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, Baltimore, MD

REPORT DATE: October 2020

TYPE OF REPORT: Annual report

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

REPORT DOCUMENTATION PAGE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-C-0188

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Sami Tuffaha, MD; Jaimie Shores, MD; Ala Elhelali, PhD

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Johns Hopkins University
Baltimore, MD 21224

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

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	132	19b. TELEPHONE NUMBER *(include area code)*

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

Table of Contents

Page

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. Recruitment was initially anticipated to begin 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. Furthermore, in response to the COVID-19 pandemic, JHM IRB halted all new enrollments and in-person research related visits, which in turn effected recruitment rates.

	Timeline	**Completed**
Major Task 1: Study Set Up	Months	
Coordinate with Theratechnologies for material transfer	1-3	Yes

agreements		
Complete Investigational New Drug (IND) application to the U.S. Food and Drug Administration	1-3	Yes
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 patient recruitment, enrollment and follow-up.

  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 patients 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**

     Changes in approach were made to the study 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 11 %)

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. Additionally, we anticipate submitting an IND to the FDA for a change in indication for Egrifta. 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) One patient is currently enrolled in the study. Patient 5 has completed his baseline visit

(b) Patient 2 successfully completed all study related visits and study drug on February 5th 2020

(c) Patient 3 completed her 12 month follow-up July 1st 2020. Due to the COVID-19 pandemic the IRB have requested that we stop all in-person study related visits. Subject 3 was followed-up via remotely by the study physicians for the remainder of her time in the study.

(d) 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) Six patients were screened for potential inclusion in to the trial. Other patients were screened and declined to enroll due to the nature of the intervention (daily injection).

(iii) Enrollment:

(b) In total six patients were enrolled in the study.

a. Two cases were subsequently withdrawn.

i. One was withdrawn from the study. It took longer than expected to receive the study medication and as a result, the patient was withdrawn.

ii. A second patient 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.

(iv) Completion:

(a) Two patients 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 four 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 patient 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) Patient 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.

(i) Given the increased risk of exposure caused by the COVID-19 pandemic the JHM IRB stopped all new enrollment on March 18th 2020. Furthermore, all in-person research visits on enrolled patients was also prohibited. HRPO COVID-19 response unit was notified of this halt in new enrollment and in-person research related visits.

(j) In response to the COVID-19 pandemic, a change in protocol was submitted to JHM IRB to implement telephone or zoom visits for our enrolled patient in lieu of on-site visit. HM IRB approved our request August 23rd 2020.

(k) We submitted a request to JHM IRB to ship the study drug to our remaining patient during the COVID-19 pandemic. JHM IRB approved our request August 23rd 2020.

(l) On August 6th 2020, Johns Hopkins University IRB approved our study to resume in-person activities and new enrollment. HRPO approved our study to restart new enrollment and in person research related visits on August 12th 2020.

(m) We updated the protocol to reflect an additional follow-up visit one month after patients discontinue the study drug. The purpose of this visit is a safety follow-up visit. We have also updated the English and Spanish informed consent forms to reflect this change. In addition to this change, we have updated our recruitment method. We will utilize MyChart recruitment services to expand our patient pool. We will send out MyChart research invitation letters to potential patients with an active MyChart account. This invitation letter was developed in accordance with newer language as requested by the MyChart Recruitment Committee. This new recruitment method was approved by JHM IRB (August 6th 2020) and HRPO on August 12th 2020.

(n) We added two new Johns Hopkins sites. Odenton and Johns Hopkins Health Care & Surgery Center and Green Spring Station, Lutherville as recruitment sites. This was approved by JHM IRB on August 6th 2020 and HRPO on August 12th 2020.

(o) The protocol was updated to incorporate teleconsent and remote consent. This new method in consenting was approved by the Johns Hopkins Medicine (JHM) IRB on August 17th 2020 and HRPO on August 19th 2020.

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

(a) One adverse events was identified during the last reporting period. These events have been submitted and acknowledged by JHM IRB (01/10/2020)

i. An unanticipated adverse event (AE) was noted during patient 3's six month follow-up visit. During patient 3's six-month follow-up visit, Dr. Salvatori noted that her transaminases levels were above normal ranges ALT 3.2 x, and AST 1.6 x upper range of normal). No liver enlargement or tenderness and no jaundice were observed. Study patient was immediately informed. IRB, sponsor and drug company will be notified of the unanticipated adverse event. As a corrective action, Dr. Salvatori has advised the patient to avoid alcohol and acetaminophen, and requested to repeat a fasting comprehensive metabolic panel on Friday 01/10/2020. 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**

Nothing to Report

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 patients. 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 patients. 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:	*0*
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:	*0*
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?**

Nothing to Report

- **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:

Tesamorelin therapy to enhance axonal regeneration, minimize muscle atrophy and improve functional outcomes following nerve injury and repair

DM153184

W81XWH-16-C-0188

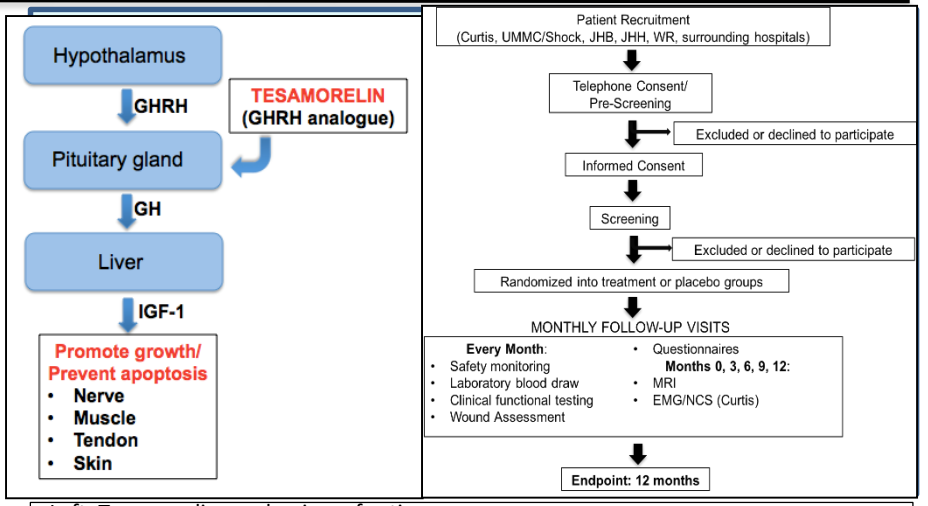
PI: Jaimie Shores, M.D. **Org:** Johns Hopkins University School of Medicine **Award Amount:** $2,926,762

Study Aims

- Specific Aim 1: Test efficacy of tesamorelin as a therapy to enhance axonal regeneration, minimize muscle atrophy and improve functional outcomes following peripheral nerve injury.
- Specific Aim 2: Confirm safety of tesamorelin treatment
- Specific Aim 3: Assess potential secondary benefits of tesamorelin treatment from wound and tendon healing
- Specific Aim 4: Prospectively validate MRI tractography as diagnostic/prognostic tool for peripheral nerve injury

Approach

Multi-institutional Phase II clinical trial comparing tesamorelin treatment to placebo. Military and civilian adult patients with ulnar nerve injuries repaired primarily will be enrolled. Endpoint will be one year. Outcome measures will include EMG/NCS, MRI, clinical functional assessments, and patient questionnaires.



Left: Tesamorelin mechanism of action
Right: Study flow chart

Timeline and Cost

Activities / CY	17	18	19	20
Regulatory approval and study set-up				
Recruit, screen, enroll 36 patients				
Patient follow up, testing, monitoring				
Final data collection, analysis				
Estimated Budget ($K)	**$200**	**$850**	**$850**	**$600**

Updated: 10/27/2020

Goals/Milestones

CY17 Goal – Study set-up, initiation
- ☑ Secure IND, IRB, (HRPO pending)
- ☑ Hire study coordinator and research tech
- ☑ Begin recruiting patients
- ☑ Patient follow up, testing, monitoring

CY18 Goals – Study continuation
- ☑ Continue recruiting patients
- ☑ Patient follow up, testing, monitoring

CY19 Goal – Study continuation
- ☐ Final patient recruitment
- ☐ Patient follow up, testing, monitoring

CY20 Goal – Study wrap-up
- ☐ Final patient follow up, testing, monitoring
- ☐ Final data collection, final analysis

Comments/Challenges/Issues/Concerns
- Completion of study set up delayed but nearly complete (pending HRPO approval)
- Actual spending less than projected because of delay in patient recruitment

Budget Expenditure to Date

Actual Expenditures (through Sept. 30, 2020): $1,203,201.30

PROTOCOL DEVIATION LOG

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

Study IRB #: IRB00110936 **Principal Investigator**: Dr. Jaimie Shores

S.No.	Date of Event (dd/mm/yyyy)	Subject ID	Description of the Deviation	Reason for the Deviation and the corrective Measures taken	IRB/ HRPO Notification (Yes/No/NA)	Investigator Initials and Date
1	1/24/2019	2	Patient 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	Protocol and consent forms have been updated as result of this deviation	**YES**	**AE 1/24/2019**
2	07/10/2019	3	Subject 3 is unable to have any more research MRIs due to complaining of warm left elbow during her baseline MRI. Dr. Ahlawat recommended that subject 3 should not have any more research related MRIs	Due to the issue raised by this deviation we will review our study protocol	**YES**	**AE 08/13/2020**
3	04/01/2020	3	Subject 3 is unable to attend her in person reach related month 9 appointment due to the COVID-19 crisis. Her 9 month EMG and NCS were not performed.	Due to COVID-19 pandemic the IRB have placed a hold on in-person research related visits. As a result subject 3 was unable to attend her in-person related visit. We have updated our protocol to allow zoom and telephone visits in lieu of in person visit.	**YES**	**AE 08/13/2020**
4		3	Subject 3 is unable to attend her in person reach related	Due to COVID-19 pandemic the IRB have placed a hold on in-	**YES**	**AE 08/13/2020**

	05/06/2020		month 10 appointment due to the COVID-19 crisis.	person research related visits. As a result subject 3 was unable to attend her in-person related visit. We have updated our protocol to allow zoom and telephone visits in lieu of in person visit		
5	06/03/2020	3	Subject 3 is unable to attend her in person reach related month 11 appointment due to the COVID-19 crisis.	Due to COVID-19 pandemic the IRB have placed a hold on in-person research related visits. As a result subject 3 was unable to attend her in-person related visit. We have updated our protocol to allow zoom and telephone visits in lieu of in person visit	**YES**	**AE 08/13/2020**
6	07/01/2020	3	Subject 3 is unable to attend her in person reach related month 12 appointment due to the COVID-19 crisis.	Due to COVID-19 pandemic the IRB have placed a hold on in-person research related visits. As a result subject 3 was unable to attend her in-person related visit. We have updated our protocol to allow zoom and telephone visits in lieu of in person visit	**YES**	**AE 08/13/2020**
7	05/19/2020	3	Due to the COVID-19 crisis subject 3 stopped taking the study during on May 19 and was unable to obtain more as she is living in California and could not fly to Maryland due to the travel restrictions and fear of COVID-19.	Due to COVID-19 pandemic the IRB have placed a hold on in-person research related visits. As a result subject 3 was unable to attend her in-person related visit. We have updated our protocol to allow zoom and telephone visits in lieu of in person visit	**YES**	**AE 08/13/2020**
8						
9						

PROTOCOL DEVIATION LOG

Adverse Event 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 #:	410-550-6995
Pager #:	
2nd Contact:	Ala Elhelali, CRC, 4439322082, aelhela1@jhmi.edu
Group:	IRB00110936

1. **Date:** 01/07/2020

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?**

☒ **Adverse Event**

☐ **Serious Adverse Event**

☐ **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:** 3

7. **Date of occurrence:** 01/03/2020 **Date of discovery:** 01/03/2020

8. **Please describe the nature of the event:**

During subject 3's six-month follow-up visit, Dr. Salvatori noted that her transaminases levels were above normal ranges ALT 3.2 x, and AST 1.6 x upper range of normal). No liver enlargement or tenderness and no jaundice were observed

9. **The findings of the organization:** Elevated transaminases levels are possibly related to the study drug.

10. **The actions taken by the organization and IRB, including plans to protect the rights and welfare of the participants:** study subject was immediately informed. IRB, sponsor and drug company will be notified of the unanticipated adverse event.

11 **The plans for continued oversight, investigation, or actio**n: As corrective action Dr. Salvatori has advised the participant to avoid alcohol and acetaminophen, and requested to repeat a fasting comprehensive metabolic panel on Friday 01/10/2020.

Electronically signed by Jaimie T. Shores, MD, FACS on 01/10/2020

	Signature of Principal Investigator	**Date**

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: November 11, 2019

CHANGE IN RESEARCH APPROVAL

Review Type:	Expedited
Principal Investigator:	Jaimie Shores
Number:	IRB00110936 / CIR00053916
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: November 6, 2019

Date of Expiration: October 9, 2020

The JHM IRB approved the above-referenced Change In Research.

Approval includes revised supplemental study document.

Johns Hopkins Study Team Members:
Shivani Ahlawat, Roberto Salvatori, Ahmet Hoke, Allan Belzberg, Sami Tuffaha, Ala Elhelali

Office of Human Subjects Research
Institutional Review Boards

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Date: February 14, 2020

CHANGE IN RESEARCH APPROVAL

Review Type:	Expedited
Principal Investigator:	Jaimie Shores
Number:	IRB00110936 / CIR00056112
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: February 13, 2020

Date of Expiration: October 9, 2020

The JHM IRB approved the above-referenced Change In Research.

Approval includes revised sample size and IFU spanish EGRIFTA SV.

Johns Hopkins Study Team Members:

Roberto Salvatori, Ahmet Hoke, Shivani Ahlawat, Allan Belzberg, Sami Tuffaha, Ala Elhelali

Office of Human Subjects Research
Institutional Review Boards

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Date: April 28, 2020

CHANGE IN RESEARCH APPROVAL

Review Type:	Convened
Principal Investigator:	Jaimie Shores
Number:	IRB00110936 / CIR00057546
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: April 23, 2020

Date of Expiration: October 9, 2020

The JHM IRB approved the above-referenced Change In Research.

Approval includes revised protocol dated 04/01/2020 with tracked changes and supplemental study document.

Communication to PI:
Issues – Response NOT required

NOTE: The JHM IRB approved this change in research. Due to the human subject research restrictions imposed by the Institution, you may not enroll new participants in the study or continue in-person research activities unless you received prior IRB Board approval. You must also cease all in-person visits specifically for research purposes. Please check the IRB website daily for updates on the restrictions regarding new enrollment.

If you believe your study meets the criteria of Tier 1 and there is a compelling reason to enroll new participants or continue in-person activities, you will need to submit a change in research with a justification to the JHM IRB. The convened IRB will need to approve this request before enrollment or in-person activities may take place.

Johns Hopkins Study Team Members:

Sami Tuffaha, Allan Belzberg, Roberto Salvatori, Ala Elhelali, Ahmet Hoke, Shivani Ahlawat

The Johns Hopkins Institutions operate under multiple Federal-Wide Assurances: The Johns Hopkins University School of Medicine - FWA00005752, Johns Hopkins Health System and Johns Hopkins Hospital - FWA00006087

Office of Human Subjects Research
Institutional Review Boards

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Baltimore, Maryland 21205-1911
410-955-3008
410-955-4367 Fax
e-mail: jhmeirb@jhmi.edu

Date: August 6, 2020

CHANGE IN RESEARCH APPROVAL

Review Type:	Convened
Principal Investigator:	Jaimie Shores
Number:	IRB00110936 / CIR00059374
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: July 30, 2020

Date of review of Administrative Changes: July 30, 2020

Date of Expiration: October 9, 2020

The JHM IRB approved the above-referenced Change In Research.

Approval includes HSRPC approval email, HSRPC restart application form, IRB petition, revised protocol dated 06/02/2020 with tracked changes, 2 new study locations, 1 new MyChart recruitment letter, 1 revised consent form, MyChart recruitment committee approval document, and revised data and safety monitoring plan section.

The IRB has approved this study to resume in-person activities and new enrollment.

Johns Hopkins Study Team Members:

Allan Belzberg, Shivani Ahlawat, Ahmet Hoke, Sami Tuffaha, Roberto Salvatori, Ala Elhelali

Office of Human Subjects Research
Institutional Review Boards

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Date: August 17, 2020

CHANGE IN RESEARCH APPROVAL

Review Type:	Expedited
Principal Investigator:	Jaimie Shores
Number:	IRB00110936 / CIR00061673
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: August 13, 2020

Date of Expiration: October 9, 2020

The JHM IRB approved the above-referenced Change In Research.

Approval includes revised protocol dated 08/10/2020 with tracked changes, revised written consent section, revised oral consent section, and new supplemental study documents.

IRB review included the following:

Use of an oral consent process.

Johns Hopkins Study Team Members:

Ahmet Hoke, Shivani Ahlawat, Ala Elhelali, Allan Belzberg, Sami Tuffaha, Roberto Salvatori

If you are using Epic, you must fax a copy of this signed consent form to 410-367-7382.

Patient I.D. plate

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **Tesamorelin to enhance nerve regeneration, minimize muscle atrophy and improve functional outcomes following peripheral nerve injury.**

Application No.: **IRB00110936**

Principal Investigator: **Jaimie Shores, MD**
601 N. Caroline Street
Johns Hopkins Outpatient Center
Suite 8161
Baltimore, MD 21287
P: 410-502-7382
F: 410-614-4333

1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in the study. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information in this informed consent that you do not understand.
- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.
- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.
- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.
- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.
- Biospecimens will be collected in this study. Biospecimen may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
- If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.
- This study is being funded by the Department of Defense (DoD) award
- During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed for your treatment can be made available to your study physician and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.

2. Why is this research being done?

This research is being done to test the effectiveness of a drug called tesamorelin in improving recovery after peripheral nerve injury.

Tesamorelin is approved by the Food and Drug Administration (FDA) for the treatment of HIV lipodystrophy. It is not approved for use in peripheral nerve injuries and has not previously been used for this purpose and its use in the study is considered investigational. The FDA is allowing the use of tesamorelin in this research study.

Tesamorelin is a drug that acts by making your body produce extra amounts of growth hormone. Based on animal studies, we believe that tesamorelin may make your nerve fibers grow more quickly and prevent your muscle from breaking down. In doing so, we believe that tesamorelin may improve the amount of movement and sensation that you regain after healing is complete.

In this study we want to see if taking tesamorelin will improve recovery strength, motion and sensation after peripheral nerve injury. After sustaining peripheral nerve injuries, people typically do not receive any drug treatments for their injuries. In this study, you will receive either tesamorelin or a placebo (an inactive material that does not contain any active study drug) for 12 months. Every month, participants will undergo testing to assess their healing and recovery. All of the tests performed are standard tests that are sometimes or typically used to assess recovery after nerve injury. However, in this study, the tests will be performed more often than they would typically be performed.

Adults with ulnar nerve injuries that were surgically repaired may join the study.

How many people will be in this study?

About 36 people will participate in this study.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Study Summary

- As a study participant, you will be randomly assigned (like flipping a coin) to receive either the tesamorelin or placebo. *You will not know if you received the study drug or the placebo until the study is complete.* The reason for this is because your knowledge of which type of study drug you are receiving (study drug or placebo) could potentially affect the outcomes of the study.
- You will be asked to administer either tesamorelin or placebo daily by subcutaneous injection (just deep to the skin). A study nurse or study physician or study affiliated nurse practitioner or physician assistant will teach you and your caregiver how to do this.

- You will be asked to come to Johns Hopkins Hospital once every month, for a total of 13 months.
    - At every appointment, you will be asked to complete 3 questionnaires.
    - At every appointment, you will have blood drawn for laboratory assessment.
    - At every appointment, you will have an in depth physical exam to test your recovery from your injury.
    - At every appointment, a video recording of your forearm and hand may be taken during your physical examination to allow for quality control of the data collection process, if you provide additional consent for this, as indicated at the end of this form. This is not required for participation in the study.
    - At every appointment, images of any wounds that you have will be taken to assess wound healing if you provide additional consent for this, as indicated at the end of this form. This is not required for participation in the study.
    - At every appointment, you will be asked questions about how potential side effects from treatment.
    - At 5 of the monthly appointments, you will undergo magnetic resonance imaging (MRI) or your injured arm.
    - At 5 of the monthly appointments, you will undergo nerve conduction studies.
    - At 3 of the monthly appointments, you will under electromyography.

      **While some or all of these tests and procedures are sometimes performed for patients with peripheral nerve injuries, they are typically not performed with this amount of frequency.

After 13 months, your participation in this study will be complete. If you agree, we may still wish to contact you afterwards for follow-up questions or testing.

Description of Study Procedures

Nerve conduction studies: This will involve a trained technician placing electrodes on the small finger and back of your affected hand. An electrical signal will be sent through your injured nerve, and the characteristics of that signal will be measured by the electrodes on your hand. This testing does not typically cause discomfort.

Electromyography (EMG): This will involve a trained technician placing very small needles in your arm and sending electrical signals through the injured nerve to measure how well the signals conduct. Needles are also placed in the muscle to measure signals associated with recovery. This type of testing is commonly performed to monitor recovery after peripheral nerve injury. However, for this study you will undergo the testing more frequently than you likely would if you do not participate in the study. This testing can cause mild discomfort and muscle soreness from the needles and temporary tingling from electrical signals and typically takes one hour to perform.

Magnetic Resonance Imaging (MRI): MRI scans create images of the body using a magnet and radio waves. While the procedure is much like a CT scan, there is no radiation involved in an MRI exam. This test involves placing your arm in a cylinder and keeping it still for up to 60 minutes. This type of testing is sometimes used to diagnose nerve injuries. Some of the image processing techniques that the radiologist will use after your imaging session are fairly new.

To be sure that it is safe for you to have an MRI exam, you will be asked to complete standard MRI screening questionnaires.

Since the MRI machine uses a strong magnet that will attract other metals, you may not take part in this study if you have a pacemaker, an implanted defibrillator, or certain other implanted electronic or metallic devices, shrapnel, or other metal.

If you have a history of metal in your head or eyes, you will need an x-ray exam of your skull in order to find out if the MRI exam is safe for you.

Although the MRI machine is open at both ends, you may still feel confined (claustrophobic). If this bothers you, please tell the MRI staff. The MRI machine periodically makes loud banging noises. We will provide earplugs or headphones for you to wear during the MRI exam. During the exam, you will be able to hear the MRI staff. They will be able to see and hear you.

How long will you be in the study?
The expected duration of your participation in the study is 13 months.

Future Contact
We would like your permission to contact you about other studies that you may be eligible for in the future.

Please check box and sign to indicate your choice below:

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

4. What are the risks or discomforts of the study?

1. Tesamorelin (study drug):
   Tesamorelin has been tested in a number of clinical trials. In general, it was well tolerated by patients.

   The following are the *most common side effects* that were noted:
   - Injection site irritation, redness, itching, and/or pain
   - Hypersensitivity reaction (rash, hives)
   - Muscle pain
   - Fluid retention, swelling in hands and feet
   - Carpal tunnel syndrome (numbness and tingling in fingers)
   - Glucose intolerance

   Less commonly observed adverse effects include:
   - Nausea
   - Vomiting
   - Dyspepsia (indigestion)
   - Abdominal pain upper
   - Night sweats
   - Palpitations
   - Depression

- Hypertension (high blood pressure)
- Muscle enzyme elevation
- Antibodies to tesamorelin or GHRH
- Increased growth of existing cancers

Although not considered side effects, you may experience the following due to subcutaneous injection of tesamorelin of placebo:

- Inconvenience of daily subcutaneous injections
- Mild discomfort from daily subcutaneous injection

Other Risks:

- Neoplasm
  - Tesamorelin treatment results in increased production of growth hormone and IGF-1 (a growth factor), which have been implicated in the development and progression of neoplasms and malignancy. Patients with active malignancy should not be treated with tesamorelin and will not be enrolled in the study. Treatment with tesamorelin has not been shown to result in increased frequency malignancy. However, development and progression of malignancy should be considered risks of treatment with tesamorelin.
- Acute Critical Illness
  - Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of growth hormone. Tesamorelin has not been studied in patients with acute critical illness. Patients with acute critical illness will not be enrolled in this study.

2. Screening (including history, physical exam):
   Infrequent-
   - Breach of privacy/confidentiality
   - Boredom
   - Discovery of previously unknown conditions

3. Magnetic Resonance Imaging:
   While no significant risks have been found from the use of MRI scans, you may be bothered by the MRI machine noise and by feelings of being closed in (claustrophobia).

