a sponsor requires prompt reporting, but that do not meet the JHM IRB requirements for prompt reporting, or B.) unanticipated problems/events as defined by JHM IRB policy, please complete and file a Further Study Action/Protocol Event Report in eIRB.

DO NOT USE TO SUBMIT SPONSOR GENERATED IND SAFETY REPORTS

JHM IRB Application Number: 00110936
Principal Investigator: Dr. Jaimie Shores
Sponsor: Department of Defense
Date Submitted to the IRB: 10/02/2019

Date of Anticipated Problem/Event	Participant ID (No PHI, please)	Description of Event (attach extra pages, if needed)	Was the event reported to the IRB during the past approval period? If yes, provide date of report.	Sponsor Notification Date (required for IND/IDE studies)
10/02/2019	2	The study participant was diagnosed with carpal tunnel syndrome (CTS) of her right hand (uninjured hand) by Dr. Shores during her month 8 visit. The cause of the carpal tunnel syndrome is possibly related to the study drug and is a known adverse event related to the use of EGRIFTA® (Tesamorelin).	No	10/02/2019

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DO NOT USE TO SUBMIT SPONSOR GENERATED IND SAFETY REPORTS

JHM IRB Application Number: 00110936
Principal Investigator: Dr. Jaimie Shores
Sponsor: Department of Defense
Date Submitted to the IRB: 7/12/2019

Date of Anticipated Problem/Event	Participant ID (No PHI, please)	Description of Event (attach extra pages, if needed)	Was the event reported to the IRB during the past approval period? If yes, provide date of report.	Sponsor Notification Date (required for IND/IDE studies)
07/08/2019	3	The study participant experienced abdominal pain after administrating study drug, which resolved within 1 to 2 hours. Injection site pain is an adverse event identified in the prescribing information.	No	07/09/2019

IND 144374

ACKNOWLEDGE/EXEMPT IND

Jaimie Shores, MD
Associate Professor, Department of Plastic & Reconstructive Surgery
601 N. Caroline Street
Johns Hopkins Outpatient Center, Suite 8161
Baltimore, MD 21287

Dear Dr. Shores:

We acknowledge receipt of your investigational new drug application (IND), received May 14, 2019, under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for tesamorelin.

After reviewing the information contained in your submission, we have concluded that your study to assess the efficacy of tesamorelin in improving functional outcomes following peripheral nerve injury meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the United States, is exempt from the requirements for an IND if all of the following apply:

(1) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

(2) The investigation is not intended to support a significant change in the advertising for a prescription drug product.

(3) The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

(4) The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

(5) The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND.

We remind you that exemption from the requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 or from initial and continuing Institutional Review Board review under 21 CFR Part 56. You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers (42 USC § 282(j)(5)(B)). Additional information regarding the certification is available at FDA.gov.[1] Additional information regarding Title VIII of FDAAA is available at NIH.gov.[2] Additional information on registering your clinical trial(s) is available at the Protocol Registration System website.[3]

For additional information, a searchable version of the IND regulations is available online for your convenience.[4]

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[1] https://www.fda.gov/regulatory-information/food-and-drug-administration-amendments-act-fdaaa-2007/fdaaa-certification-accompany-drug-biological-product-and-device-applications-or-submissions
[2] http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html
[3] http://prsinfo.clinicaltrials.gov/

[4] https://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

If you have any questions, contact Brenda Reggettz, PharmD, Regulatory Health Project Manager, by email at Brenda.Reggettz@fda.hhs.gov or by phone at (240) 402-6220.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
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