   If you require an x-ray examination of your head and eyes, because you have metal in your head or eyes:

   - This research study includes exposure to radiation from x-rays or gamma rays. This radiation exposure is for research purposes only and is not part of your medical care. X-rays and gamma rays can damage cells, but at low doses, the body is usually able to repair these cells.

     The radiation exposure that you will get in this research study is 0.001 rem (a rem is a unit of absorbed radiation). This is less than the 0.3 rem that the average person in the United States gets each year from natural sources like the sun, outer space, air, food, and soil. The risk from the radiation exposure in this research study is very small.

The radiation exposure described here is what you will get from this research study only. It does not include any exposure you may have received or will receive from other medical tests outside of this study that are a part of your medical care. Radiation risk builds up with each exposure. You should think about your own history of radiation exposure from tests (like x-rays or CT scans) in deciding about the radiation in this study. If you have questions about the total amount of radiation you will be receiving, you should ask your doctor

4. Electromyography:
   - Transient tingling
   - Transient discomfort from electrical stimulation
   - Transient discomfort from EMG needle

   Infrequent-
   - Mild muscle soreness following EMG

5. Venipuncture (laboratory assessments):
   Taking blood may cause discomfort, bleeding or bruising where the needle enters the body. In rare cases, it may result in fainting. There is a small risk of infection.

6. Study Questionnaires:
   You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.

Additional Considerations
Although every effort will be made to keep your personal information confidential, there is a risk that confidentially will be breached which could adversely affect your privacy.

There may be side effects and discomforts that are not yet known.

5. Are there risks related to pregnancy?

The effects of tesamorelin on an embryo or fetus or a nursing child are unknown. Women who are pregnant or nursing a child must not participate in this study. You must not be pregnant or intend to become pregnant during the study.

If you are capable of having children, you may only participate if you are using a reliable method of birth control (at least 2 months prior to participation in the study, during the course of the study and at least 2 months after completing the study drug administration) and if you have a negative pregnancy test throughout the study (urine dipstick). Your study doctor will discuss appropriate birth control measures with you.

If you suspect a pregnancy during the study, you must notify the study doctor immediately. If you are pregnant you will be withdrawn from the study.

Nursing mothers are not permitted in the study.

This research may hurt an embryo or fetus in ways we do not currently know.

6. Are there benefits to being in the study?

There may or may not be a direct benefit to you from being in the study. If you are assigned to take tesamorelin, it may improve the amount of movement and sensation you regain but this cannot be guaranteed. If you are assigned to take placebo, no benefit is expected.

If you take part in this study, you may help others in the future.

7. What are your options if you do not want to be in the study?

There are currently no alternative drugs available to treat peripheral nerve injuries. However, some patients achieve satisfactory function after healing from their peripheral nerve injuries without additional treatment beyond surgery and physical rehabilitation. You do not have to join this study to receive standard treatment, including surgical repair of your injured nerve, physical rehabilitation, and routine monitoring of recovery. If you chose not to participate in this study, you and your doctor can chose another appropriate treatment plan.

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

8. Will it cost you anything to be in this study?

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).

- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. Will you be paid if you join this study?

You will be paid a total of $7,062.00 if you complete the study. Of this amount, $1,177.00 is a bonus, which you will be eligible to receive if you have shown up on time for all study visits as scheduled, taken your study drug as directed and followed the directions of the study staff. Please note that the payments are meant to be fair reimbursement for the hardships associated with participation in the study and are not meant to be an enticement to encourage enrollment.

If you do not finish the study, you will be paid only for the amount you complete as follows:

Outpatient visit: $50 (x14) = $700
Blood sample-single venipuncture: $10 (x14) = $140
Neurodiagnostic study: $40 (x5) = $200
Electromyography: $130 (x3) = $390
Magnetic Resonance Imaging: $35 (x5) = $175
Questionnaire ($15) (x42) = $630
Subcutaneous injection: $10 (x365) = $3650
Sum: $5,885
Completion bonus 20%: $1177
Total per participant: $7062

Payment will be made by prepaid credit cards at the final visit. If you need to make extra visits at our request, you will be paid $25 per visit.

You will receive a validated parking ticket for every visit.

You will receive a reimbursement of up to $50 for travel and food expenses (e.g., bus fare, taxi from home to study site, food etc.) incurred at each visit. If you are travelling by car, mileage will be reimbursed as receipts are presented at the current Internal Revenue Service business reimbursement rate of $0.545 per mile for private automobiles. We will use Google Map to calculate the round-trip mileage from your home address to the study site. We will not provide a daily stipend for the incidentals mentioned above, but rather we will reimburse for these types of expenses as receipts are presented.

You will be required to provide your personal details to set up the prepaid credit cards. You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from Johns Hopkins exceed $600 per year, Johns Hopkins will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us.

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or give out your health information they have already collected if the information is needed for this study or any follow-up activities.

11. Why might we take you out of the study early?

You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You fail to follow instructions.
- You become pregnant.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that they have already collected if the information is needed for this study or any follow-up activities.

12. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records (which may include information about HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

The research team will know your identity and that you are in the research study. Other people at Johns Hopkins, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

The Department of Defense (DoD) and the U.S. Army Medical Research and Materiel Command (USAMRMC) will have access to records for audit purposes.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other health care providers.

- You may be asked to give us a list of other health care providers that you use.

14. What treatment costs will be paid if you are injured in this study?

Johns Hopkins and the federal government do not have a program to pay you if you are hurt or have other bad results from being in the study.

The costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you.

By signing this form you will not give up any rights you have to seek compensation for injury.

15. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The Johns Hopkins Medicine IRB is made up of:

- Doctors
- Nurses
- Ethicists
- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine Institutional Review Board (IRB) reviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?

Call the principal investigator, Dr. Jaimie Shores at 410-502-7382. If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?

If you think you are injured or ill because of this study, call Dr. Jaimie Shores at 410-502-7382 during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call 410-955-5000 and ask to speak with the Plastic Surgery on-call resident during regular office hours and after hours and on weekends.

d. What happens to Data and Biospecimens that are collected in the study?

Johns Hopkins and our research partners work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, Johns Hopkins may share your biospecimens and information with our research sponsors and partners.

16. What does your signature on this consent form mean?

Your signature on this form means that: You understand the information given to you in this form, you accept the provisions in the form and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant	(Print Name)	Date/Time

Signature of Person Obtaining Consent	(Print Name)	Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

Signature of Participant	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

DOCUMENTATION OF PHYSICIAN/MID-LEVEL PROVIDER CONSENT

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

Signature of Physician/Mid-Level Provider	(Print Name)	Date/Time

Signature of Participant	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

17. CONSENT TO VIDEO & PHOTOGRAPY RECORDING

I understand that video recording of my clinical function assessment and images of my wound will recorded by the researcher. These recordings will be kept by the researcher in a locked filing cabinet. I understand that only the researcher will have access to these files and that they will destroyed five years after video and/or photography recording.

Video recording of the participants clinical function assessment

Clinical function assessment may be recorded using video devices to assist with assessing your functional outcome at each appointment. You have the right to refuse the video recording. You will not be excluded from the trial if you refuse video recording. Please select one of the following options:

I consent to video recording: Yes _____ No_____

_____

Signature of Participant (Print Name) Date/Time

_____

Signature of Person Obtaining Consent (Print Name) Date/Time

Photographing of study participants wound

Photographs of participants surgical wound will be taken at each appointment which will only be used for this study. You have the right to refuse to allow photographs to be taken. You will not be excluded from the trial if you refuse photographs being taken. Please select one of the following options:

I consent to photographs: Yes _____ No_____

_____

Signature of Participant (Print Name) Date/Time

_____

Signature of Person Obtaining Consent (Print Name) Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

JOHNS HOPKINS
MEDICINE

TELEMEDICINE ACKNOWLEDGEMENT

TELEMEDICINE/TELEHEALTH SERVICES ACKNOWLEDGEMENT

Patient Identification Information

Patient Name

Date of Birth

Telehealth services (also known as telemedicine, e.g. interactive video, remote video monitoring, store and forward, or other electronic media interactions) give you the ability to communicate with your healthcare team or your healthcare team to communicate with one another without having to be in the same physical location. You may communicate with your healthcare team using technology, such as a mobile device, tablet or computer.

Telehealth services are not an option for all of your care needs. Your provider may need to see you in person for certain medical conditions.

No video, audio or photo recordings will be taken of you in the course of telehealth services without your consent.

I UNDERSTAND THE FOLLOWING:

- I understand that I may see my healthcare team using this technology for some of my care needs.
- I understand that a telehealth provider who is not present in the room with me may provide a portion of my care.
- I understand that my telehealth provider may not perform an in-person physical examination of me at the time my telehealth services are provided.
- I understand that technology platforms used for telehealth sometimes malfunction. My healthcare team or I can stop or cancel a telehealth service if the technology is not working properly or if my healthcare team determines that the provision of telehealth services will not adequately address my medical needs.
- Generally, I have the right to cancel my telehealth service without affecting my ability to receive care in the future. There may be exceptions to my right to cancel the visit/consult due to clinical and safety reasons (e.g. remote video monitoring).
- A healthcare provider will explain to me how the telehealth services will be provided.
- I understand that the laws that protect privacy and the confidentiality of medical information also apply to telehealth services and that no information obtained in the use of telehealth services which identifies me may be disclosed to researchers or other entities or used as part of a research study without my consent, except as otherwise permitted by law.
- I understand that there are alternative forms of communication available between me and a physician for urgent matters.
- I may receive more than one bill related to my telemedicine services. I understand that my telehealth provider may be an independent consultant and that this consultation may result in separate charges from the telehealth provider. I also understand that my telehealth service provider may not be an employee of the hospital/health care facility from which I am receiving treatment. I further understand that I am responsible for the self-pay (co-pay, deductible, etc.) portion of all billing related to these interactions. I understand that if telehealth services are not a covered service by my insurer, I may be responsible for the entire bill.

PATIENT ACKNOWLEDGEMENT FOR TELEMEDICINE/TELEHEALTH SERVICES - I have read and understand the items as defined in the above Telemedicine/Telehealth Services Acknowledgement Form.

Date | Patient Signature | Patient PRINTED Signature

For D health care agent / D guardian / D surrogate / D parent (check one), I am the representative for the patient.

Date | Representative's Signature | Representative's PRINTED Signature

Process for conducting teleconsent / remote consent process

A copy of the IRB approved Informed Consent document must be provided to the participant prior to the teleconsent meeting either via email, fax or mail or must have been previously provided during an in person visit. If the consent divulges PHI, such as a diagnosis, inform participants that email sent over the Internet is not secure prior to sending the consent form via email and confirm the participant agrees to receive the document via email. Information sent by email may not remain confidential.

The person conducting the consent process may conduct the process via telephone or video. The following is a step-by-step teleconsent / remote consent process:

- ☐ All research participants must complete the Telemedicine Acknowledgement form in accordance with standard clinical practice.
  - The form may be completed in person or via mail or using the remote process detailed below.
  - Study team members may access the form from Epic Forms on Demand, print, obtain signature and upload it to the media tab, storing it under Telemedicine Consent
  - For mailed forms, please review with the research participant via video. The participant should sign the form on video and may email/text image of the signed form or send a hardcopy of the form through the mail. The video should not be recorded unless it is part of the approved process.
  - In cases where a signature cannot be obtained, the following remote process is permitted:
    - Review the telemedicine acknowledgement with patient via video or phone
    - A second Johns Hopkins employee [the witness] must join the video or phone call and confirm that the participant has agreed to the use of telemedicine.
    - The study team member then notes on the form that consent was obtained and the method used [e.g. phone or video], and documents in the note the name of the witness who was present to affirm the participant's agreement.
  - For research participants who utilize MyChart, the acknowledgement may be transmitted to the participant through MyChart eCheckIn. Research participants will be prompted to eSign the form and it will be auto filed.
- ☐ Research Teams must ensure providers have licensure in states where research participants are consented
  - If additional licensure (permanent or temporary) is obtained, send a confirmation email to bstrohm1@jhmi.edu in order for the license to file in MSOW and Epic
  - During the COVID crisis there are flexibilities for licensing by state, see these Legal FAQs
- ☐ Research Teams must ensure providers are credentialed in facilities where participating subjects are located (if applicable)
  - If patient is within a facility (hospital, nursing home), the provider must be credentialed at that facility
  - During the COVID crisis, there are flexibilities within the JHHS system for credentialing, see these Legal FAQs

- After the consent designee and participant or LAR review the consent form, the participant or LAR is offered the opportunity to ask any questions and have those questions answered.
- The consent designee must verify the participant or LAR physically signed the consent document either by viewing via video conference, obtaining a photo of the complete signed consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically.
- The participant or LAR will sign and date/time the informed consent document.
- The signed document is then mailed, emailed or faxed to the consent designee.
- If the signed consent is emailed or faxed or returned via photo, the participant or LAR will be asked to return the original signed document on their first in person visit.
- If the informed consent form is mailed to the consent designee by the participant or LAR, the IRB-approved consent designee will sign the copy which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be attached to make a single document.
- In all other instances, once received, the IRB-approved consent designee signs, dates/times the informed consent document.

JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

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1. ABSTRACT

a. Provide no more than a one-page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Peripheral nerve injuries (PNIs) often result in permanent, debilitating motor and sensory deficits, particularly when complete nerve transection or large segmental defects are present. Following surgical repair of proximal PNIs, useful recovery of function is rare. Despite successful reconstruction of vascular, soft tissue and bony defects, a lack of adequate peripheral nerve re-innervation renders an injured extremity useless and is often an indication for amputation. *Unfortunately, there are no therapeutic agents currently available to treat PNIs.*

Injured peripheral nerve axons can regenerate, but they do so at a very slow rate relative to the long distances they must often travel to reach their targets. While waiting to be reinnervated, denervated muscle becomes progressively atrophied in a process that cannot be reversed. Because of this, after nerve regeneration is complete, patients often fail to regain full muscle function and sensation and remain permanently debilitated.

Our goal is to introduce tesamorelin as the first therapy clinically indicated for treatment of peripheral nerve injuries. Tesamorelin is a growth hormone releasing hormone analogue that stimulates release of endogenous growth hormone. Many animal studies have shown that growth hormone, via its downstream IGF-1 signaling, can speed peripheral nerve regeneration following injury and can also directly act on muscle to prevent atrophy, thereby improving functional outcomes. There is also reason to believe tesamorelin may accelerate bone, tendon and wound healing when those tissues are also injured. Importantly, because tesamorelin is already an FDA-approved drug with a benign safety profile, it is well suited for clinical investigations.

To introduce tesamorelin as a therapy for peripheral nerve injuries, a multi-disciplinary team of investigators will test the efficacy of the drug in a randomized, double-blinded, placebo-controlled, clinical trial. At the end of this 4-year study, if we find tesamorelin is effective in speeding nerve regeneration, preventing muscle atrophy, and ultimately improving functional outcomes after peripheral nerve injuries, there will be the potential for immediate off-label use. Larger studies will then be conducted, likely requiring an additional 4-6 years, to confirm efficacy and officially change the label of the tesamorelin to include treatment of peripheral nerve injuries.

2. OBJECTIVES

Specific Aim I: Test the efficacy of tesamorelin as a therapeutic agent in the setting of PNI. Efficacy is defined as enhancement in axonal regeneration (as measured by MRI and EMG/NCS), minimization of muscle atrophy (as measured by MRI), and improvement in functional outcomes (as measured by clinical functional testing, EMG/NCS, and questionnaires).
Specific Aim II: Assess for secondary benefits of tesamorelin therapy with regards to improved wound, tendon and bone healing as measured by MRI (bone and tendon) and visual assessment (wound healing).
Specific Aim III: Confirm safety of tesamorelin therapy established in previous clinical trials.
Specific Aim IV: Prospectively evaluate MRI DTI as a diagnostic and prognostic tool in the setting of peripheral nerve injury by comparing to other outcome assessment modalities (EMG/NCS, clinical functional exam, questionnaires).

3. BACKGROUND (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The following text was selected from the background portion of the study narrative, which has been included in the submission

Peripheral nerve injury (PNI) frequently occurs in the civilian population, with an estimated incidence of 67,800 major PNI per year in the U.S. (5) Causes of civilian PNI include trauma, iatrogenic causes and cancer to name a few. As with military PNI, outcomes in the civilian population also tend to be poor, with a reported 1-year return-to-work rate following median, ulnar and radial nerve injuries of only 59%. (6) Unfortunately, there are no therapeutic agents currently available to treat PNIs. To address this important problem, we are proposing a randomized, double-blinded, placebo-controlled clinical trial testing the efficacy of tesamorelin as a therapy to improve outcomes after PNIs.

Poor outcomes following PNIs result from a prolonged period of latency prior to reinnervation of distal targets (motor endplates and sensory receptors). Following surgical repair, axons often must travel long distances at a relatively slow rate to reach distal muscle and skin. Throughout this process, progressive and permanent muscle atrophy occurs. Given the importance of prompt reinnervation, much attention has been directed towards developing strategies to accelerate axonal regeneration. Most experimental therapeutic agents being investigated work by speeding axonal regeneration so as to decrease the amount of time needed for reinnervation to occur. In addition to accelerating axonal regeneration, tesamorelin has the potential to also maintain denervated muscle and Schwann cells (SCs) prior to reinnervation.

There is a wealth of basic and translational research demonstrating the positive effects of IGF-1 as a potent trophic factor for motor and sensory neurons. Because the effects of GHRH and GH are primarily mediated by circulating and locally produced IGF-1, methods to study the effects of the GHRH/GH/IGF-1 axis in vitro typically utilize IGF-1. A number of elegant mechanistic studies have demonstrated the important role of IGF-1 in neuronal regeneration and muscle reinnervation

(12-20); specifically, these studies have demonstrated promotion of neurite outgrowth, growth cone motility, and anti-apoptotic neuroprotection, as well as enhanced intramuscular nerve sprouting in vitro. Beyond exhibiting direct pro-regenerative effects on neuronal cells, IGF-1 has also been shown to have a multitude of positive effects on Schwann cells (SCs) in culture. SCs play a critical role in peripheral nerve regeneration by releasing neurotrophic factors and supporting and directing regenerating axons. Numerous studies have demonstrated the potent effects of IGF-1 in promoting Schwann cell survival, maturation and myelination in vitro. (21-25) IGF-1 is also well known to have beneficial effects on muscle growth and regeneration as well as on prevention of atrophy in denervated muscle tissue in vitro. (26-28) These studies, in addition to many others, have elucidated the mechanisms by which augmenting the GHRH/GH/IGF-1 axis enhances peripheral nerve regeneration and promotes improved functional outcomes following PNI.

Building on the mechanistic studies described above, a number of translational studies in small animal models have demonstrated the ability of IGF-1, delivered locally or systemically, to enhance both motor and sensory nerve regeneration and improve functional recovery following nerve injury (29-34). These studies utilized a number of different animal models of PNI, including nerve transection-and-repair, crush injury, and autografting of larger defects. They demonstrated greater number and density of regenerating axons, greater axonal regenerative velocity, maintenance of motor endplates and muscle weight, and improved functional outcomes in IGF-1 treated animal as compared to controls. In some cases, this effect was found to be dose-dependent. Studies have also demonstrated the ability of IGF-1 to prevent atrophy and increase tetanic strength in denervated muscle in vivo. (35)

Our group performed a study assessing the effects of IGF-1 on nerve regeneration in a rat hindlimb transplant model. Animals received either systemic IGF-1 treatment or saline placebo. At 5 weeks, the animals were sacrificed for histomorphometric analysis of axonal regeneration within the distal sciatic nerve. Our results indicated significantly greater number and density of regenerating axons in the treated group as compared to the control group.

A number of studies have also demonstrated the positive effects of systemic GH treatment on nerve regeneration and functional outcomes. All of these studies utilized small animal models for PNI. Saceda, et al., demonstrated greater nerve fiber density, myelination, and recovery of nerve conduction velocity and amplitude with GH treatment following ulnar nerve transection and repair in rats. (36) Studies by Kanje and Skottner found greater velocity of nerve regeneration with GH treatment following sciatic nerve crush injury in normal and hypophysectomized rats. (37, 38) Devesa, et al. demonstrated greater nerve fiber number, density, and myelination, as well as greater Schwann cell number, and improved compound muscle action potential (CMAP) latency and amplitude following sciatic nerve transection and repair in GH treated rats. (39) Our group has shown that GH therapy accelerates axonal regeneration, enhances muscle reinnervation, reduces muscle atrophy and maintains proliferating SCs in a rat sciatic nerve injury and repair model. (40)

Although exogenous GH and IGF-1 therapy have been shown to be effective therapies for PNI in many basic and preclinical studies, there are factors limiting clinical application. The systemic delivery of IGF-1 is limited by its high cost and its hypoglycemic effect. (41) Because of the lack of negative feedback control, exogenous GH therapy poses a risk for overdosing, resulting in

significant side effects (fluid retention, insulin resistance with worsening glucose control, joint pain). (42, 43)

Conversely, by mimicking the action of GHRH and stimulating release of endogenous GH from the pituitary, tesamorelin provides a safer and more physiologic approach to therapeutic growth hormone augmentation. With tesamorelin treatment, pituitary secretion of GH is still controlled by IGF-1 negative feedback, thereby reducing the risk of overdosing. Furthermore, tesamorelin therapy maintains the physiologic pulsatility of GH release from the pituitary. (44)

Clinical trials have demonstrated more consistent elevations in IGF-1 levels and fewer side effects with tesamorelin as compared to GH in patients being treated for HIV lipodystrophy. (45) These patients, like most patients with nerve injuries, have an intact pituitary gland that is able to respond to tesamorelin stimulus. Therefore, the improved safety profile and efficacy in HIV lipodystrophy patients would likely translate well to the patient population in the proposed study.

Importantly, tesamorelin is a human GHRH analogue that does not exhibit the same biologic activity in animals. The clinical trials for a number of indications described below were not preceded by animal studies assessing the efficacy of tesamorelin for those indications. Rather, the preclinical studies demonstrating efficacy with GH for those indications were deemed sufficient to justify clinical testing with tesamorelin.

Beyond the potential of tesamorelin to improve functional outcomes following PNI by enhancing axonal regeneration and minimizing denervation atrophy, there is also reason to believe that augmenting the growth hormone axis could potentially have secondary benefits with regards to improved bone, tendon, and wound healing.

Trauma resulting in peripheral nerve injury often involves concomitant injury to other tissue types, including bone, tendon, and skin. Bony mal-union and non-union, failure of tendon repair, and chronic non-healing wounds can all contribute to poor outcomes following extremity trauma. *The global anabolic effects mediated by the GH axis have led researchers to investigate the potential of GH therapy to accelerate and enhance recovery from injury to all of these tissues*. (46) A number of translational studies in small animals have demonstrated accelerated bony healing and improved mechanical strength with growth hormone treatment, some of which demonstrated dose-dependent response. (47-51) Following tibial bone fracture, rats treated with GH demonstrated 400% maximum stiffness and 270% ultimate stress and energy absorption at the fracture site as compared to controls (47). Enhancement of bony healing with GH therapy has been shown to be dose-dependent (48), and also dependent on the timing and duration of treatment, with early and continuous therapy showing greater benefit than therapy initiated late in the healing process (49). In a double-blinded, placebo controlled clinical trial, GH therapy was found to significantly accelerate bony healing of closed tibial fractures (52). There have also been a number of basic and translational studies demonstrating the positive effects of GH therapy on wound healing, with stimulation of fibroblasts and improved granulation and collagen deposition. (53-55) Clinical trials have demonstrated the efficacy of GH therapy in improving healing of burn wounds. (56)

It is important to emphasize that this study is designed to assess the efficacy of tesamorelin therapy in improving functional outcomes following PNI through enhanced axonal regeneration and

decreased muscle atrophy. The presence of fractures, tendon injuries and wounds are not inclusion criteria. As such, it is possible that there will not be enough power or homogeneity in the participant pool to draw definitive conclusions regarding the efficacy of tesamorelin in healing these concomitant injuries. That being said, modest conclusions regarding observed trends in healing may provide the basis for future studies designed specifically to investigate these potential secondary benefits.

Summary: Rationale for Tesamorelin as Therapy for PNI

The following conclusions summarized from the extensive research described above lead us to believe that tesamorelin is ideally suited for clinical investigation as a therapeutic agent in the setting of PNI:

- There is a wealth of evidence from basic and translational research demonstrating the positive effects of GH and IGF-1 therapy on axonal regeneration, muscle atrophy, and functional outcomes following PNI.

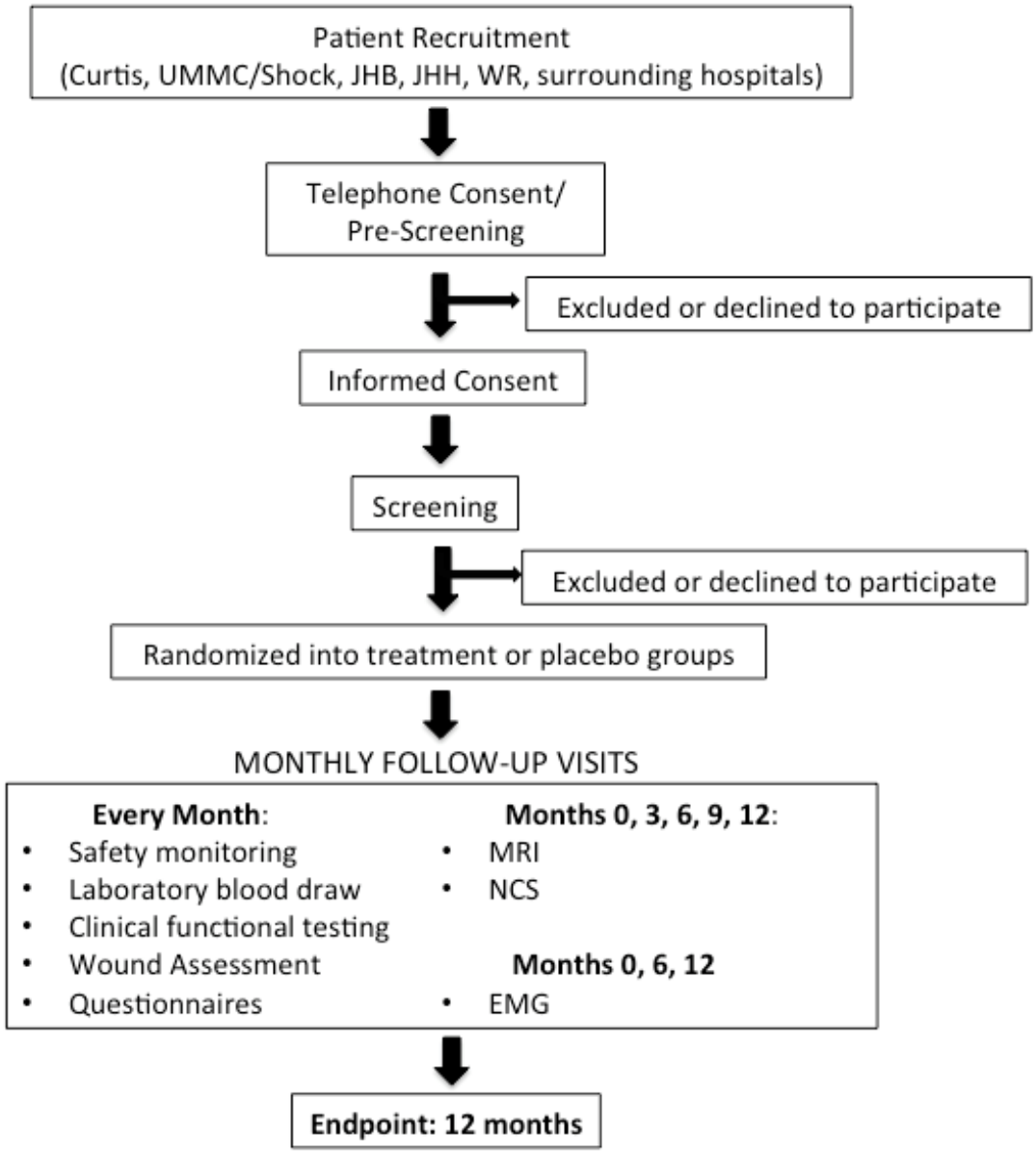
- Tesamorelin is an FDA-approved drug that provides a safe and physiologic approach to augmenting the growth hormone axis by producing stable elevation in GH and IGF-1 levels.

- Preclinical studies demonstrating efficacy with GH have been deemed to be sufficient to justify clinical testing of tesamorelin for HIV lipodystrophy, visceral adiposity and cognitive disorders

- Tesamorelin may provide secondary benefits with regards to bone, tendon, and wound healing.

4. STUDY PROCEDURES

a) Study Design



Subject recruitment:
The study population will include military and civilian men and women of all ethnicities and races who have sustained ulnar nerve injuries repaired primarily. The pool of potential patients will include those treated by the surgeons involved with the study, as well as those referred by other surgeons and emergency medicine physicians. To further expand the participant pool, the key personnel will raise awareness about the study among other surgeons and emergency medicine physicians at their own institutions and at other hospitals in the community. This will be done through public presentations (i.e.- grand rounds presentations), IRB-approved flyers, and personal communications. We will also utilize MyChart recruitment services to expand our participant pool. We will send out MyChart research invitation letters to potential participants with an active MyChart account. This invitation letter was developed in accordance with newer language as requested by the MyChart Recruitment Committee.

Patients will be provided information about the study, if appropriate, during clinic visits and in the emergency room. When a patient is identified as a potential candidate for enrollment (presence of lower ulnar nerve injury repaired primarily), they will be given basic information about the study from their provider derived from an IRB-approved recruitment flyer. Contact information for the study coordinator will be included such that an interested potential candidate can schedule a telephone interview.

Telephone Consent/Screening:
Before initiating the telephone interview, potential subjects will be informed that the conversation may be used as part of the preliminary screening and verbal permission will be obtained to request some personal details that may qualify as protected health information (PHI). With the potential participants' permission, their information will be securely stored. The telephone screening script is attached.

Combined Informed Consent Process:
Potential participants who clear the telephone screening will be provided the combined (for screening and study participation) Informed Consent Form (ICF) (attached) at the time of screening tests. He/she will have ample time to review the ICF and prepare questions regarding the study while awaiting the results of screening procedures. At all follow-up screening appointments, subjects will have the opportunity and be invited to discuss the ICF with qualified study staff to clarify any questions the participant may have regarding the study, long-term treatment, and follow-up assessments. Participants are strongly encouraged to have a family member (or members) or patient advocate present at the meeting when the main ICF is signed.

The informed consent process will be administered to participants in a private area by a trained, IRB-approved study team member prior to enrollment in the study. (Private areas include clinic rooms, inpatient rooms, and other spaces approved for clinical use at JHH.) Participants will be advised of the potential risks and benefits of the study. Participants will be able to discuss the ICF with qualified study staff, be invited to ask any questions they might have, and will have the opportunity to discuss the ICF with their family and/or friends prior to signing. The informed consent process will take as long as necessary to ensure that the patient has had all of his/her questions answered and until the study team member is satisfied that the participant understands what study participation involves.

The ICF contains a written statement informing the participant of his/her rights regarding PHI, what PHI will be recorded, and what groups may have access to it. Potential participants will be informed that they have the right to withdraw consent at any time and will be provided with necessary information on how to do so. Participants who complete and sign the ICF will be provided with a copy signed by the appropriate study personnel for their records.

Participants are expected to attend appointments sober and not under the influence of alcohol or recreational or prescription drugs. Study staff administering consent will watch participants for any unusual behaviors that may indicate an altered mental state and respond in compliance with institutional policies to handle the situation in an appropriate manner. Study candidates will not be consented for study participation if suspected of being in an altered mental state. Similarly, candidates suspected of being under undue emotional stress will not be consented to participate in the study.

Screening/Consent:

Telephone Consent/Screening
Before initiating the telephone interview, potential subjects will be informed that the conversation may be used as part of the preliminary screening and verbal permission will be obtained to request some personal details that may qualify as protected health information (PHI). With the potential participants' permission, their information will be securely stored.

Combined Informed Consent Process
Potential participants who clear the telephone screening will be provided the combined (for screening and study participation) Informed Consent Form (ICF) (Attachment 6, Appendix 3) at the time of screening tests. He/she will have ample time to review the ICF and prepare questions regarding the study while awaiting the results of screening procedures. At all follow-up screening appointments, subjects will have the opportunity and be invited to discuss the ICF with qualified study staff to clarify any questions the participant may have regarding the study, long-term treatment, and follow-up assessments. Participants are strongly encouraged to have a family member (or members) or patient advocate present at the meeting when the main ICF is signed. Liz Martinez, RN, BSN, CCRC is a research participant advocate with the Institute for Clinical and Translational Research at Johns Hopkins University, and has offered to assist with any patient advocacy needs for the study.

The informed consent process will be administered to participants in a private area by a trained, IRB-approved study team member prior to enrollment in the study. (Private areas include clinic rooms, inpatient rooms, and other spaces approved for clinical use at JHH.) Participants will be advised of the potential risks and benefits of the study. Participants will be able to discuss the ICF with qualified study staff, be invited to ask any questions they might have, and will have the opportunity to discuss the ICF with their family and/or friends prior to signing. The informed consent process will take as long as necessary to ensure that the patient has had all of his/her questions answered and until the study team member is satisfied that the participant understands what study participation involves.

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Participants are expected to attend appointments sober and not under the influence of alcohol or recreational or prescription drugs. Study staff administering consent will watch participants for any unusual behaviors that may indicate an altered mental state and respond in compliance with institutional policies to handle the situation in an appropriate manner. Study candidates will not be consented for study participation if suspected of being in an altered mental state. Similarly, candidates suspected of being under undue emotional stress will not be consented to participate in the study.

Screening Procedures:
A member of the study team will review the combined ICF with the participant and invite the participant to ask any questions he/she might have. Candidates will then be asked to complete the ICF before being enrolled in the study and undergoing further evaluation/medical screening procedures. The ICF includes a written authorization allowing the study team to obtain the candidate's relevant PHI. Once the ICF is completed, potential participants will undergo standardized screening procedures that include a number of examinations and investigations to determine eligibility for this study. The screening evaluation tests, procedures, and evaluations include the following, all of which are either standard medical procedures or are clinically approved for human use:

HISTORY AND PHYSICAL EXAM– A routine medical history and physical exam that specifically addresses potential exclusion criteria will be performed. A detailed history regarding the ulnar nerve injury will be obtained, including timing, mechanism of injury, surgery and motor and sensory deficits related to ulnar nerve injury. Specific areas addressed will include the following:

1. History of neoplasm in any organ or active neoplasm
2. Family history of cancer
3. Symptoms of prostatic enlargement in male participants, including prostate cancer screening history
4. History of diabetes or poor glucose control
5. History of hypothyroidism
6. History of head injury or hypopituitarism
7. History of estrogen use, include oral contraceptives
8. Family structure (i.e., marital history, offspring)
9. Employment history
10. Tobacco, alcohol or illicit drug use
11. Social history (with emphasis on factors that may influence ability to successfully participate in study)

2. LABORATORY TESTS AND EXAMS - All of the following tests are required unless otherwise noted:
    1. Blood Tests
        a. Complete blood count (CBC or Heme 8) w/Differential
        b. Complete Metabolic Panel (CMP)
        c. Clotting Profile (PT/PTT with INR)
        d. Liver Function Tests [including total bilirubin, AST, ALT, and Alkaline Phosphatase]
        e. Lipid Profile
        f. HA1-C
        g. Pregnancy screen (Urine Hcg)
        h. Alpha Fetoprotein (AFP)
        i. TSH
        j. PSA (men over 40 years)
        k. IGF-1
    2. Mammography- for female patients >40 years who are not up to date on screening

3. VIDEO AND PHOTOGRAPHY RECORDINGS IN CLINICAL CONTEXT

During every appointment, patients' clinical functional assessment will be recorded if the subject provides additional consent for this. This will allow for retrospective quality checks of the data being collected. Only the region of the forearm, wrist and hand will be recorded during the assessment. Additionally, images of only the wound area will be taken at each appointment, in order to assess wound healing. The video and photographs will be retained for five years after taking the recordings. Images and videos will be stored electronically in an encrypted computer solely dedicated to this study. The camera will be stored in a secure filling cabinet. Only researchers involved in this clinical trial will have access to these recordings.

Randomization Procedure:

RedCAP manager (Andre Hackam) will generate a randomization schedule prior to the start of study, with stratification of subjects who do not have concomitant nerve, tendon or bone injury (other than flexor carpi ulnaris and ulnar artery lacerations, which are expected to occur with ulnar nerve lacerations). Only the RedCAP manager and the data safety management board will have access to the stratification schedule key. A number will be assigned to each subject that corresponds to one of the numbered study kits that contain either placebo or study drug but are otherwise identical. The study kits will be sent by Theratechnologies directly to the JH Investigational Drug Service Pharmacy from where they will be distributed to study participants under the supervision of Janet Mighty.

b) Study duration and number of study visits required of research participants:

The study duration is 13 months. Each participant will have 14 study visits, including initial consent and screening and 13 subsequent monthly assessment visits.

c) Blinding, including justification for blinding:

Blinding is necessary in this study to account for the possibility of observer bias or conscious deception by the study team as well as the possibility that participants' knowledge of their assigned group (placebo vs. study drug) may influence their recovery process and reported outcomes. To achieve blinding of the study team and research participants, the RedCAP manager (Andre Hackam) will generate a randomization schedule prior to start of study. Only the RedCAP manager and the data safety management board will have access to the stratification schedule key. A number will be assigned to each subject that corresponds to one of the numbered study kits that contain either placebo or study drug but are otherwise identical. The study kits will be sent by Theratechnologies directly to the JH Investigational Drug Service Pharmacy, which will have the randomization schedule, but not the randomization schedule key. The study kits will be distributed to directly to each study participant according to the number he or she was assigned by the randomization schedule.

d) Justification of why participants will not receive routine care or will have current therapy stopped:

All participants will receive routine care and will not have any current therapy stopped.

e) Justification for inclusion of a placebo or non-treatment group:

Without the inclusion of a placebo group, it would not be possible to determine the therapeutic effect of the study drug. Historical outcomes data for ulnar nerve injuries is sparse and of poor quality. There is also the possibility of a placebo effect that must be controlled for.

f) Definition of treatment failure or participant removal criteria

1. Hemoglobin value < 100 g/L and a decrease of at least 20 g/L from screening;
2. Subjects with AST and/or ALT > 5x ULN will be immediately discontinued from the study. For any subject who has an AST and/or ALT > 3 x ULN but ≤ 5 x ULN, the tests will be repeated at the following visit. If the repeat value is still > 3 x ULN, the subject will be discontinued;
3. Creatinine value > 2 x ULN;
4. Glycemia:
    - FBG > 10 mmol/L (180 mg/dL) after exposure to study drug, the subject will return in 7 working days for a repeat test:
    1. FBG > 10 mmol/L (180 mg/dL), the subject will be discontinued.
        2. FBG ≤ 10 mmol/L (180 mg/dL), the subject will remain in the study unless symptomatic, and return in 7 working days for a repeat test
            - FBG is > 10 mmol/L (180 mg/dL), the subject will be discontinued;

- FBG ≤ 10 mmol/L (180 mg/dL), the subject will remain in the study.

- Subjects displaying at any time symptoms related to hyperglycemia (i.e., polyuria, polydipsia, etc) will be immediately discontinued from the study and receive appropriate therapy;

5. Should there be a clinically significant elevation in CPK during the study, the Investigator will perform a strict evaluation of the clinical signs and medication of the subject. Any subject with suspicion of rhabdomyolysis will be withdrawn from the study. The primary diagnostic indicator of rhabdomyolysis is an elevated CPK of at least 5 x the ULN;
6. Any worsening of adverse reactions at the site of injection such as hives, extended redness and rash occurring anywhere in the body should be promptly reported to the sponsor and recorded in the injection site reaction log.

   Any systemic symptoms occurring within minutes of the injection that are observed along with reactions at the site of injection should be also promptly reported. These systemic symptoms include, but are not limited to, nausea, shortness of breath, abundant sweating and tachycardia.

Discontinued subjects will return for regular follow-up visits every 6 to 7 weeks for a period of at least 3 months and, if needed, up to 6 months.

g) Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Following completion of participation (either at study endpoint or prematurely), participants will be notified of the option to continue to receive follow up care from the primary investigator related to their injury or study treatment. They will be encouraged to do so for any concerns that arise related to injury recovery or sequelae from treatment. Any sequelae potentially related to study treatment that are observed following completion of study participation will be reported to the medical monitor. Study participants will be given the option of consenting to allow the study team to contact them to request follow up evaluations following completion of study participation.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

1. *Lower ulnar nerve injury repaired primarily*

- To limit variability in outcome measures, we have defined a very specific injury type and location. Each nerve in the upper extremity innervates a distinct set of muscles and skin distribution. Injuries to different nerves, or the same nerve at different levels, are associated with very different functional deficits, rendering meaningful comparison of recovery difficult if not impossible. The method of nerve repair (primary vs. graft vs. biosynthetic conduit) also significantly impacts regeneration and recovery.

- The ulnar nerve was chosen because of its important role in innervating the intrinsic muscles of the hand. In comparison to lower median and radial nerve injuries, ulnar nerve injuries are associated with worse functional outcomes, and therefore exhibit greater potential for improvement in response to a therapy.

- Lower (distal to motor branch innervating the flexor digitorum profudus) injury was chosen because the time until recovery is less (as compared to upper injuries) allowing timely completion of the study. Furthermore, for the purpose of MRI and electrophysiologic testing, lower injuries provide more useful landmarks to facilitate consistent measurement.

- Primary repair, with direct suture coaptation, was chosen to limit variability in surgical approach. Where-as nerve grafting and conduit use vary with regards to length, type of graft/conduit, and methodology, primary repair is consistently performed in a similar manner.

2. *Time since injury ≤ 6 weeks*

- Caveat: Patients enrolled > 4 weeks and ≤ 6 weeks after surgical repair will be included, but will not have month 0 outcome measures included in the study. Instead, the first outcome measures for these participants will be at month 1.

- Explanation: A 6 week-enrollment window will allow ample time for recruitment, screening and informed consent without introducing significant variability in outcomes. However, the process of nerve regeneration and recovery from nerve injury begins at the time of surgical repair, and this must be taken into account when characterizing the timing of collected outcome measures.

3. *Adult (>18 years of age)*

- Therapies that manipulate the growth hormone axis should be used with caution in children with open long bone epiphyseal plates as it can result in excessive growth.

- Age has been consistently shown to affect outcomes following PNI, with younger patients demonstrating greater regenerative capacity. Therefore, limiting inclusion criteria to adults will also serve to limit variability.

Exclusion Criteria:

1. *History of malignancy of any organ (with the exception of basal cell carcinoma of the skin, in situ carcinoma of the cervix, and other malignancies that were successfully treated and deemed by treated physician to have minimal risk of recurrence) or any active neoplasm*
   - Augmenting the growth hormone axis carries a theoretical risk of accelerating cancer growth.

2. *For male patients > 40 years of age, suspicion of cancer by prostate examination and PSA >5 ng/mL at screening*
   - Augmenting the growth hormone axis carries a theoretical risk of accelerating cancer growth.

3. *History of breast cancer or proven family history of breast cancer in 2 or more first degree relatives for female patient*
   - Augmenting the growth hormone axis carries a theoretical risk of accelerating cancer growth.

4. *Hypopituitarism, or history of pituitary tumor/surgery, head irradiation or head trauma that has affected the growth hormone axis*
   - These conditions can affect response to tesamorelin treatment

5. *Untreated hypothyroidism*
   - Hypothyroidism can adversely affect nerve regeneration

6. *Co-morbid conditions that will not allow the patient to complete the study as per the Investigator's judgment*
   - It is difficult to anticipate and delineate all potential co-morbidities and psychosocial circumstances that would adversely affect compliance with the study. As such, there may be situations in which a patient is excluded for reasons other than those explicitly listed if there is sufficient concern for poor compliance or ability to complete the study.

7. *Type 1 diabetics and type 2 diabetics previously treated with insulin (except during pregnancy when not required following delivery)*
   - Manipulating the growth hormone axis has been shown to affect glucose metabolism. Diabetic patients will be excluded to minimize risk to the patient.
   - Hyperglycemia is known to adversely affect peripheral nerve regeneration. Exclusion of diabetic patients will also serve to limit variability.

8. *Evidence of the following at screening:*

- *Hepatic dysfunction: ALT or AST >3 x upper limit of normal (ULN)*
- *Renal dysfunction: serum creatinine >133 µmol/L (1.5 mg/dL)- adjusted for sex/weight*
- *Anemia: hemoglobin (hgb) < 7 g/dL*
- *Fasting blood glucose > 8 mmol/L (144 mg/dL)*
- *Lipid metabolism severe dysfunction: fasting triglycerides > 500 g/dL*

- Abnormalities in the above listed laboratory values indicate potential underlying comorbidities that may affect a patient's baseline regenerative capacities and, as such, would introduce excessive variability.

9. *Treatment with oral estrogen, including oral contraceptives*
   - Oral estrogen treatment can cause significant liver resistance to GH stimuli, reducing the efficacy of tesamorelin.
   - Female participants who are pre-menopausal will be given the option of switching to barrier contraceptive with pregnancy screening at each monthly visit.

10. *Untreated hypertension as defined by the American Heart Association Guidelines*
    - Therapies that augment the growth hormone axis can exacerbate hypertension by causing excess fluid retention.

11. *Drug or alcohol dependence within the last 6 months*
    - These comorbidities may adversely affect patient compliance.

**No study exclusions will be made on the basis of gender, race, or ethnicity*

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose:

Tesamorelin is a long-acting growth hormone-releasing hormone analogue that stimulates endogenous release of growth hormone from the pituitary. Research from our group and others suggests augmenting the growth hormone axis has the potential to improve outcomes following peripheral nerve injury (See Background). We have chosen to use a dose of 2mg per day because this suggested dose used for treatment of HIV lipodystrophy, the only FDA-approved indication for tesamorelin. Furthermore, in Phase II clinical trials, a 2mg dose was found to be more efficacious and equally safe as compared to a 1mg dose.

Theratechnologies has developed two FDA-approved formulations a 1mg/vial and a 2mg/vial bioequivalent formulation of tesamorelin. This bioequivalent formulation of tesamorelin will be more user-friendly for participants as it comes in a single vial instead of two and is stable at room temperature.

The participants will be instructed to reconstitute two 1mg/vial with 2.2ml of sterile water or 1.4mg/vial with 0.5 mL of sterile water. 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.

Theratechnologies plan to stop production of their 1mg/vial formulation and as a result we will only have access to their new FDA approved 2mg/vial bioequivalent formulation. By including the bioequivalent formulation into our protocol, will allow us to interchange between the two formulations as required and use the drug as approved by the FDA.

Based on comparative reviews of the approved prescribing information for the new 2mg/vial (Revised 11/2018) and 1 mg/vial formulations (Revised 7/2018) (See the "label" posted under EGRIFTA NDA 022505/ Supplement 11 on the "Drugs@FDA Website", Action date 1/18/19), it was determined that for both:

1. The approved indication remains "the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy."
2. The active ingredient remains tesamorelin as the acetate salt
3. The route of administration is still by a once daily subcutaneous injection.

More importantly "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 Polysorbate 20

There is no reason to suspect that any of the new inactive ingredients may be contraindicated in our study population. As the changes made to create the 2 mg/vial formulation 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.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Tesamorelin in FDA approved for treatment of HIV lipodystrophy and will be administered for the non-FDA approved indication of peripheral nerve injury. The dosing and route of administration will be the same as is used for treatment of HIV lipodystrophy.

Treatment has been shown to be safe in multiple phase II and phase II clinical trials, with minimal side effects and no serious adverse events. Compiled safety data from Theratechnologies that has been filed with the FDA is attached.

A study nurse or study physician or study affiliated nurse practitioner or physician assistant will teach the study participant and their caregiver how to administer tesamorelin or placebo subcutaneously.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

NA

d. Dose modification

EGRIFTA® stimulates GH production and increases serum IGF-1. Given that IGF-1 is a growth factor and the effect of prolonged elevations in IGF-1 levels on the development or progression of malignancies is unknown, IGF-1 levels will be monitored closely during this trial. Occurrence of persistent elevations of IGF-1 levels (e.g., >3 SDS) will be assessed on an individual basis and withdrawal from the study medication should be considered based on a careful risk-benefit evaluation particularly if the efficacy response is not robust (e.g., based on visceral adipose tissue changes measured by waist circumference).

e. Drug Dispensing

In response to the COVID-19 pandemic, the study drug will be shipped to study participants living in Maryland. A prescription will be submitted in EPIC for a refill and request this be shipped in the EPIC order. After study participant agrees to receive the study drug shipment and confirming

their address, we will then agree to send the study drug, using FedEx for overnight delivery with signature required and this will be endorsed in writing by the Study PI.

7. Utilization of alternate visit options

To ensure patient safety and to eliminate immediate apparent hazards including those based on the risk of exposure to COVID-19 we will implement telephone or zoom visits for participants in lieu of on-site visits during the COVID-19 pandemic.

STUDY STATISTICS

a. Primary outcome variable:

Definition: The primary outcome is motor amplitude (uV) as measured by nerve conduction studies. The target standardized effect size of treatment as compared to placebo in this 12 month study is 0.4, which falls in the range of a 'medium' effect size. Setting the statistical significance at 0.05, within-participation correlation among measures across the time points (0, 3, 6, 9, and 12 months) at 0.5, and power at 80%, a total sample of 30 participants (15 per group) would allow a between-group effect size of 0.4 to be detected. Assuming 15% dropout rate, total recruitment goal is 36 participants.

Rationale: Motor amplitude was chosen as the primary outcome because it is an objective measure of nerve regeneration that is reproducible and unaffected by concomitant injuries. While clinical functional outcome measures (ie- grip strength, MBMRC motor grade, etc.) are more clinically meaningful, they will be affected by concomitant injuries (tendon lacerations, fractures, median nerve injury, etc) and therefore excluded in some subjects. Setting a clinically meaningful absolute difference in mean amplitude between the treatment and control groups for this study is not possible, given the lack of prior placebo-controlled treatment studies that prospectively assess differences in amplitude for patients with ulnar nerve lacerations at the wrist. Of note, a secondary aim of this study is to provide information that can be used to guide the design of similar studies in the future. It should also be noted that this study is meant to be a Phase 2 clinical trial, and larger Phase 3 studies will likely be needed to confirm promising findings.

Testing Methodology: An active surface electrode will be placed on the ulnar aspect of the hand at the longitudinal midpoint of the abductor digiti minimi muscle. A reference electrode will be placed 4cm distal to the active electrode and a ground electrode 4 cm proximal. The ulnar nerve will be stimulated 8cm proximal to the active electrode and distal to the ulnar nerve repair. Latency and amplitude of the evoked response will be recorded. Only amplitude will be used a primary outcome measure.

b. Secondary outcome variables:

- Motor and sensory latency (ms)

- Sensory amplitude (uV)
- Electromyography (Daube score 0-4+)
- Magnetic resonance imaging (functional anisotropy; apparent diffusion coefficient; muscle/tendon/bone healing scores)
- Clinical functional assessments (MBMRC motor/sensory grade, grip strength, Tinel sign, presence of clawing, Froment's sign, ability to cross fingers)
- Questionnaires (DASH, MHQ, SF-36)
- Wound healing assessment (diameter, depth, presence of granulation/epitheliazation)
- Laboratory values (Serum IGF-1, ALT, AST, HbgA1c, fasting glucose, hemoglobin, total cholesterol, lipid profile (triglycerides, HDL-cholesterol, LDL-cholesterol), thyroid-stimulating hormone (TSH), free T4, Pregnancy screen (urine dipstick), PSA (men over 40), Coagulation measures (PT/PTT), Complete blood count (CBC) and complete metabolic panel (CMP).

c. Statistical plan including sample size justification and interim data analysis:

Primary Efficacy Analysis:
After unblinding of the trial, complete efficacy and safety analyses will be prepared to evaluate the study hypotheses. By patient and by treatment group, plots of outcome measures over time will be prepared and reviewed as part of the data quality assurance process before data analysis. Basic exploratory analyses will be performed on each outcome at each time point and across time points to identify potential outliers, trends and missingness patterns. A comparison of treatment groups will be performed on demographic characteristics and baseline outcomes using appropriate summary statistics for categorical, ordinal and continuous variables, to review the groups' similarity before the intervention is initiated.

The data will be analyzed primarily with an intention-to-treat (ITT) approach. To evaluate the difference between treatment groups over time, the outcome measurements will be compared using a multi-level model (MLM) approach (81) with two groups and measurements at multiple time points, where the within-participant correlation is taken into account. Participant characteristics and baseline outcome measurements may be included as adjustors in the models. The MLM approach can estimate the parameters for the marginal distribution of an outcome with unbalanced measurements across participants, so that low levels of missing data can be tolerated. The main test in these models is of the interaction between the groups and measurements post-intervention over time. Depending on the level of missingness across the time points, this approach can be extended to a pattern mixture model (82) to evaluate any difference between those with complete measurements and those with at least one missing measurement with respect to its impact on the outcome measurement. The Holm-Bonferroni correction (83) will be used to adjust the significance level for multiple comparisons across the outcomes.

Secondary Efficacy Analysis:
The secondary efficacy variables will be analyzed in a similar fashion to the methodology described above for primary efficacy analysis.

Statistical Assessment of Safety:

The safety variables (laboratory values, presence or absence of adverse drug events) will be analyzed using a similar methodology as described above for primary efficacy analysis.

Correlation of MRI DTI to other efficacy measures:
To prospectively assess the clinical utility of MRI DTI in defining the progress of peripheral nerve regeneration and predicting functional outcomes, data from MRI DTI will be evaluated against data from NCS, EMG and clinical functional assessments also using a MLM approach, but within each group initially. Each of the other assessment measures will be used as the outcome, and MRI DTI will be considered an individual predictor of each of the other assessment measures across time or with some time lags.

Power Analysis:
With the assistance of the Johns Hopkins Biostatics Center, power analysis was performed based on nerve conduction studies as the primary efficacy measure. The statistical model for power analysis was the F-test ANOVA with 4 repeated measures (based on the 3, 6, 9 and 12 month post-intervention measurement periods). Assuming a significance level of 0.05, a within-participation correlation among measures across the time points of 0.5, and power of 80%, a total sample of 30 participants (15 per group) would allow a between-group effect size of 0.4 to be detected. Assuming 15% dropout rate, total recruitment goal will be **36 participants**.

Unblinding of data for the purpose of interim analysis of results will not occur.

d. Early stopping rules:

Early stopping will not occur unless there is a serious risk associated with the study drug that becomes apparent that was previously unknown. This is highly unlikely given the benign risk profile noted in other studies that have tested tesamorelin.

8. RISKS

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Drug-Related Risks:

Tesamorelin has been tested in a number of clinical trials. In general, it was well tolerated by patients.

The following are the most common side effects that were noted:

- Injection site irritation, redness, itching, and/or pain
- Hypersensitivity reaction (rash, hives)
- Muscle pain
- Fluid retention, swelling in hands and feet
- Carpal tunnel syndrome (numbness and tingling in fingers)

- Glucose intolerance

Although not considered side effects, you may experience the following due to subcutaneous injection of tesamorelin of placebo:

- Inconvenience of daily subcutaneous injections
- Mild discomfort from daily subcutaneous injection

Other Risks:

- Neoplasm
  - Tesamorelin treatment results in increased production of growth hormone and IGF-1 (a growth factor), which have been implicated in the development and progression of neoplasms and malignancy. Patients with active malignancy should not be treated with tesamorelin and will not be enrolled in the study. Treatment with tesamorelin has not been shown to result in increased frequency malignancy. However, development and progression of malignancy should be considered risks of treatment with tesamorelin.
- Acute Critical Illness
  - Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of growth hormone. Tesamorelin has not been studied in patients with acute critical illness. Patients with acute critical illness will not be enrolled in this study.

Screening (including history, physical exam):

Infrequent-

- Breach of privacy/confidentiality
- Boredom
- Discovery of previously unknown conditions

Magnetic Resonance Imaging:

Infrequent-

- Claustrophobia
- Boredom
- Mild discomfort from trying to remain still

Neurodiagnostics (Nerve Conduction Studies/Electromyography):

Common-

- Transient tingling
- Transient mild discomfort from electrical stimulation
- Transient mild to moderate discomfort from EMG needle

Infrequent-

- Mild muscle soreness following EMG

Venipuncture (laboratory assessments):

Common-

- Mild discomfort from venipuncture

Infrequent-

- Bleeding
- Bruising
- Clotting

Rare-

- Fainting
- Local infection

Study Questionnaires:

Common-

- Boredom

Rare-

- Discomfort with questions

Video and Photography Recordings

Infrequent-

- Breach of privacy/confidentiality

b. Steps taken to minimize the risks.

Patients will be carefully monitored for adverse events. This monitoring includes monthly clinical laboratory tests and assessment of adverse events volunteered by the patient or discovered by investigator questioning or detected through physical examination or other means. Adverse events will be assessed in terms of their seriousness, severity, duration and relationship to the study drug,

Todd Brown, MD (Associate Professor, Medicine Department, Johns Hopkins) will serve as independent medical monitor. At a minimum, the research monitor: may discuss the research protocol with the investigators, interview human subjects, consult with others outside of the study about the research; shall have the authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

A data safety monitoring board (DSMB) will convene in person or via teleconference every 6 months to review the progress and safety of the study, with the assistance of the biostatistician. The DSMB will consist of Dr. Ramon DeJesus, MD, a hand surgeon in private practice with subspecialty training in peripheral nerve, and Dr. Clare Lee, MD, assistant professor of medicine in the endocrinology division at JHU.

a. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems and study deviations will be reported to the study monitor and IRB.

b. Legal risks such as the risks that would be associated with breach of confidentiality.

If breach of confidentiality occurs, the study participant, IRB, and legal office at Johns Hopkins will be notified.

c. Financial risks to the participants.

9. BENEFITS

a. Description of the probable benefits for the participant and for society.

10. PAYMENT AND REMUNERATION

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Patients will be reimbursed for participation in the study at an estimated $7,062 per patient over the course of the study. The following remuneration schedule was developed in conjunction with Liz Martinez at the ICTR :

Outpatient visit: $50 (x14) = $700
Blood sample-single venipuncture: $10 (x14) = $140
Neurodiagnostic study: $40 (x5) = $200
Electromyography: $130 (x3) = $390
Magnetic Resonance Imaging: $35 (x5) = $175
Questionnaire ($15) (x42) = $630
Subcutaneous injection: $10 (x365) = $3650
Sum: $5,885
Completion bonus 20%: $1177
Total per participant: $7062

The sum total amount to the study participant will be paid to them following his or her final study appointment.

In addition travel allowance will be provide to study participants

Travel and Food allowance:

- Patient will be reimbursed up to $50 for each visit to cover the cost of travel and food expenses incurred (e.g., bus fare, taxi from home to study site, food etc.). We will not provide a daily stipend for the incidentals mentioned above, but rather will reimburse for these types of expenses as receipts are presented.

- For patients travelling by car, round trip mileage will be calculated using Google Map

indicating home address of subject and address of the study site. Mileage will be reimbursed as receipts are presented at the current Internal Revenue Service business reimbursement rate of $0.545 per mile for private automobiles.

11. COSTS

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to participants for participation in this study.

JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

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1. ABSTRACT

a. Provide no more than a one-page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Peripheral nerve injuries (PNIs) often result in permanent, debilitating motor and sensory deficits, particularly when complete nerve transection or large segmental defects are present. Following surgical repair of proximal PNIs, useful recovery of function is rare. Despite successful reconstruction of vascular, soft tissue and bony defects, a lack of adequate peripheral nerve re-innervation renders an injured extremity useless and is often an indication for amputation. *Unfortunately, there are no therapeutic agents currently available to treat PNIs.*

Injured peripheral nerve axons can regenerate, but they do so at a very slow rate relative to the long distances they must often travel to reach their targets. While waiting to be reinnervated, denervated muscle becomes progressively atrophied in a process that cannot be reversed. Because of this, after nerve regeneration is complete, patients often fail to regain full muscle function and sensation and remain permanently debilitated.

Our goal is to introduce tesamorelin as the first therapy clinically indicated for treatment of peripheral nerve injuries. Tesamorelin is a growth hormone releasing hormone analogue that stimulates release of endogenous growth hormone. Many animal studies have shown that growth hormone, via its downstream IGF-1 signaling, can speed peripheral nerve regeneration following injury and can also directly act on muscle to prevent atrophy, thereby improving functional outcomes. There is also reason to believe tesamorelin may accelerate bone, tendon and wound healing when those tissues are also injured. Importantly, because tesamorelin is already an FDA-approved drug with a benign safety profile, it is well suited for clinical investigations.

To introduce tesamorelin as a therapy for peripheral nerve injuries, a multi-disciplinary team of investigators will test the efficacy of the drug in a randomized, double-blinded, placebo-controlled, clinical trial. At the end of this 4-year study, if we find tesamorelin is effective in speeding nerve regeneration, preventing muscle atrophy, and ultimately improving functional outcomes after peripheral nerve injuries, there will be the potential for immediate off-label use. Larger studies will then be conducted, likely requiring an additional 4-6 years, to confirm efficacy and officially change the label of the tesamorelin to include treatment of peripheral nerve injuries.

2. OBJECTIVES

Specific Aim I: Test the efficacy of tesamorelin as a therapeutic agent in the setting of PNI. Efficacy is defined as enhancement in axonal regeneration (as measured by MRI and EMG/NCS), minimization of muscle atrophy (as measured by MRI), and improvement in functional outcomes (as measured by clinical functional testing, EMG/NCS, and questionnaires).
Specific Aim II: Assess for secondary benefits of tesamorelin therapy with regards to improved wound, tendon and bone healing as measured by MRI (bone and tendon) and visual assessment (wound healing).
Specific Aim III: Confirm safety of tesamorelin therapy established in previous clinical trials.
Specific Aim IV: Prospectively evaluate MRI DTI as a diagnostic and prognostic tool in the setting of peripheral nerve injury by comparing to other outcome assessment modalities (EMG/NCS, clinical functional exam, questionnaires).

3. BACKGROUND (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The following text was selected from the background portion of the study narrative, which has been included in the submission

Peripheral nerve injury (PNI) frequently occurs in the civilian population, with an estimated incidence of 67,800 major PNI per year in the U.S. (5) Causes of civilian PNI include trauma, iatrogenic causes and cancer to name a few. As with military PNI, outcomes in the civilian population also tend to be poor, with a reported 1-year return-to-work rate following median, ulnar and radial nerve injuries of only 59%. (6) Unfortunately, there are no therapeutic agents currently available to treat PNIs. To address this important problem, we are proposing a randomized, double-blinded, placebo-controlled clinical trial testing the efficacy of tesamorelin as a therapy to improve outcomes after PNIs.

Poor outcomes following PNIs result from a prolonged period of latency prior to reinnervation of distal targets (motor endplates and sensory receptors). Following surgical repair, axons often must travel long distances at a relatively slow rate to reach distal muscle and skin. Throughout this process, progressive and permanent muscle atrophy occurs. Given the importance of prompt reinnervation, much attention has been directed towards developing strategies to accelerate axonal regeneration. Most experimental therapeutic agents being investigated work by speeding axonal regeneration so as to decrease the amount of time needed for reinnervation to occur. In addition to accelerating axonal regeneration, tesamorelin has the potential to also maintain denervated muscle and Schwann cells (SCs) prior to reinnervation.

There is a wealth of basic and translational research demonstrating the positive effects of IGF-1 as a potent trophic factor for motor and sensory neurons. Because the effects of GHRH and GH are primarily mediated by circulating and locally produced IGF-1, methods to study the effects of the GHRH/GH/IGF-1 axis in vitro typically utilize IGF-1. A number of elegant mechanistic studies have demonstrated the important role of IGF-1 in neuronal regeneration and muscle reinnervation

(12-20); specifically, these studies have demonstrated promotion of neurite outgrowth, growth cone motility, and anti-apoptotic neuroprotection, as well as enhanced intramuscular nerve sprouting in vitro. Beyond exhibiting direct pro-regenerative effects on neuronal cells, IGF-1 has also been shown to have a multitude of positive effects on Schwann cells (SCs) in culture. SCs play a critical role in peripheral nerve regeneration by releasing neurotrophic factors and supporting and directing regenerating axons. Numerous studies have demonstrated the potent effects of IGF-1 in promoting Schwann cell survival, maturation and myelination in vitro. (21-25) IGF-1 is also well known to have beneficial effects on muscle growth and regeneration as well as on prevention of atrophy in denervated muscle tissue in vitro. (26-28) These studies, in addition to many others, have elucidated the mechanisms by which augmenting the GHRH/GH/IGF-1 axis enhances peripheral nerve regeneration and promotes improved functional outcomes following PNI.

Building on the mechanistic studies described above, a number of translational studies in small animal models have demonstrated the ability of IGF-1, delivered locally or systemically, to enhance both motor and sensory nerve regeneration and improve functional recovery following nerve injury (29-34). These studies utilized a number of different animal models of PNI, including nerve transection-and-repair, crush injury, and autografting of larger defects. They demonstrated greater number and density of regenerating axons, greater axonal regenerative velocity, maintenance of motor endplates and muscle weight, and improved functional outcomes in IGF-1 treated animal as compared to controls. In some cases, this effect was found to be dose-dependent. Studies have also demonstrated the ability of IGF-1 to prevent atrophy and increase tetanic strength in denervated muscle in vivo. (35)

Our group performed a study assessing the effects of IGF-1 on nerve regeneration in a rat hindlimb transplant model. Animals received either systemic IGF-1 treatment or saline placebo. At 5 weeks, the animals were sacrificed for histomorphometric analysis of axonal regeneration within the distal sciatic nerve. Our results indicated significantly greater number and density of regenerating axons in the treated group as compared to the control group.

A number of studies have also demonstrated the positive effects of systemic GH treatment on nerve regeneration and functional outcomes. All of these studies utilized small animal models for PNI. Saceda, et al., demonstrated greater nerve fiber density, myelination, and recovery of nerve conduction velocity and amplitude with GH treatment following ulnar nerve transection and repair in rats. (36) Studies by Kanje and Skottner found greater velocity of nerve regeneration with GH treatment following sciatic nerve crush injury in normal and hypophysectomized rats. (37, 38) Devesa, et al. demonstrated greater nerve fiber number, density, and myelination, as well as greater Schwann cell number, and improved compound muscle action potential (CMAP) latency and amplitude following sciatic nerve transection and repair in GH treated rats. (39) Our group has shown that GH therapy accelerates axonal regeneration, enhances muscle reinnervation, reduces muscle atrophy and maintains proliferating SCs in a rat sciatic nerve injury and repair model. (40)

Although exogenous GH and IGF-1 therapy have been shown to be effective therapies for PNI in many basic and preclinical studies, there are factors limiting clinical application. The systemic delivery of IGF-1 is limited by its high cost and its hypoglycemic effect. (41) Because of the lack of negative feedback control, exogenous GH therapy poses a risk for overdosing, resulting in

significant side effects (fluid retention, insulin resistance with worsening glucose control, joint pain). (42, 43)

Conversely, by mimicking the action of GHRH and stimulating release of endogenous GH from the pituitary, tesamorelin provides a safer and more physiologic approach to therapeutic growth hormone augmentation. With tesamorelin treatment, pituitary secretion of GH is still controlled by IGF-1 negative feedback, thereby reducing the risk of overdosing. Furthermore, tesamorelin therapy maintains the physiologic pulsatility of GH release from the pituitary. (44)

Clinical trials have demonstrated more consistent elevations in IGF-1 levels and fewer side effects with tesamorelin as compared to GH in patients being treated for HIV lipodystrophy. (45) These patients, like most patients with nerve injuries, have an intact pituitary gland that is able to respond to tesamorelin stimulus. Therefore, the improved safety profile and efficacy in HIV lipodystrophy patients would likely translate well to the patient population in the proposed study.

Importantly, tesamorelin is a human GHRH analogue that does not exhibit the same biologic activity in animals. The clinical trials for a number of indications described below were not preceded by animal studies assessing the efficacy of tesamorelin for those indications. Rather, the preclinical studies demonstrating efficacy with GH for those indications were deemed sufficient to justify clinical testing with tesamorelin.

Beyond the potential of tesamorelin to improve functional outcomes following PNI by enhancing axonal regeneration and minimizing denervation atrophy, there is also reason to believe that augmenting the growth hormone axis could potentially have secondary benefits with regards to improved bone, tendon, and wound healing.

Trauma resulting in peripheral nerve injury often involves concomitant injury to other tissue types, including bone, tendon, and skin. Bony mal-union and non-union, failure of tendon repair, and chronic non-healing wounds can all contribute to poor outcomes following extremity trauma. *The global anabolic effects mediated by the GH axis have led researchers to investigate the potential of GH therapy to accelerate and enhance recovery from injury to all of these tissues*. (46) A number of translational studies in small animals have demonstrated accelerated bony healing and improved mechanical strength with growth hormone treatment, some of which demonstrated dose-dependent response. (47-51) Following tibial bone fracture, rats treated with GH demonstrated 400% maximum stiffness and 270% ultimate stress and energy absorption at the fracture site as compared to controls (47). Enhancement of bony healing with GH therapy has been shown to be dose-dependent (48), and also dependent on the timing and duration of treatment, with early and continuous therapy showing greater benefit than therapy initiated late in the healing process (49). In a double-blinded, placebo controlled clinical trial, GH therapy was found to significantly accelerate bony healing of closed tibial fractures (52). There have also been a number of basic and translational studies demonstrating the positive effects of GH therapy on wound healing, with stimulation of fibroblasts and improved granulation and collagen deposition. (53-55) Clinical trials have demonstrated the efficacy of GH therapy in improving healing of burn wounds. (56)

It is important to emphasize that this study is designed to assess the efficacy of tesamorelin therapy in improving functional outcomes following PNI through enhanced axonal regeneration and

decreased muscle atrophy. The presence of fractures, tendon injuries and wounds are not inclusion criteria. As such, it is possible that there will not be enough power or homogeneity in the participant pool to draw definitive conclusions regarding the efficacy of tesamorelin in healing these concomitant injuries. That being said, modest conclusions regarding observed trends in healing may provide the basis for future studies designed specifically to investigate these potential secondary benefits.

Summary: Rationale for Tesamorelin as Therapy for PNI

The following conclusions summarized from the extensive research described above lead us to believe that tesamorelin is ideally suited for clinical investigation as a therapeutic agent in the setting of PNI:

- There is a wealth of evidence from basic and translational research demonstrating the positive effects of GH and IGF-1 therapy on axonal regeneration, muscle atrophy, and functional outcomes following PNI.

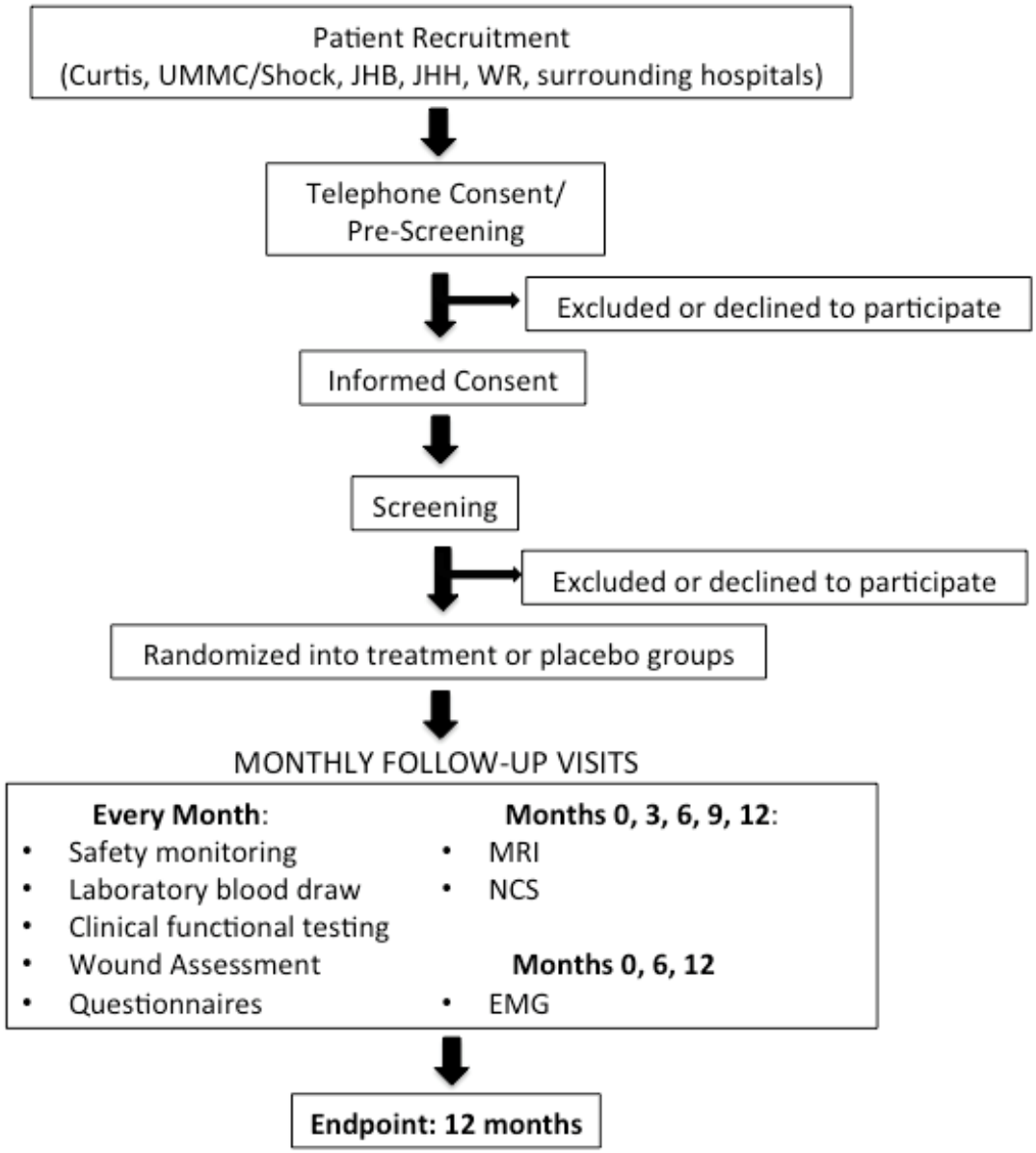
- Tesamorelin is an FDA-approved drug that provides a safe and physiologic approach to augmenting the growth hormone axis by producing stable elevation in GH and IGF-1 levels.

- Preclinical studies demonstrating efficacy with GH have been deemed to be sufficient to justify clinical testing of tesamorelin for HIV lipodystrophy, visceral adiposity and cognitive disorders

- Tesamorelin may provide secondary benefits with regards to bone, tendon, and wound healing.

4. STUDY PROCEDURES

a) Study Design



Subject recruitment:
The study population will include military and civilian men and women of all ethnicities and races who have sustained ulnar nerve injuries repaired primarily. The pool of potential patients will include those treated by the surgeons involved with the study, as well as those referred by other surgeons and emergency medicine physicians. To further expand the participant pool, the key personnel will raise awareness about the study among other surgeons and emergency medicine physicians at their own institutions and at other hospitals in the community. This will be done through public presentations (i.e.- grand rounds presentations), IRB-approved flyers, and personal communications. We will also utilize MyChart recruitment services to expand our participant pool. We will send out MyChart research invitation letters to potential participants with an active MyChart account. This invitation letter was developed in accordance with newer language as requested by the MyChart Recruitment Committee.

Patients will be provided information about the study, if appropriate, during clinic visits and in the emergency room. When a patient is identified as a potential candidate for enrollment (presence of lower ulnar nerve injury repaired primarily), they will be given basic information about the study from their provider derived from an IRB-approved recruitment flyer. Contact information for the study coordinator will be included such that an interested potential candidate can schedule a telephone interview.

Telephone Consent/Screening:
Before initiating the telephone interview, potential subjects will be informed that the conversation may be used as part of the preliminary screening and verbal permission will be obtained to request some personal details that may qualify as protected health information (PHI). With the potential participants' permission, their information will be securely stored. The telephone screening script is attached.

In order to minimize the need for research-only in-person visits, teleconsent or remote consent may be substituted for in person clinical trial visits

A copy of the IRB approved Informed Consent document will be provided to the participant prior to the teleconsent meeting either via email, fax or mail or must have been previously provided during an in person visit. If the consent divulges PHI, such as a diagnosis, we will inform participants that email sent over the internet is not secure prior to sending the consent form via email and we will confirm the participant agrees to receive the document via email. Information sent by email may not remain confidential.

The person conducting the consent process may conduct the process via telephone or video. The following is a step-by-step teleconsent / remote consent process:

- After the consent designee and participant or LAR review the consent form, the participant or LAR is offered the opportunity to ask any questions and have those questions answered.
- The consent designee must verify the participant or LAR physically signed the consent document either by viewing via video conference, obtaining a photo of the complete signed

consent document; or obtaining verbal confirmation from the participant that he/she signed the consent form or agreed to participate electronically.

- The participant or LAR will sign and date/time the informed consent document.
- The signed document is then mailed, emailed or faxed to the consent designee.
- If the signed consent is emailed or faxed or returned via photo, the participant or LAR will be asked to return the original signed document on their first in person visit.
- If the informed consent form is mailed to the consent designee by the participant or LAR, the IRB-approved consent designee will sign the copy which they possess after the participant has acknowledged signature on their copy. Once the original is received by the consent designee the copies will be attached to make a single document.
- In all other instances, once received, the IRB-approved consent designee signs, dates/times the informed consent document.

Combined Informed Consent Process:

Potential participants who clear the telephone screening will be provided the combined (for screening and study participation) Informed Consent Form (ICF) (attached) at the time of screening tests. He/she will have ample time to review the ICF and prepare questions regarding the study while awaiting the results of screening procedures. At all follow-up screening appointments, subjects will have the opportunity and be invited to discuss the ICF with qualified study staff to clarify any questions the participant may have regarding the study, long-term treatment, and follow-up assessments. Participants are strongly encouraged to have a family member (or members) or patient advocate present at the meeting when the main ICF is signed.

The informed consent process will be administered to participants in a private area by a trained, IRB-approved study team member prior to enrollment in the study. (Private areas include clinic rooms, inpatient rooms, and other spaces approved for clinical use at JHH.) Participants will be advised of the potential risks and benefits of the study. Participants will be able to discuss the ICF with qualified study staff, be invited to ask any questions they might have, and will have the opportunity to discuss the ICF with their family and/or friends prior to signing. The informed consent process will take as long as necessary to ensure that the patient has had all of his/her questions answered and until the study team member is satisfied that the participant understands what study participation involves.

The ICF contains a written statement informing the participant of his/her rights regarding PHI, what PHI will be recorded, and what groups may have access to it. Potential participants will be informed that they have the right to withdraw consent at any time and will be provided with necessary information on how to do so. Participants who complete and sign the ICF will be provided with a copy signed by the appropriate study personnel for their records.

Participants are expected to attend appointments sober and not under the influence of alcohol or recreational or prescription drugs. Study staff administering consent will watch participants for any unusual behaviors that may indicate an altered mental state and respond in compliance with institutional policies to handle the situation in an appropriate manner. Study candidates will not be consented for study participation if suspected of being in an altered mental state. Similarly,

candidates suspected of being under undue emotional stress will not be consented to participate in the study.

Screening/Consent:

Telephone Consent/Screening
Before initiating the telephone interview, potential subjects will be informed that the conversation may be used as part of the preliminary screening and verbal permission will be obtained to request some personal details that may qualify as protected health information (PHI). With the potential participants' permission, their information will be securely stored.

Combined Informed Consent Process
Potential participants who clear the telephone screening will be provided the combined (for screening and study participation) Informed Consent Form (ICF) (Attachment 6, Appendix 3) at the time of screening tests. He/she will have ample time to review the ICF and prepare questions regarding the study while awaiting the results of screening procedures. At all follow-up screening appointments, subjects will have the opportunity and be invited to discuss the ICF with qualified study staff to clarify any questions the participant may have regarding the study, long-term treatment, and follow-up assessments. Participants are strongly encouraged to have a family member (or members) or patient advocate present at the meeting when the main ICF is signed. Liz Martinez, RN, BSN, CCRC is a research participant advocate with the Institute for Clinical and Translational Research at Johns Hopkins University, and has offered to assist with any patient advocacy needs for the study.

The informed consent process will be administered to participants in a private area by a trained, IRB-approved study team member prior to enrollment in the study. (Private areas include clinic rooms, inpatient rooms, and other spaces approved for clinical use at JHH.) Participants will be advised of the potential risks and benefits of the study. Participants will be able to discuss the ICF with qualified study staff, be invited to ask any questions they might have, and will have the opportunity to discuss the ICF with their family and/or friends prior to signing. The informed consent process will take as long as necessary to ensure that the patient has had all of his/her questions answered and until the study team member is satisfied that the participant understands what study participation involves.

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candidates suspected of being under undue emotional stress will not be consented to participate in the study.

Screening Procedures:
A member of the study team will review the combined ICF with the participant and invite the participant to ask any questions he/she might have. Candidates will then be asked to complete the ICF before being enrolled in the study and undergoing further evaluation/medical screening procedures. The ICF includes a written authorization allowing the study team to obtain the candidate's relevant PHI. Once the ICF is completed, potential participants will undergo standardized screening procedures that include a number of examinations and investigations to determine eligibility for this study. The screening evaluation tests, procedures, and evaluations include the following, all of which are either standard medical procedures or are clinically approved for human use:

HISTORY AND PHYSICAL EXAM– A routine medical history and physical exam that specifically addresses potential exclusion criteria will be performed. A detailed history regarding the ulnar nerve injury will be obtained, including timing, mechanism of injury, surgery and motor and sensory deficits related to ulnar nerve injury. Specific areas addressed will include the following:

1. History of neoplasm in any organ or active neoplasm
2. Family history of cancer
3. Symptoms of prostatic enlargement in male participants, including prostate cancer screening history
4. History of diabetes or poor glucose control
5. History of hypothyroidism
6. History of head injury or hypopituitarism
7. History of estrogen use, include oral contraceptives
8. Family structure (i.e., marital history, offspring)
9. Employment history
10. Tobacco, alcohol or illicit drug use
11. Social history (with emphasis on factors that may influence ability to successfully participate in study)

2. LABORATORY TESTS AND EXAMS - All of the following tests are required unless otherwise noted:
    1. Blood Tests
        a. Complete blood count (CBC or Heme 8) w/Differential
        b. Complete Metabolic Panel (CMP)
        c. Clotting Profile (PT/PTT with INR)
        d. Liver Function Tests [including total bilirubin, AST, ALT, and Alkaline Phosphatase]
        e. Lipid Profile
        f. HA1-C
        g. Pregnancy screen (Urine Hcg)
        h. Alpha Fetoprotein (AFP)

i. TSH
j. PSA (men over 40 years)
k. IGF-1

2. Mammography- for female patients >40 years who are not up to date on screening

3. VIDEO AND PHOTOGRAPHY RECORDINGS IN CLINICAL CONTEXT

During every appointment, patients' clinical functional assessment will be recorded if the subject provides additional consent for this. This will allow for retrospective quality checks of the data being collected. Only the region of the forearm, wrist and hand will be recorded during the assessment. Additionally, images of only the wound area will be taken at each appointment, in order to assess wound healing. The video and photographs will be retained for five years after taking the recordings. Images and videos will be stored electronically in an encrypted computer solely dedicated to this study. The camera will be stored in a secure filling cabinet. Only researchers involved in this clinical trial will have access to these recordings.

Randomization Procedure:

RedCAP manager (Andre Hackam) will generate a randomization schedule prior to the start of study, with stratification of subjects who do not have concomitant nerve, tendon or bone injury (other than flexor carpi ulnaris and ulnar artery lacerations, which are expected to occur with ulnar nerve lacerations). Only the RedCAP manager and the data safety management board will have access to the stratification schedule key. A number will be assigned to each subject that corresponds to one of the numbered study kits that contain either placebo or study drug but are otherwise identical. The study kits will be sent by Theratechnologies directly to the JH Investigational Drug Service Pharmacy from where they will be distributed to study participants under the supervision of Janet Mighty.

b) Study duration and number of study visits required of research participants:

The study duration is 13 months. Each participant will have 14 study visits, including initial consent and screening and 13 subsequent monthly assessment visits.

c) Blinding, including justification for blinding:

Blinding is necessary in this study to account for the possibility of observer bias or conscious deception by the study team as well as the possibility that participants' knowledge of their assigned group (placebo vs. study drug) may influence their recovery process and reported outcomes. To achieve blinding of the study team and research participants, the RedCAP manager (Andre Hackam) will generate a randomization schedule prior to start of study. Only the RedCAP manager and the data safety management board will have access to the stratification schedule key. A number will be assigned to each subject that corresponds to one of the numbered study kits that contain either placebo or study drug but are otherwise identical. The study kits will be sent by Theratechnologies directly to the JH Investigational Drug Service Pharmacy,

which will have the randomization schedule, but not the randomization schedule key. The study kits will be distributed to directly to each study participant according to the number he or she was assigned by the randomization schedule.

d) Justification of why participants will not receive routine care or will have current therapy stopped:

All participants will receive routine care and will not have any current therapy stopped.

e) Justification for inclusion of a placebo or non-treatment group:

Without the inclusion of a placebo group, it would not be possible to determine the therapeutic effect of the study drug. Historical outcomes data for ulnar nerve injuries is sparse and of poor quality. There is also the possibility of a placebo effect that must be controlled for.

f) Definition of treatment failure or participant removal criteria

1. Hemoglobin value < 100 g/L and a decrease of at least 20 g/L from screening;
2. Subjects with AST and/or ALT > 5x ULN will be immediately discontinued from the study. For any subject who has an AST and/or ALT > 3 x ULN but ≤ 5 x ULN, the tests will be repeated at the following visit. If the repeat value is still > 3 x ULN, the subject will be discontinued;
3. Creatinine value > 2 x ULN;
4. Glycemia:
    - FBG > 10 mmol/L (180 mg/dL) after exposure to study drug, the subject will return in 7 working days for a repeat test:
    1. FBG > 10 mmol/L (180 mg/dL), the subject will be discontinued.
        2. FBG ≤ 10 mmol/L (180 mg/dL), the subject will remain in the study unless symptomatic, and return in 7 working days for a repeat test
            - FBG is > 10 mmol/L (180 mg/dL), the subject will be discontinued;
            - FBG ≤ 10 mmol/L (180 mg/dL), the subject will remain in the study.
    - Subjects displaying at any time symptoms related to hyperglycemia (i.e., polyuria, polydipsia, etc) will be immediately discontinued from the study and receive appropriate therapy;
5. Should there be a clinically significant elevation in CPK during the study, the Investigator will perform a strict evaluation of the clinical signs and medication of the subject. Any subject with suspicion of rhabdomyolysis will be withdrawn from the study. The primary diagnostic indicator of rhabdomyolysis is an elevated CPK of at least 5 x the ULN;

6. Any worsening of adverse reactions at the site of injection such as hives, extended redness and rash occurring anywhere in the body should be promptly reported to the sponsor and recorded in the injection site reaction log.

   Any systemic symptoms occurring within minutes of the injection that are observed along with reactions at the site of injection should be also promptly reported. These systemic symptoms include, but are not limited to, nausea, shortness of breath, abundant sweating and tachycardia.

Discontinued subjects will return for regular follow-up visits every 6 to 7 weeks for a period of at least 3 months and, if needed, up to 6 months.

g) Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Following completion of participation (either at study endpoint or prematurely), participants will be notified of the option to continue to receive follow up care from the primary investigator related to their injury or study treatment. They will be encouraged to do so for any concerns that arise related to injury recovery or sequelae from treatment. Any sequelae potentially related to study treatment that are observed following completion of study participation will be reported to the medical monitor. Study participants will be given the option of consenting to allow the study team to contact them to request follow up evaluations following completion of study participation.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

1. *Lower ulnar nerve injury repaired primarily*

- To limit variability in outcome measures, we have defined a very specific injury type and location. Each nerve in the upper extremity innervates a distinct set of muscles and skin distribution. Injuries to different nerves, or the same nerve at different levels, are associated

with very different functional deficits, rendering meaningful comparison of recovery difficult if not impossible. The method of nerve repair (primary vs. graft vs. biosynthetic conduit) also significantly impacts regeneration and recovery.

- The ulnar nerve was chosen because of its important role in innervating the intrinsic muscles of the hand. In comparison to lower median and radial nerve injuries, ulnar nerve injuries are associated with worse functional outcomes, and therefore exhibit greater potential for improvement in response to a therapy.

- Lower (distal to motor branch innervating the flexor digitorum profudus) injury was chosen because the time until recovery is less (as compared to upper injuries) allowing timely completion of the study. Furthermore, for the purpose of MRI and electrophysiologic testing, lower injuries provide more useful landmarks to facilitate consistent measurement.

- Primary repair, with direct suture coaptation, was chosen to limit variability in surgical approach. Where-as nerve grafting and conduit use vary with regards to length, type of graft/conduit, and methodology, primary repair is consistently performed in a similar manner.

2. *Time since injury ≤ 6 weeks*

- Caveat: Patients enrolled > 4 weeks and ≤ 6 weeks after surgical repair will be included, but will not have month 0 outcome measures included in the study. Instead, the first outcome measures for these participants will be at month 1.

- Explanation: A 6 week-enrollment window will allow ample time for recruitment, screening and informed consent without introducing significant variability in outcomes. However, the process of nerve regeneration and recovery from nerve injury begins at the time of surgical repair, and this must be taken into account when characterizing the timing of collected outcome measures.

3. *Adult (>18 years of age)*

- Therapies that manipulate the growth hormone axis should be used with caution in children with open long bone epiphyseal plates as it can result in excessive growth.

- Age has been consistently shown to affect outcomes following PNI, with younger patients demonstrating greater regenerative capacity. Therefore, limiting inclusion criteria to adults will also serve to limit variability.

Exclusion Criteria:

1. *History of malignancy of any organ (with the exception of basal cell carcinoma of the skin, in situ carcinoma of the cervix, and other malignancies that were successfully treated and deemed by treated physician to have minimal risk of recurrence) or any active neoplasm*
   - Augmenting the growth hormone axis carries a theoretical risk of accelerating cancer growth.

2. *For male patients > 40 years of age, suspicion of cancer by prostate examination and PSA >5 ng/mL at screening*
   - Augmenting the growth hormone axis carries a theoretical risk of accelerating cancer growth.

3. *History of breast cancer or proven family history of breast cancer in 2 or more first degree relatives for female patient*
   - Augmenting the growth hormone axis carries a theoretical risk of accelerating cancer growth.

4. *Hypopituitarism, or history of pituitary tumor/surgery, head irradiation or head trauma that has affected the growth hormone axis*
   - These conditions can affect response to tesamorelin treatment

5. *Untreated hypothyroidism*
   - Hypothyroidism can adversely affect nerve regeneration

6. *Co-morbid conditions that will not allow the patient to complete the study as per the Investigator's judgment*
   - It is difficult to anticipate and delineate all potential co-morbidities and psychosocial circumstances that would adversely affect compliance with the study. As such, there may be situations in which a patient is excluded for reasons other than those explicitly listed if there is sufficient concern for poor compliance or ability to complete the study.

7. *Type 1 diabetics and type 2 diabetics previously treated with insulin (except during pregnancy when not required following delivery)*
   - Manipulating the growth hormone axis has been shown to affect glucose metabolism. Diabetic patients will be excluded to minimize risk to the patient.
   - Hyperglycemia is known to adversely affect peripheral nerve regeneration. Exclusion of diabetic patients will also serve to limit variability.

8. *Evidence of the following at screening:*
   - *Hepatic dysfunction: ALT or AST >3 x upper limit of normal (ULN)*
   - *Renal dysfunction: serum creatinine >133 µmol/L (1.5 mg/dL)- adjusted for sex/weight*
   - *Anemia: hemoglobin (hgb) < 7 g/dL*
   - *Fasting blood glucose > 8 mmol/L (144 mg/dL)*
   - *Lipid metabolism severe dysfunction: fasting triglycerides > 500 g/dL*

- Abnormalities in the above listed laboratory values indicate potential underlying comorbidities that may affect a patient's baseline regenerative capacities and, as such, would introduce excessive variability.

9. *Treatment with oral estrogen, including oral contraceptives*
   - Oral estrogen treatment can cause significant liver resistance to GH stimuli, reducing the efficacy of tesamorelin.
   - Female participants who are pre-menopausal will be given the option of switching to barrier contraceptive with pregnancy screening at each monthly visit.

10. *Untreated hypertension as defined by the American Heart Association Guidelines*
    - Therapies that augment the growth hormone axis can exacerbate hypertension by causing excess fluid retention.

11. *Drug or alcohol dependence within the last 6 months*
    - These comorbidities may adversely affect patient compliance.

**No study exclusions will be made on the basis of gender, race, or ethnicity*

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose:

Tesamorelin is a long-acting growth hormone-releasing hormone analogue that stimulates endogenous release of growth hormone from the pituitary. Research from our group and others suggests augmenting the growth hormone axis has the potential to improve outcomes following peripheral nerve injury (See Background). We have chosen to use a dose of 2mg per day because this suggested dose used for treatment of HIV lipodystrophy, the only FDA-approved indication for tesamorelin. Furthermore, in Phase II clinical trials, a 2mg dose was found to be more efficacious and equally safe as compared to a 1mg dose.

Theratechnologies has developed two FDA-approved formulations a 1mg/vial and a 2mg/vial bioequivalent formulation of tesamorelin. This bioequivalent formulation of tesamorelin will be more user-friendly for participants as it comes in a single vial instead of two and is stable at room temperature.

The participants will be instructed to reconstitute two 1mg/vial with 2.2ml of sterile water or 1.4mg/vial with 0.5 mL of sterile water. 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.

Theratechnologies plan to stop production of their 1mg/vial formulation and as a result we will only have access to their new FDA approved 2mg/vial bioequivalent formulation. By including

the bioequivalent formulation into our protocol, will allow us to interchange between the two formulations as required and use the drug as approved by the FDA.

Based on comparative reviews of the approved prescribing information for the new 2mg/vial (Revised 11/2018) and 1 mg/vial formulations (Revised 7/2018) (See the "label" posted under EGRIFTA NDA 022505/ Supplement 11 on the "Drugs@FDA Website", Action date 1/18/19), it was determined that for both:

1. The approved indication remains "the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy."
2. The active ingredient remains tesamorelin as the acetate salt
3. The route of administration is still by a once daily subcutaneous injection.

More importantly "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 Polysorbate 20

There is no reason to suspect that any of the new inactive ingredients may be contraindicated in our study population. As the changes made to create the 2 mg/vial formulation 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.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Tesamorelin in FDA approved for treatment of HIV lipodystrophy and will be administered for the non-FDA approved indication of peripheral nerve injury. The dosing and route of administration will be the same as is used for treatment of HIV lipodystrophy.

Treatment has been shown to be safe in multiple phase II and phase II clinical trials, with minimal side effects and no serious adverse events. Compiled safety data from Theratechnologies that has been filed with the FDA is attached.

A study nurse or study physician or study affiliated nurse practitioner or physician assistant will teach the study participant and their caregiver how to administer tesamorelin or placebo subcutaneously.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

NA

d. Dose modification

EGRIFTA® stimulates GH production and increases serum IGF-1. Given that IGF-1 is a growth factor and the effect of prolonged elevations in IGF-1 levels on the development or progression of malignancies is unknown, IGF-1 levels will be monitored closely during this trial. Occurrence of persistent elevations of IGF-1 levels (e.g., >3 SDS) will be assessed on an individual basis and withdrawal from the study medication should be considered based on a careful risk-benefit evaluation particularly if the efficacy response is not robust (e.g., based on visceral adipose tissue changes measured by waist circumference).

e. Drug Dispensing

In response to the COVID-19 pandemic, the study drug will be shipped to study participants living in Maryland. A prescription will be submitted in EPIC for a refill and request this be shipped in the EPIC order. After study participant agrees to receive the study drug shipment and confirming their address, we will then agree to send the study drug, using FedEx for overnight delivery with signature required and this will be endorsed in writing by the Study PI.

7. Utilization of alternate visit options

To ensure patient safety and to eliminate immediate apparent hazards including those based on the risk of exposure to COVID-19 we will implement telephone or zoom visits for participants in lieu of on-site visits during the COVID-19 pandemic.

STUDY STATISTICS

a. Primary outcome variable:

Definition: The primary outcome is motor amplitude (uV) as measured by nerve conduction studies. The target standardized effect size of treatment as compared to placebo in this 12 month study is 0.4, which falls in the range of a 'medium' effect size. Setting the statistical significance at 0.05, within-participation correlation among measures across the time points (0, 3, 6, 9, and 12 months) at 0.5, and power at 80%, a total sample of 30 participants (15 per group) would allow a between-group effect size of 0.4 to be detected. Assuming 15% dropout rate, total recruitment goal is 36 participants.

Rationale: Motor amplitude was chosen as the primary outcome because it is an objective measure of nerve regeneration that is reproducible and unaffected by concomitant injuries. While clinical functional outcome measures (ie- grip strength, MBMRC motor grade, etc.) are more clinically meaningful, they will be affected by concomitant injuries (tendon lacerations, fractures, median nerve injury, etc) and therefore excluded in some subjects. Setting a clinically meaningful absolute difference in mean amplitude between the treatment and control groups for this study is not possible, given the lack of prior placebo-controlled treatment studies that prospectively assess differences in amplitude for patients with ulnar nerve lacerations at the wrist. Of note, a secondary aim of this study is to provide information that can be used to guide the design of similar studies in the future. It should also be noted that this study is meant to be a Phase 2 clinical trial, and larger Phase 3 studies will likely be needed to confirm promising findings.

Testing Methodology: An active surface electrode will be placed on the ulnar aspect of the hand at the longitudinal midpoint of the abductor digiti minimi muscle. A reference electrode will be placed 4cm distal to the active electrode and a ground electrode 4 cm proximal. The ulnar nerve will be stimulated 8cm proximal to the active electrode and distal to the ulnar nerve repair. Latency and amplitude of the evoked response will be recorded. Only amplitude will be used a primary outcome measure.

b. Secondary outcome variables:

- Motor and sensory latency (ms)
- Sensory amplitude (uV)
- Electromyography (Daube score 0-4+)
- Magnetic resonance imaging (functional anisotropy; apparent diffusion coefficient; muscle/tendon/bone healing scores)
- Clinical functional assessments (MBMRC motor/sensory grade, grip strength, Tinel sign, presence of clawing, Froment's sign, ability to cross fingers)
- Questionnaires (DASH, MHQ, SF-36)
- Wound healing assessment (diameter, depth, presence of granulation/epitheliazation)

- Laboratory values (Serum IGF-1, ALT, AST, HbgA1c, fasting glucose, hemoglobin, total cholesterol, lipid profile (triglycerides, HDL-cholesterol, LDL-cholesterol), thyroid-stimulating hormone (TSH), free T4, Pregnancy screen (urine dipstick), PSA (men over 40), Coagulation measures (PT/PTT), Complete blood count (CBC) and complete metabolic panel (CMP).

c. Statistical plan including sample size justification and interim data analysis:

Primary Efficacy Analysis:
After unblinding of the trial, complete efficacy and safety analyses will be prepared to evaluate the study hypotheses. By patient and by treatment group, plots of outcome measures over time will be prepared and reviewed as part of the data quality assurance process before data analysis. Basic exploratory analyses will be performed on each outcome at each time point and across time points to identify potential outliers, trends and missingness patterns. A comparison of treatment groups will be performed on demographic characteristics and baseline outcomes using appropriate summary statistics for categorical, ordinal and continuous variables, to review the groups' similarity before the intervention is initiated.

The data will be analyzed primarily with an intention-to-treat (ITT) approach. To evaluate the difference between treatment groups over time, the outcome measurements will be compared using a multi-level model (MLM) approach (81) with two groups and measurements at multiple time points, where the within-participant correlation is taken into account. Participant characteristics and baseline outcome measurements may be included as adjustors in the models. The MLM approach can estimate the parameters for the marginal distribution of an outcome with unbalanced measurements across participants, so that low levels of missing data can be tolerated. The main test in these models is of the interaction between the groups and measurements post-intervention over time. Depending on the level of missingness across the time points, this approach can be extended to a pattern mixture model (82) to evaluate any difference between those with complete measurements and those with at least one missing measurement with respect to its impact on the outcome measurement. The Holm-Bonferroni correction (83) will be used to adjust the significance level for multiple comparisons across the outcomes.

Secondary Efficacy Analysis:
The secondary efficacy variables will be analyzed in a similar fashion to the methodology described above for primary efficacy analysis.

Statistical Assessment of Safety:
The safety variables (laboratory values, presence or absence of adverse drug events) will be analyzed using a similar methodology as described above for primary efficacy analysis.

Correlation of MRI DTI to other efficacy measures:
To prospectively assess the clinical utility of MRI DTI in defining the progress of peripheral nerve regeneration and predicting functional outcomes, data from MRI DTI will be evaluated against data from NCS, EMG and clinical functional assessments also using a MLM approach, but within each group initially. Each of the other assessment measures will be used as the outcome, and MRI

DTI will be considered an individual predictor of each of the other assessment measures across time or with some time lags.

Power Analysis:
With the assistance of the Johns Hopkins Biostatics Center, power analysis was performed based on nerve conduction studies as the primary efficacy measure. The statistical model for power analysis was the F-test ANOVA with 4 repeated measures (based on the 3, 6, 9 and 12 month post-intervention measurement periods). Assuming a significance level of 0.05, a within-participation correlation among measures across the time points of 0.5, and power of 80%, a total sample of 30 participants (15 per group) would allow a between-group effect size of 0.4 to be detected. Assuming 15% dropout rate, total recruitment goal will be **36 participants**.

Unblinding of data for the purpose of interim analysis of results will not occur.

d. Early stopping rules:

Early stopping will not occur unless there is a serious risk associated with the study drug that becomes apparent that was previously unknown. This is highly unlikely given the benign risk profile noted in other studies that have tested tesamorelin.

8. RISKS

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Drug-Related Risks:

Tesamorelin has been tested in a number of clinical trials. In general, it was well tolerated by patients.

The following are the most common side effects that were noted:

- Injection site irritation, redness, itching, and/or pain
- Hypersensitivity reaction (rash, hives)
- Muscle pain
- Fluid retention, swelling in hands and feet
- Carpal tunnel syndrome (numbness and tingling in fingers)
- Glucose intolerance

Although not considered side effects, you may experience the following due to subcutaneous injection of tesamorelin of placebo:

- Inconvenience of daily subcutaneous injections
- Mild discomfort from daily subcutaneous injection

Other Risks:

- Neoplasm
  - Tesamorelin treatment results in increased production of growth hormone and IGF-1 (a growth factor), which have been implicated in the development and progression of neoplasms and malignancy. Patients with active malignancy should not be treated with tesamorelin and will not be enrolled in the study. Treatment with tesamorelin has not been shown to result in increased frequency malignancy. However, development and progression of malignancy should be considered risks of treatment with tesamorelin.
- Acute Critical Illness
  - Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of growth hormone. Tesamorelin has not been studied in patients with acute critical illness. Patients with acute critical illness will not be enrolled in this study.

Screening (including history, physical exam):

Infrequent-

- Breach of privacy/confidentiality
- Boredom
- Discovery of previously unknown conditions

Magnetic Resonance Imaging:

Infrequent-

- Claustrophobia
- Boredom
- Mild discomfort from trying to remain still

Neurodiagnostics (Nerve Conduction Studies/Electromyography):

Common-

- Transient tingling
- Transient mild discomfort from electrical stimulation
- Transient mild to moderate discomfort from EMG needle

Infrequent-

- Mild muscle soreness following EMG

Venipuncture (laboratory assessments):

Common-

- Mild discomfort from venipuncture

Infrequent-

- Bleeding
- Bruising
- Clotting

Rare-

- Fainting
- Local infection

Study Questionnaires:

Common-

- Boredom

Rare-

- Discomfort with questions

Video and Photography Recordings

Infrequent-

- Breach of privacy/confidentiality

b. Steps taken to minimize the risks.

Patients will be carefully monitored for adverse events. This monitoring includes monthly clinical laboratory tests and assessment of adverse events volunteered by the patient or discovered by investigator questioning or detected through physical examination or other means. Adverse events will be assessed in terms of their seriousness, severity, duration and relationship to the study drug,

Todd Brown, MD (Associate Professor, Medicine Department, Johns Hopkins) will serve as independent medical monitor. At a minimum, the research monitor: may discuss the research protocol with the investigators, interview human subjects, consult with others outside of the study about the research; shall have the authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

A data safety monitoring board (DSMB) will convene in person or via teleconference every 6 months to review the progress and safety of the study, with the assistance of the biostatistician. The DSMB will consist of Dr. Ramon DeJesus, MD, a hand surgeon in private practice with subspecialty training in peripheral nerve, and Dr. Clare Lee, MD, assistant professor of medicine in the endocrinology division at JHU.

a. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems and study deviations will be reported to the study monitor and IRB.

b. Legal risks such as the risks that would be associated with breach of confidentiality.

If breach of confidentiality occurs, the study participant, IRB, and legal office at Johns Hopkins will be notified.

c. Financial risks to the participants.

9. BENEFITS

a. Description of the probable benefits for the participant and for society.

10. PAYMENT AND REMUNERATION

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Patients will be reimbursed for participation in the study at an estimated $7,062 per patient over the course of the study. The following remuneration schedule was developed in conjunction with Liz Martinez at the ICTR :

Outpatient visit: $50 (x14) = $700
Blood sample-single venipuncture: $10 (x14) = $140
Neurodiagnostic study: $40 (x5) = $200
Electromyography: $130 (x3) = $390
Magnetic Resonance Imaging: $35 (x5) = $175
Questionnaire ($15) (x42) = $630
Subcutaneous injection: $10 (x365) = $3650
Sum: $5,885
Completion bonus 20%: $1177
Total per participant: $7062

The sum total amount to the study participant will be paid to them following his or her final study appointment.

In addition travel allowance will be provide to study participants

Travel and Food allowance:

- Patient will be reimbursed up to $50 for each visit to cover the cost of travel and food expenses incurred (e.g., bus fare, taxi from home to study site, food etc.). We will not provide a daily stipend for the incidentals mentioned above, but rather will reimburse for these types of expenses as receipts are presented.

- For patients travelling by car, round trip mileage will be calculated using Google Map indicating home address of subject and address of the study site. Mileage will be reimbursed as receipts are presented at the current Internal Revenue Service business reimbursement rate of $0.545 per mile for private automobiles.

11. COSTS

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to participants for participation in this study.

Instrucciones de uso

EGRIFTA SV™
(tesamorelina para inyección)
para uso subcutáneo
vial de 2 mg

Estas Instrucciones de uso contienen información paso a paso sobre cómo usar el **vial de 2 mg** de EGRIFTA SV. **Cada vial de 2 mg de EGRIFTA SV debe mezclarse con 0,5 ml de agua estéril para inyección** proporcionada en la caja de la inyección que le entrega la farmacia. **Use solo un vial** de 2 mg de EGRIFTA SV **de la caja del medicamento** para preparar la dosis. La dosis recomendada de **EGRIFTA SV es de 1,4 mg (0,35 ml).**

Asegúrese de leer, comprender y seguir estas Instrucciones de uso antes de usar EGRIFTA SV. Su proveedor de atención médica debe mostrarle cómo mezclar e inyectar EGRIFTA SV antes de que se aplique la inyección por primera vez. Consulte a su proveedor de atención médica si tiene alguna pregunta.

Conserve estas Instrucciones de uso por si necesita consultarlas nuevamente más adelante.

Información importante para el uso de EGRIFTA SV

- **No** use una jeringa o aguja más de 1 vez.
- **No comparta sus jeringas o agujas con otras personas, incluso si se ha cambiado la aguja. Puede contagiar una infección grave a otras personas o contagiarse usted una infección grave de ellas.**
- Si le falta algún suministro de las cajas que le entregaron en la farmacia o si alguno de los suministros parece dañado, llame a su farmacéutico o comuníquese THERA patient support™ sin cargo al 1-833-23THERA (1-833-238-4372) de inmediato.

Cómo prepararse para la inyección de EGRIFTA SV

Paso 1: Busque una superficie limpia, plana y bien iluminada, como una mesa.

Paso 2: Reúna los suministros:

- Caja del medicamento que contiene 30 viales de dosis única de 2 mg de EGRIFTA SV
- Caja de la inyección que contiene lo siguiente:
  - 30 frascos de dosis única de 10 ml de agua estéril para inyección, que se usa para mezclar
  - 60 jeringas estériles de 1 ml
  - 60 agujas estériles de 1" y calibre 20, que se usan para mezclar
  - 30 agujas estériles de ½" y calibre 30, que se usan para la inyección
- Otros suministros necesarios
  - Dos paños con alcohol
  - Una gasa estéril
  - Una venda adhesiva

- Recipiente para objetos punzocortantes o recipiente resistente a punciones, para desechar las agujas y jeringas usadas cuando ya no las necesite. (Consulte **"¿Cómo debo desechar las jeringas, agujas, frascos y viales usados?"**)

Para cada inyección con el vial de 2 mg de EGRIFTA SV necesitará: (Consulte la Figura A)

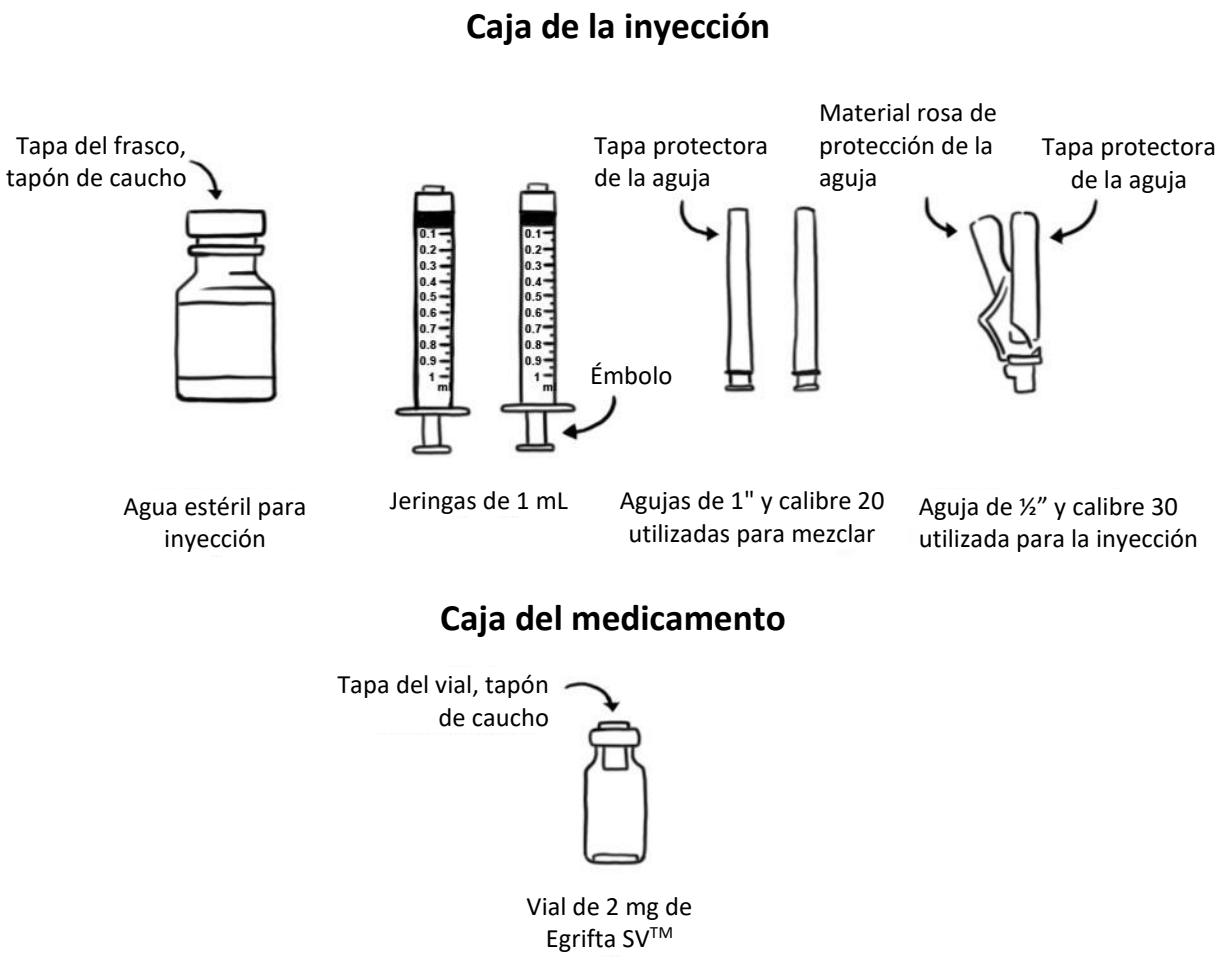

Figura A

Paso 3: Retire los siguientes elementos de la caja de la inyección:

- Un frasco de agua estéril para inyección
- Dos jeringas de 1 ml
- Dos agujas de 1" y calibre 20, que se usan para mezclar
- Una aguja de ½" y calibre 30, que se usa para la inyección

Paso 4: Retire **1 vial** de 2 mg de EGRIFTA SV de la caja del medicamento.
Paso 5: Prepárese para usar los suministros:

- Lávese las manos con agua y jabón. Séquese las manos con una toalla limpia.
- Quite los capuchones de plástico del vial de 2 mg de EGRIFTA SV y del frasco de agua estéril para inyección.
- Limpie los tapones de caucho en la parte superior del vial de 2 mg de EGRIFTA SV y del frasco de agua estéril para inyección con un paño con alcohol.

Cómo mezclar el vial de 2 mg de EGRIFTA SV

Paso 1: Coloque una jeringa de 1" y calibre 20 utilizada para mezclar, con la tapa protectora en su lugar, en una jeringa de 1 ml. Sostenga la jeringa con firmeza y gire la tapa de la aguja en sentido horario (hacia la derecha) hasta que se cierre en forma segura. (Consulte la Figura B)

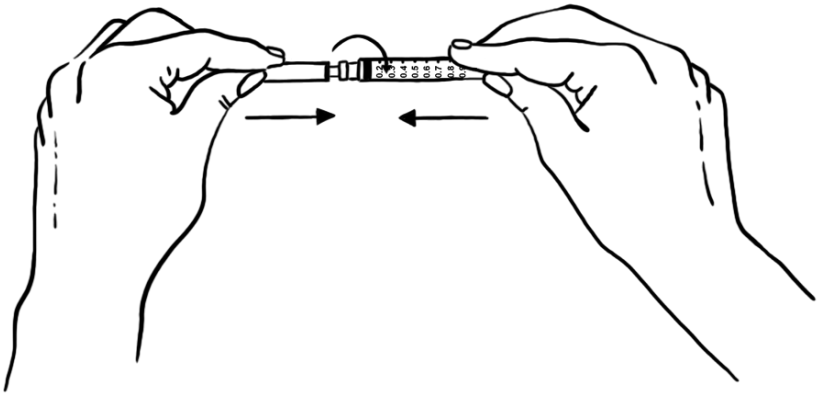

Figura B

Paso 2: Retire cuidadosamente la tapa protectora de la aguja tirando hacia afuera en línea recta. **No** gire la tapa de la aguja.
Inserte la aguja a través del tapón de caucho del frasco de agua estéril para inyección. (Consulte la Figura C)

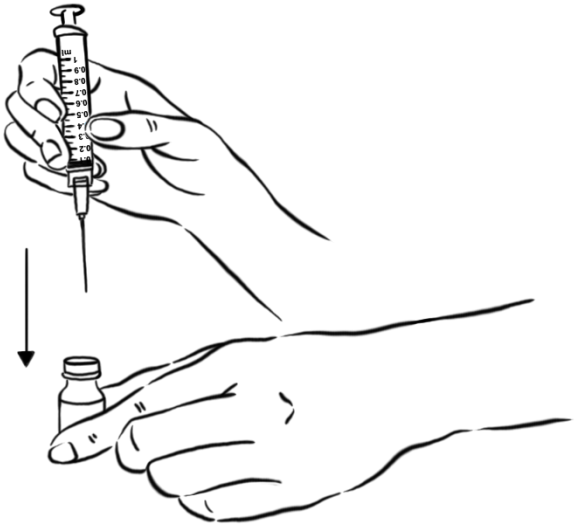

Figura C

Paso 3: Con la aguja aún insertada en el frasco de agua estéril para inyección, ponga el frasco y la jeringa boca abajo.
Tire del émbolo hasta que el agua estéril llegue a la marca de 0,5 ml en la jeringa. (Consulte la Figura D)

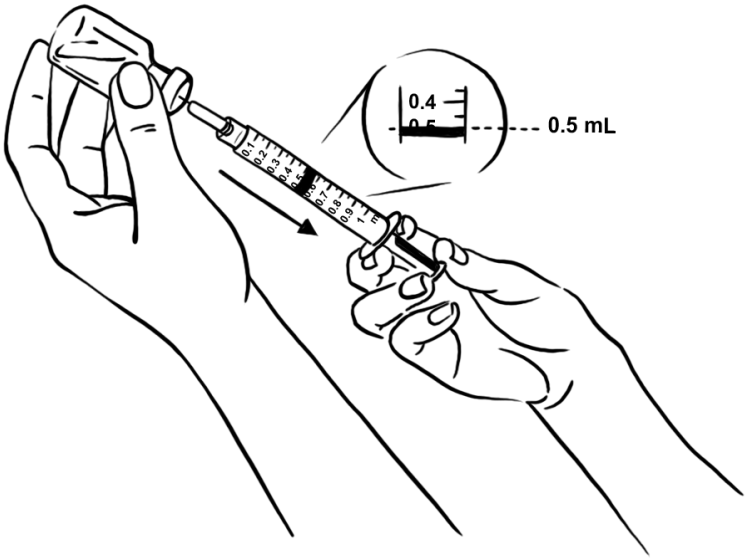

Figura D

- Deseche el frasco que contiene el agua estéril para inyección sin usar. (Consulte **"¿Cómo debo desechar las jeringas, agujas, frascos y viales usados?"**)

Paso 4: Retire la jeringa con aguja colocada del frasco de agua estéril.
Inserte la aguja en el tapón de caucho del vial de 2 mg de EGRIFTA SV.
Con la aguja en un leve ángulo, empuje lentamente el émbolo de la jeringa en todo su recorrido de modo que el agua estéril descienda por la pared interior del vial de 2 mg de EGRIFTA SV en lugar de directamente en el polvo para evitar la formación de espuma. (Consulte la Figura E)

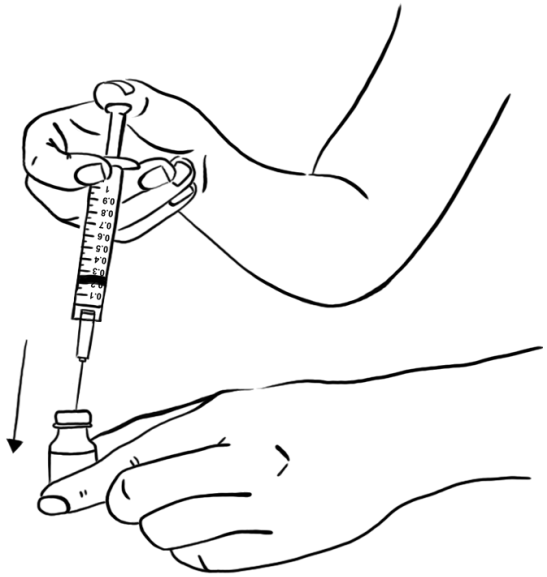

Figura E

Paso 5: Retire la aguja del vial de 2 mg de EGRIFTA SV (consulte la Figura F) y deseche la jeringa y la aguja. (Consulte **"¿Cómo debo desechar las jeringas, agujas, frascos y viales usados?"**)

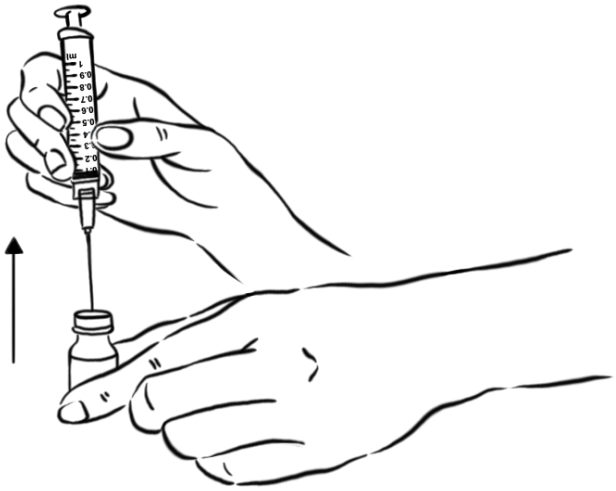

Figura F

Paso 6: Haga girar el vial de 2 mg de EGRIFTA SV suavemente en sus manos durante 30 segundos, hasta que el agua estéril y el polvo de EGRIFTA SV estén bien mezclados. **No** agite el vial. (Consulte la Figura G)

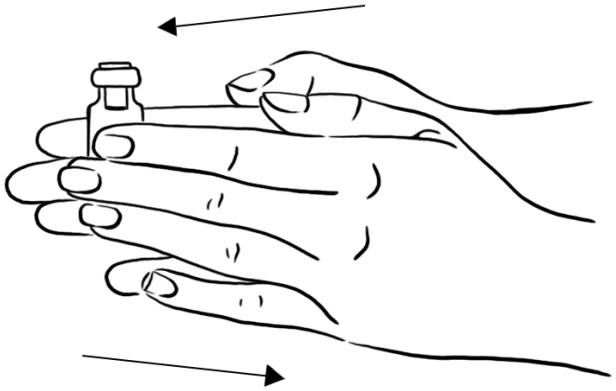

Figura G

Nota:

- Después de mezclar, la solución debe ser transparente e incolora y no debe tener partículas.
- No use EGRIFTA SV si tiene un aspecto turbio, descolorido o si se observan partículas.
- Llame a su proveedor de atención médica, al farmacéutico o comuníquese sin cargo THERA patient support™ al 1-833-23THERA (1-833-238-4372) de inmediato si la solución está turbia, descolorida o contiene partículas.

Paso 7: Coloque una nueva jeringa sin usar de 1" y calibre 20 utilizada para mezclar, con la tapa protectora en su lugar, en una nueva jeringa sin usar de 1 ml. Sostenga la jeringa con firmeza y gire la tapa de la aguja en sentido horario (hacia la derecha) hasta que se cierre en forma segura. (Consulte la Figura H)

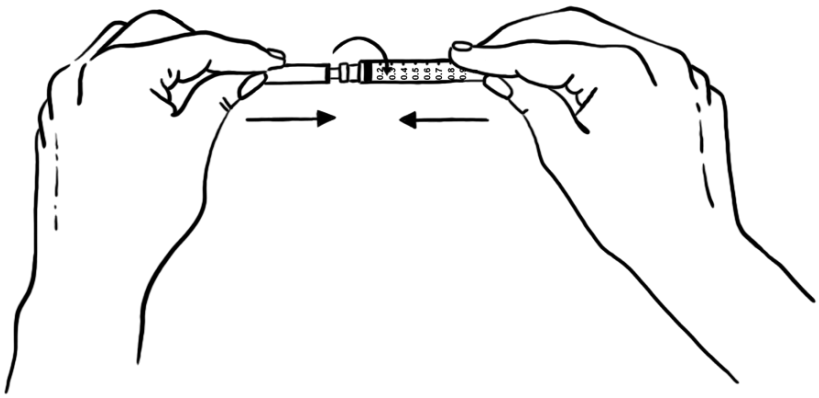

Figura H

Paso 8: Retire cuidadosamente la tapa protectora de la aguja tirando hacia afuera en línea recta. No gire la tapa de la aguja.
No deseche la tapa de la aguja.

Inserte la aguja a través del tapón de caucho del vial de 2 mg de EGRIFTA SV. (Consulte la Figura I)

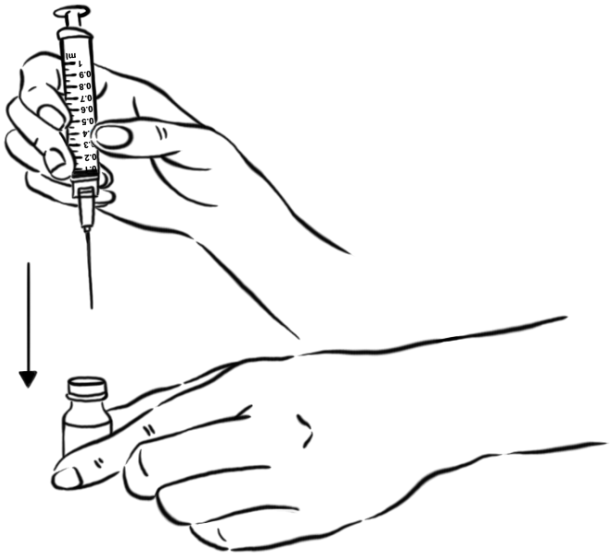

Figura I

Paso 9: Con la aguja todavía en el vial de 2 mg de EGRIFTA SV, ponga el vial y la jeringa boca abajo. Tire la jeringa hacia atrás hasta ver que solo la punta de la aguja atraviesa el tapón de caucho.
Tire del émbolo de la jeringa hasta que **todo** el líquido dentro del vial esté en la jeringa. El medicamento debe estar aproximadamente en la marca de 0,4 ml de la jeringa. (Consulte la Figura J)

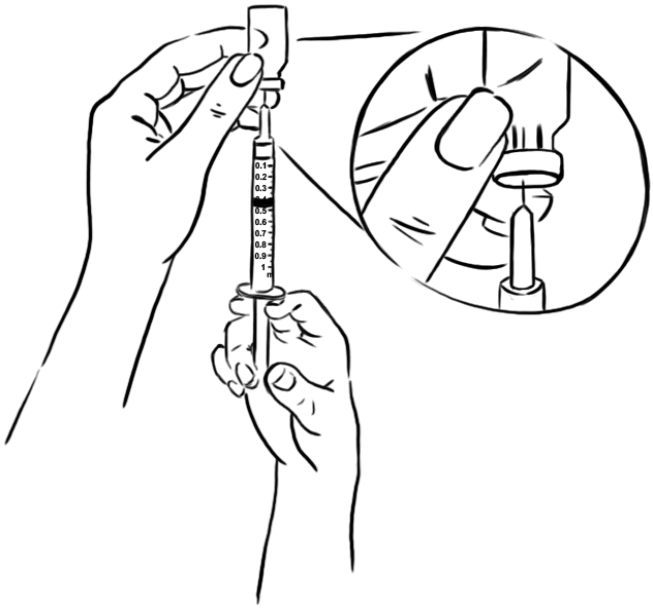

Figura J

Paso 10: Retire la aguja del vial. (Consulte la Figura K)

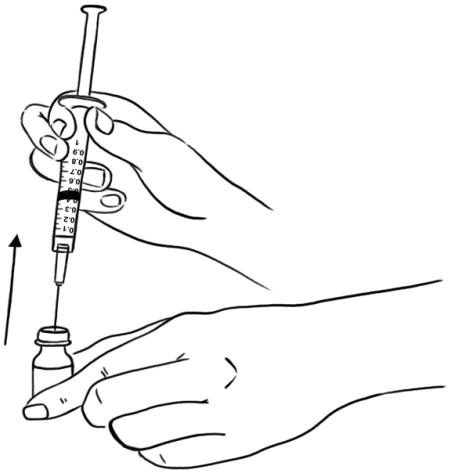

Figura K

Paso 11: Coloque la tapa protectora a un costado en una superficie limpia y plana. Sin tocar la aguja, sostenga la jeringa y deslice la aguja cuidadosamente hacia la tapa de la aguja. (Consulte la Figura L)

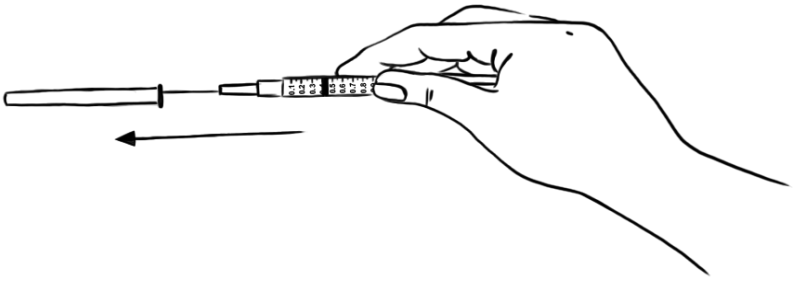

Figura L

Paso 12: Empuje la tapa protectora de la aguja en todo su recorrido o hasta que encaje en su lugar (consulte la Figura M). **No** toque la tapa de la aguja hasta que cubra la aguja por completo.

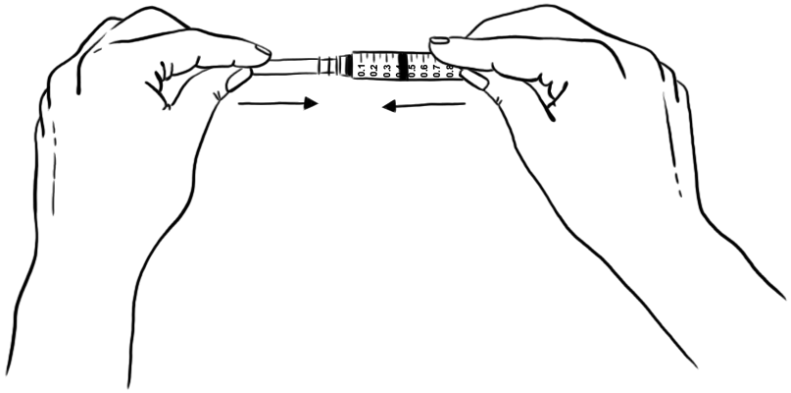

Figura M

Paso 13: Con la tapa protectora de la aguja colocada en la aguja de manera segura, retire la aguja sosteniendo la jeringa firmemente y girando la tapa de la aguja en sentido antihorario (hacia la izquierda). (Consulte la Figura N) Deseche la aguja. (Consulte **"¿Cómo debo desechar las jeringas, agujas, frascos y viales usados?"**)

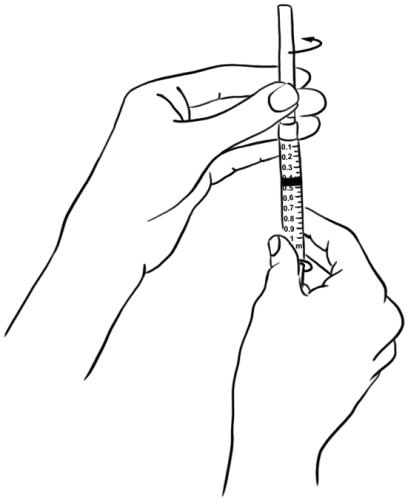

Figura N

Paso 14: Coloque en la jeringa una aguja de ½" y calibre 30 para la inyección, con la tapa protectora de la aguja y la protección de la aguja de color rosa colocadas. Sostenga la jeringa con firmeza y gire la tapa de la aguja y la protección de la aguja de color rosa en sentido horario (hacia la derecha) hasta que se cierre en forma segura. (Consulte la Figura O)

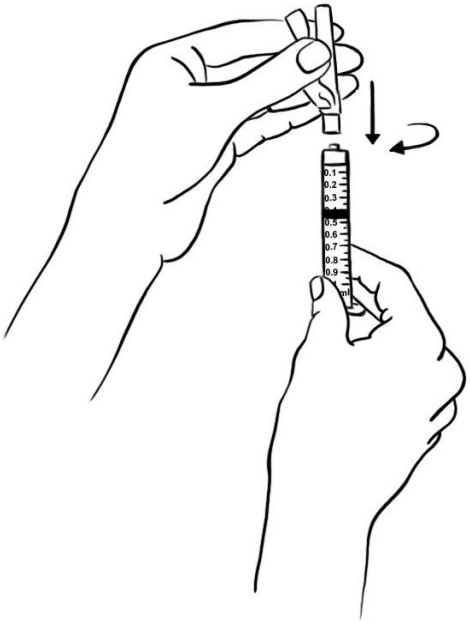

Figura O

¿Dónde debo inyectar el vial de 2 mg de EGRIFTA SV?

Inyecte EGRIFTA SV en el área del estómago (abdomen). (Consulte la Figura P)

- Elija un lugar de aplicación de la inyección que se encuentre a una distancia mínima de 2 pulgadas (5 cm) del ombligo. (Consulte el área sombreada en la Figura P)
- **No** se inyecte en áreas con tejido cicatrizal o moretones.
- **No** se inyecte en el ombligo.
- Evite las zonas en las que haya protuberancias duras a causa de inyecciones previas.
- Cambie el lugar de aplicación para cada inyección. Esto puede ayudar a prevenir la formación de moretones o irritación. Es conveniente anotar la fecha y la ubicación de cada inyección diaria para ayudarlo a recordar.

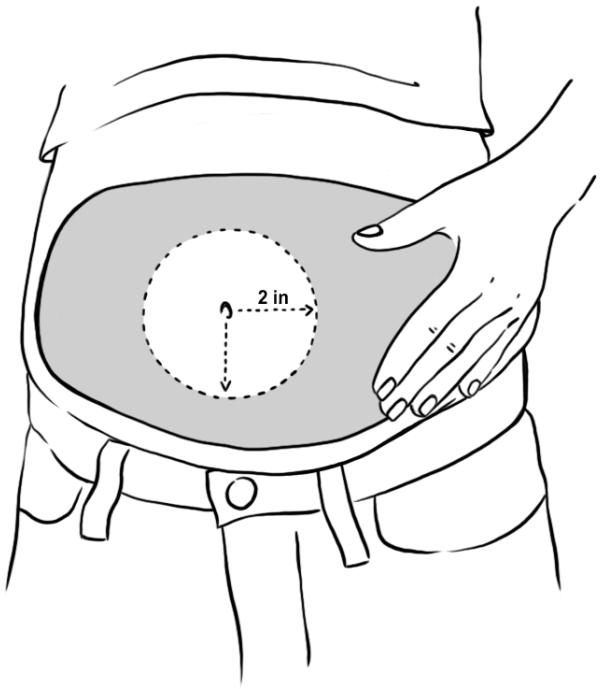

Figura P

Cómo inyectarse la dosis de 1,4 mg de EGRIFTA SV

No quite la tapa de la aguja hasta que esté listo para inyectarla.

Paso 1: Sostenga la jeringa con la aguja hacia arriba. Retire la protección de la aguja de color rosa de la tapa blanca protectora de la aguja.

Retire cuidadosamente la tapa de la aguja tirando hacia afuera en línea recta. **No** gire la tapa de la aguja. (Consulte la Figura Q)
No toque la aguja.

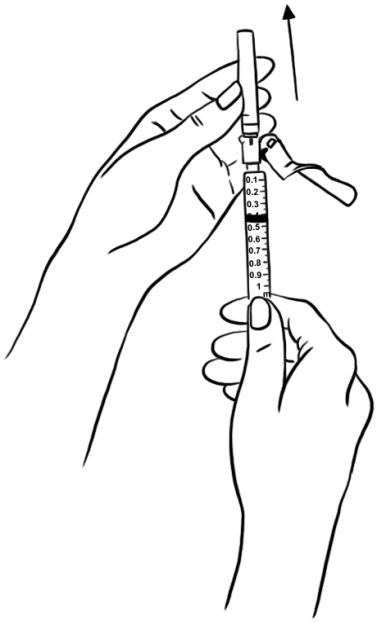

Figura Q

Paso 2: Dé golpecitos ligeros y suaves con el dedo para hacer que las burbujas de aire suban. Presione lentamente el émbolo para que salga el aire y las burbujas y hasta que el medicamento en la jeringa se encuentre en la marca de 0,35 ml de la jeringa. (Consulte la Figura R)

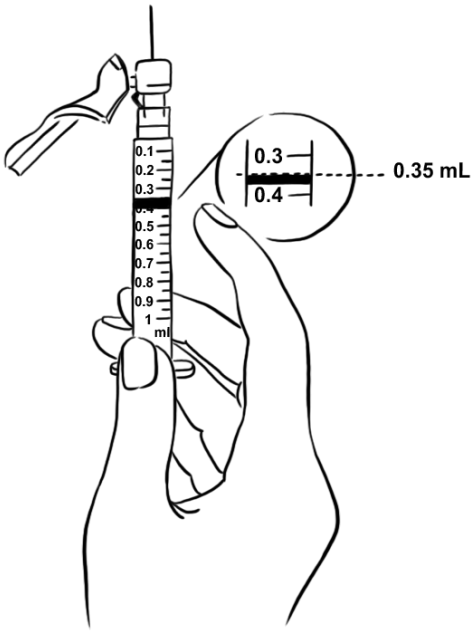

Figura R

Paso 3: Limpie el lugar de la inyección que ha seleccionado con un paño con alcohol y déjelo secar. Sostenga la jeringa con una mano. Con la otra mano, pellizque suavemente un pliegue de piel en el lugar de inyección limpio. Sostenga la piel entre el pulgar y los dedos de las manos. (Consulte la Figura S)

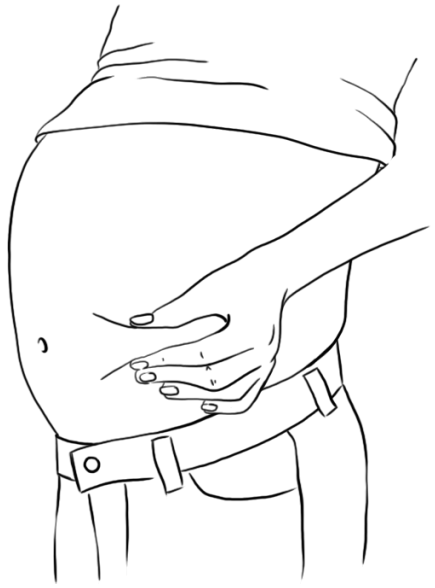

Figura S

Paso 4: Sostenga la jeringa en un ángulo de 90 grados respecto de la piel.
Con un movimiento rápido, como cuando se tira un dardo, inserte la aguja en la piel. Casi toda la aguja debe quedar debajo de la piel. (Consulte la Figura T)

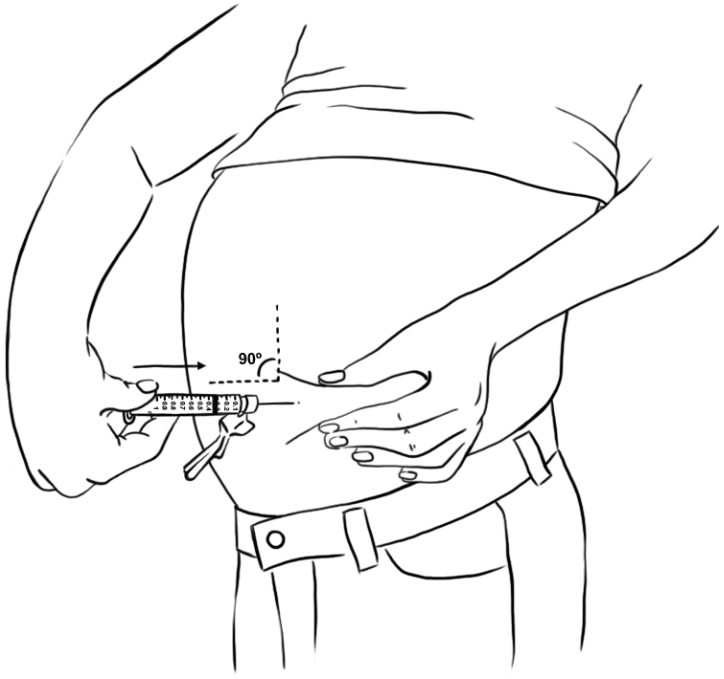

Figura T

Paso 5: Retire la mano del área de la piel pellizcada después de insertar la aguja. Tenga cuidado de no retirar la aguja de la piel.

Paso 6: Lentamente, empuje el émbolo de la jeringa hasta que todo el medicamento en la jeringa se haya inyectado. (Consulte la Figura U)

Figura U

Retire la aguja de la piel. Tenga cuidado de retirar la aguja en el mismo ángulo en el que se insertó.

Paso 7: Mientras sostiene la jeringa en una mano, presione suavemente la protección de la aguja de color rosa contra una superficie plana y firme hasta escuchar un “clic” y la aguja de la inyección quede cubierta por la protección de la aguja de color rosa. (Consulte la Figura V)

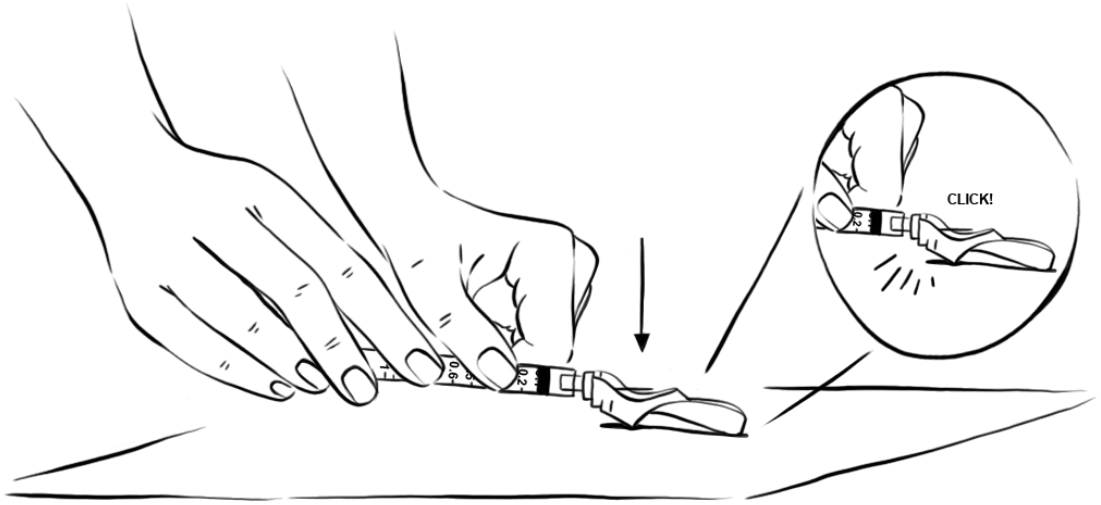

Figura V

- Aplique presión en el lugar de la inyección con la gasa durante 30 segundos. Si se produce sangrado, aplique una venda adhesiva en el lugar.
- Deseche la jeringa. (Consulte **"¿Cómo debo desechar las jeringas, agujas, frascos y viales usados?"**)

¿Cómo debo desechar las jeringas, agujas, frascos y viales usados?

- **No** vuelva a tapar la aguja ni retire la aguja de la jeringa después de inyectarse EGRIFTA SV.
- Coloque las agujas y las jeringas de EGRIFTA SV usadas en un recipiente para objetos punzocortantes aprobado por la Administración de Alimentos y Medicamentos (Food and Drug Administration, FDA) inmediatamente después de usar. **No deseche (tire) ninguna aguja o jeringa suelta en la basura del hogar.**
- Si no tiene un recipiente para objetos punzocortantes aprobado por la FDA, puede usar un recipiente doméstico que:
    - esté hecho de plástico duro;
    - pueda cerrarse bien fuerte, con tapa resistente a punciones, de manera que los objetos punzantes no puedan salirse;
    - esté vertical y estable durante el uso;
    - sea resistente a filtraciones; y
    - este adecuadamente etiquetado para advertir que contiene desechos peligrosos en su interior.
- Cuando el recipiente para objetos punzocortantes esté casi lleno, deberá seguir las pautas de su comunidad para el desecho adecuado de este tipo de recipiente. Pueden existir leyes estatales o locales acerca de cómo se deben desechar las agujas y las jeringas usadas. Para obtener más información acerca de cómo desechar objetos punzocortantes de manera segura e información específica sobre el desecho de objetos punzocortantes en su estado de residencia, visite el sitio web de la FDA: http://www.fda.gov/safesharpsdisposal.
- **No** deseche el recipiente para objetos punzocortantes usado en la basura de su hogar, a menos que las pautas de su comunidad lo permitan. **No** recicle el recipiente para objetos punzocortantes.
- Si otra persona se pincha con una aguja usada, se debe informar a esa persona que se comunique con un proveedor de atención médica de inmediato.
- Mantenga el recipiente de objetos punzocortantes lejos de niños y mascotas.

Si tiene alguna pregunta, llame a su proveedor de atención médica.
Puede llamar sin cargo THERA patient support™ al 1-833-23THERA (1-833-238-4372) o visitar el sitio web de EGRIFTA SV en www.EGRIFTASV.com para obtener más información.

¿Cómo debo almacenar los viales de 2 mg de EGRIFTA SV, el agua estéril para inyección, las jeringas y las agujas?

- La farmacia le entregará 2 cajas cuando reciba su medicamento recetado EGRIFTA SV:

- Almacene los viales de 2 mg de EGRIFTA SV en la caja del medicamento en la que vienen, a temperatura ambiente, entre 68 °F y 77 °F (entre 20 °C y 25 °C).
- Almacene el agua estéril para inyección, las jeringas y las agujas que vienen en la caja de la inyección a temperatura ambiente, entre 68 °F y 77 °F (entre 20 °C y 25 °C).

- Mantenga los viales de EGRIFTA SV fuera de la luz.
- Después de mezclar, uso EGRIFTA SV **de inmediato.** Deseche cualquier resto de EGRIFTA SV sin usar después de mezclar.
- **No** almacenar, congelar ni refrigerar EGRIFTA SV después de haberlo mezclado con el agua estéril.
- Deseche el agua estéril para inyección que quede en el frasco después de su uso.
- No use EGRIFTA SV después de la fecha de vencimiento (VENC.) impresa en la caja y las etiquetas del vial.

Mantenga EGRIFTA SV y todos los medicamentos fuera del alcance de los niños.

Estas Instrucciones de uso han sido aprobadas por la Administración de Alimentos y Medicamentos de los EE. UU.

THERA technologies

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Revisado: 07/2019

Instructions for Use

EGRIFTA SV™ (eh-GRIF-tuh ESS-vee)
(tesamorelin for injection)
for subcutaneous use
2 mg vial

This Instructions for Use contains step-by-step information on how to use the **2 mg vial** of EGRIFTA SV. **Each 2 mg vial of EGRIFTA SV must be mixed with 0.5 mL of the Sterile Water for Injection** provided in the Injection Box given to you by the pharmacy. **Use only one** EGRIFTA SV 2 mg **vial from the Medication Box** to prepare your dose. The recommended **dose of EGRIFTA SV is 1.4 mg (0.35 mL).**

Be sure that you read, understand, and follow this Instructions for Use before using EGRIFTA SV. Your healthcare provider should show you how to mix and inject EGRIFTA SV before you inject it for the first time. Ask your healthcare provider if you have any questions.

Keep this Instructions for Use in case you need to look at it again later.

Important information for use of EGRIFTA SV

- **Do not** use a syringe or needle more than 1 time.
- **Do not share your syringe or needles with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.**
- If you are missing any supplies from the boxes given to you by the pharmacy or if any of the supplies look damaged, call your pharmacist or contact THERA patient support™ toll-free at 1-833-23THERA (1-833-238-4372) right away.

Preparing for your EGRIFTA SV injection

Step 1: Find a well-lit, clean, and flat surface, such as a table.

Step 2: Gather your supplies:

- Medication Box that contains 30 EGRIFTA SV 2 mg single-dose vials
- Injection Box that contains the following:
  - 30 single-dose 10 mL bottles of Sterile Water for Injection, used for mixing
  - 60 sterile 1 mL syringes
  - 60 sterile 1" 20-gauge needles, used for mixing
  - 30 sterile ½" 30-gauge needles, used for injection
- Other Supplies Needed
  - Two alcohol pads
  - One sterile gauze
  - One adhesive bandage
  - Sharps disposal container or a puncture resistant container for throwing away used needles and syringes after you are done with them. (See "**How should I dispose of the used syringes, needles, bottles and vials?**")

For each injection using EGRIFTA SV 2 mg vial you will need: (See Figure A)

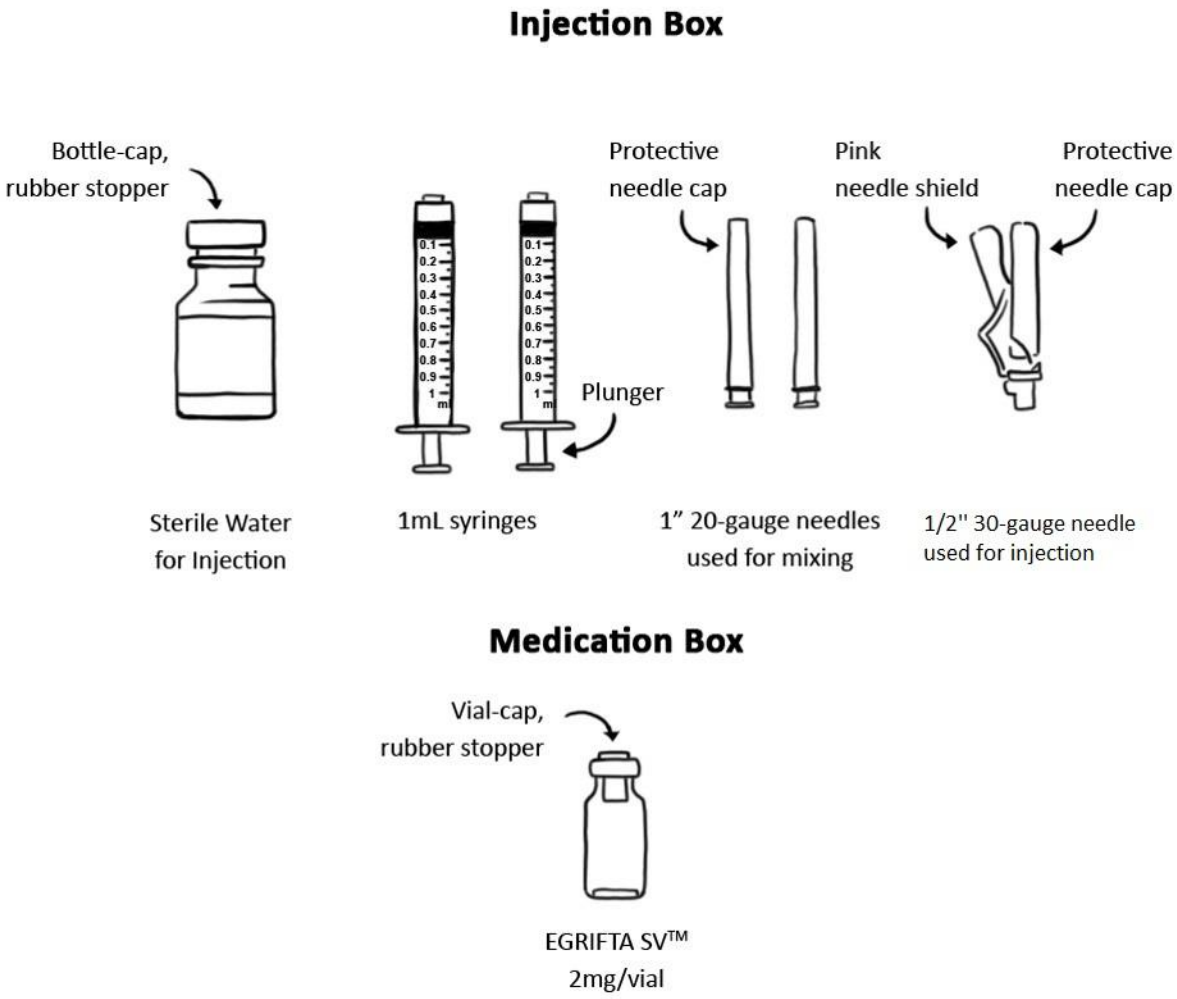

Figure A

Step 3: Take out the following from the Injection Box:

- One Sterile Water for Injection bottle
- Two 1 mL syringes
- Two 1" 20-gauge needles used for mixing
- One ½" 30-gauge needle used for injection

Step 4: Take **1 vial** of EGRIFTA SV 2 mg from the Medication Box.

Step 5: Prepare to use your supplies:

- Wash your hands with soap and water. Dry your hands with a clean towel.
- Take off the plastic caps from the EGRIFTA SV 2 mg vial and the Sterile Water for Injection bottle.
- Clean the rubber stoppers on the top of the EGRIFTA SV 2 mg vial and Sterile Water for Injection bottle with an alcohol pad.

How to mix EGRIFTA SV 2 mg vial

Step 1: Place a 1" 20-gauge needle used for mixing, with its protective needle cap in place, onto a 1 mL syringe. Hold the syringe firmly and twist the needle cap clockwise (to the right) until it closes securely. (See Figure B)

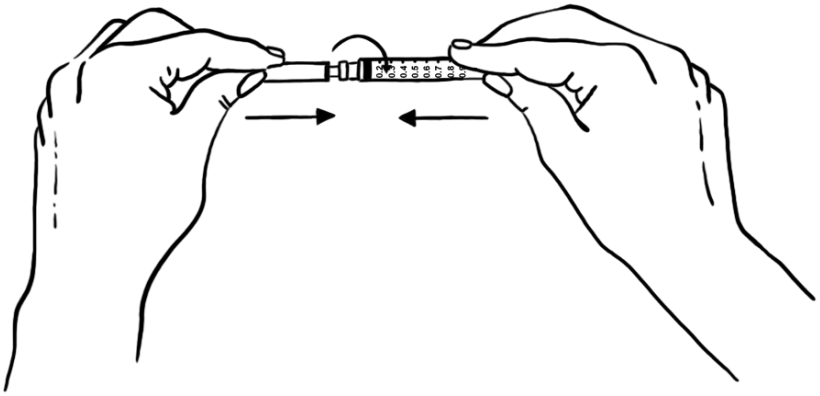

Figure B

Step 2: Carefully remove the protective needle cap by pulling it straight off. **Do not** twist the needle cap.
Insert the needle through the rubber stopper of the Sterile Water for Injection bottle. (See Figure C)

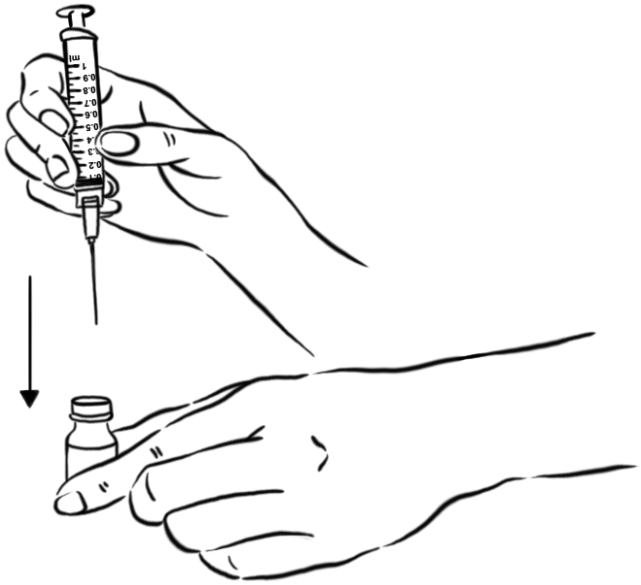

Figure C

Step 3: With the needle still in the Sterile Water for Injection bottle, turn the bottle and syringe upside down.
Pull back the plunger until the Sterile Water reaches the 0.5 mL mark on the syringe. (See Figure D)

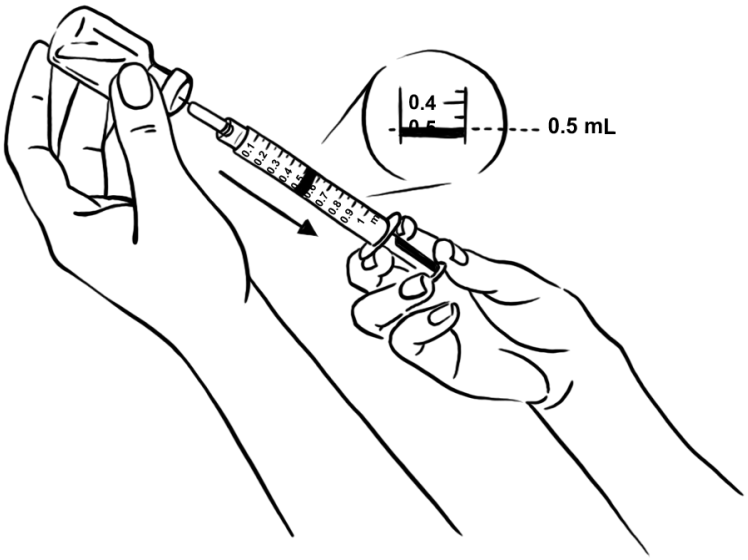

Figure D

- Throw away the bottle containing the unused Sterile Water for Injection. (See **"How should I dispose of the used syringes, needles, bottles and vials?"**)

Step 4: Remove the syringe with needle attached from the Sterile Water bottle.
Insert the needle into the rubber stopper of the EGRIFTA SV 2 mg vial.
With the needle at a slight angle, slowly push the plunger of the syringe all the way down so that the Sterile Water goes down the inside wall of the EGRIFTA SV 2 mg vial instead of directly onto the powder to avoid foaming. (See Figure E)

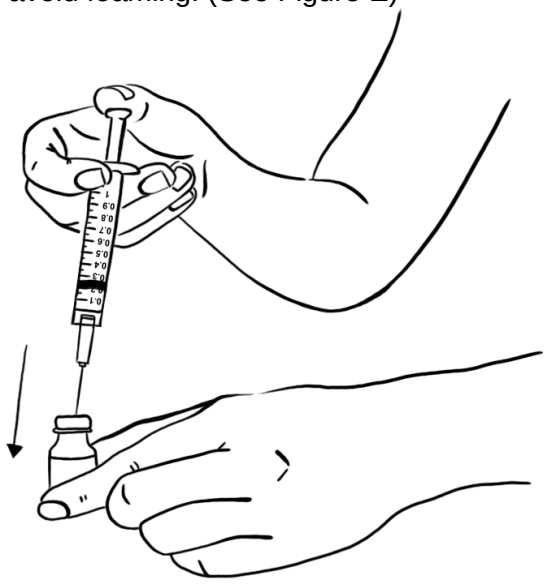

Figure E

Step 5: Remove the needle from the EGRIFTA SV 2 mg vial (see Figure F) and throw away the syringe and needle. (See **"How should I dispose of the used syringes, needles, bottles and vials?"**)

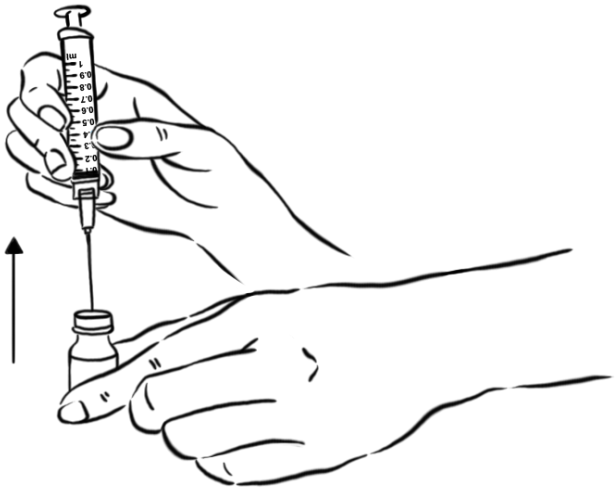

Figure F

Step 6: Roll the EGRIFTA SV 2 mg vial gently in your hands for 30 seconds, until the Sterile Water and EGRIFTA SV powder are mixed well. **Do not** shake the vial. (See Figure G)

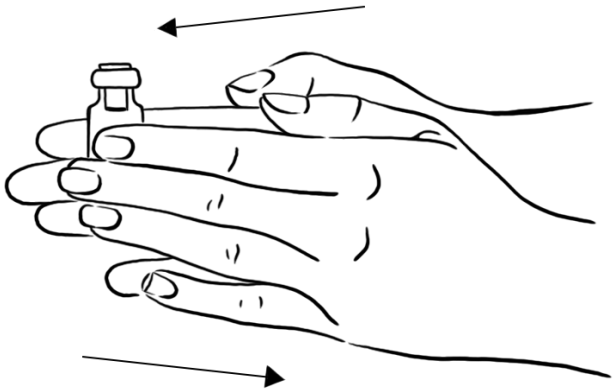

Figure G

Note:

- After mixing, the solution should look clear and colorless, with no particles in it.
- Do not use EGRIFTA SV if it looks cloudy, discolored, or if you see particles in it.
- Call your healthcare provider, pharmacist, or contact THERA patient support™ toll-free at 1-833-23THERA (1-833-238-4372) right away if the solution is cloudy, discolored, or contains particles.

Step 7: Place a new unused 1" 20-gauge needle used for mixing, with its protective needle cap in place, onto a new unused 1 mL syringe. Hold the syringe firmly and twist the needle cap clockwise (to the right) until it closes securely. (See Figure H)

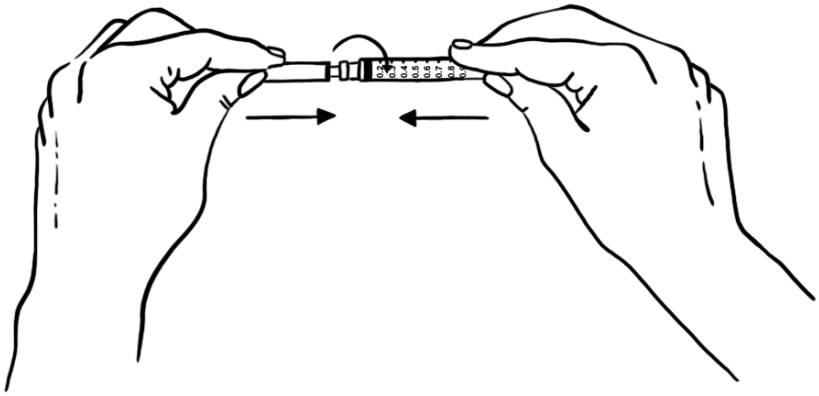

Figure H

Step 8: Carefully remove the protective needle cap by pulling it straight off. **Do not** twist the needle cap.
Do not throw away the needle cap.
Insert the needle through the rubber stopper of the EGRIFTA SV 2 mg vial. (See Figure I)

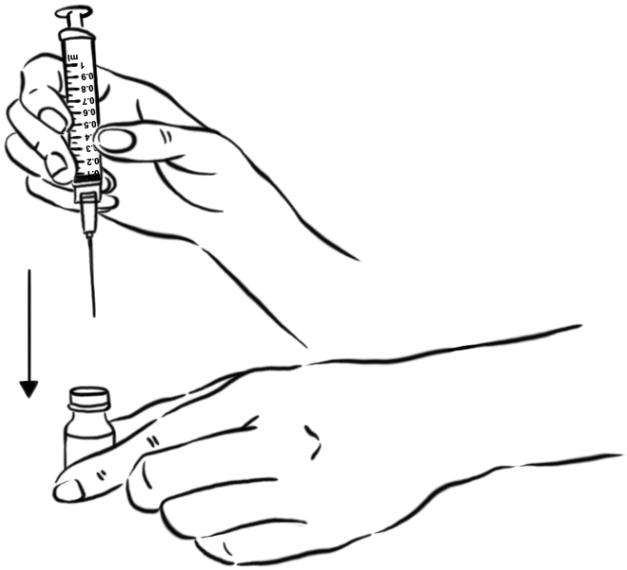

Figure I

Step 9: With the needle still in the EGRIFTA SV 2 mg vial, turn the vial and syringe upside down.
Pull the syringe back until you see just the tip of the needle going through the rubber stopper.
Pull back on the plunger of the syringe until **all** of the liquid inside the vial is in the syringe. The medicine should be at around the 0.4 mL mark on the syringe. (See Figure J)

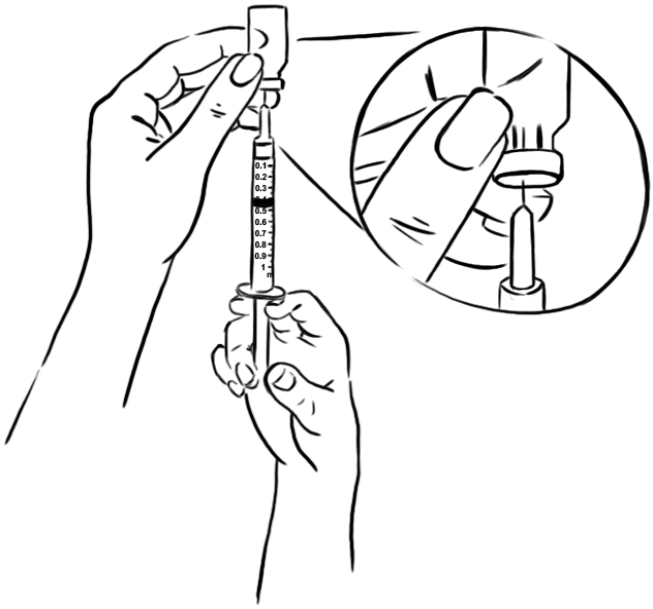

Figure J

Step 10: Remove the needle from the vial. (See Figure K)

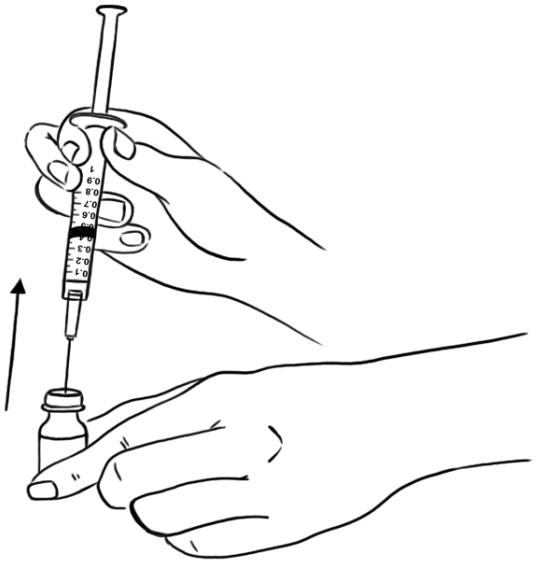

Figure K

Step 11: Place the protective needle cap on its side on a clean flat surface. Without touching the needle, hold the syringe and slide the needle carefully into the needle cap. (See Figure L)

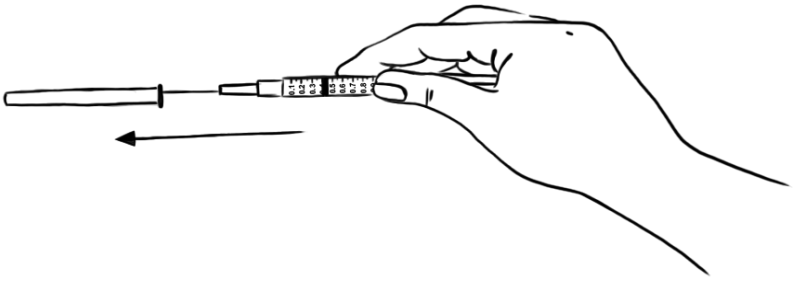

Figure L

Step 12: Push the protective needle cap all the way in or until it snaps shut (See Figure M). **Do not** touch the needle cap until it covers the needle completely.

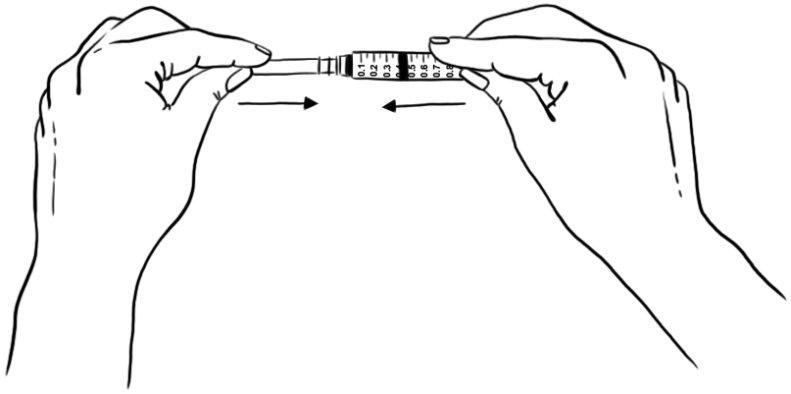

Figure M

Step 13: With the protective needle cap securely on the needle, remove the needle by holding the syringe firmly and twisting the needle cap counterclockwise (to the left). (See Figure N) Throw away the needle. (See **"How should I dispose of the used syringes, needles, bottles and vials?"**)

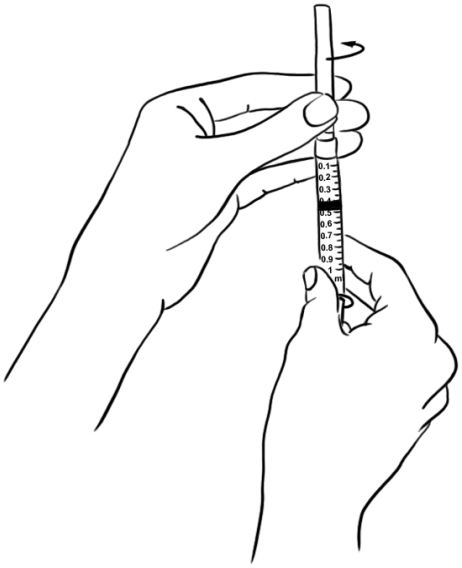

Figure N

Step 14: Place a ½" 30-gauge needle to be used for your injection, with its protective needle cap and pink needle shield in place, onto the syringe. Hold the syringe firmly and twist the needle cap and pink needle shield clockwise (to the right) until it closes securely. (See Figure O)

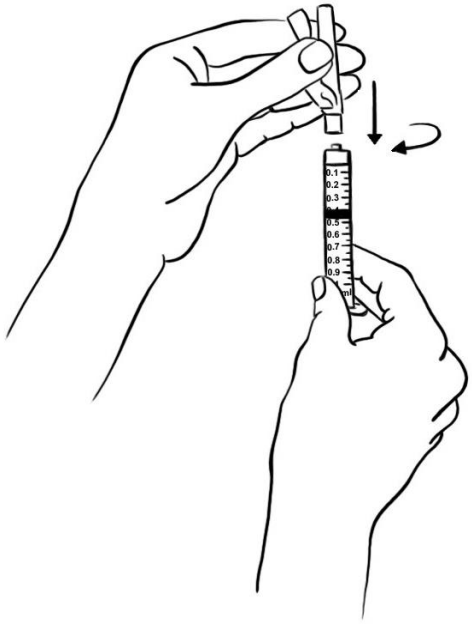

Figure O

Where do I inject EGRIFTA SV 2 mg vial?

Inject EGRIFTA SV into the stomach-area (abdomen). (See Figure P)

- Choose an injection site that is at least 2 inches (5 cm) away from your belly button. (See the shaded area in Figure P)
- **Do not** inject into areas with scar tissue or bruises.
- **Do not** inject into your belly button.
- Avoid areas with any hard bumps from previous injections.
- Rotate the site for each injection. This may help prevent bruising or irritation. You may want to write down the date and location of each daily injection to help you remember.

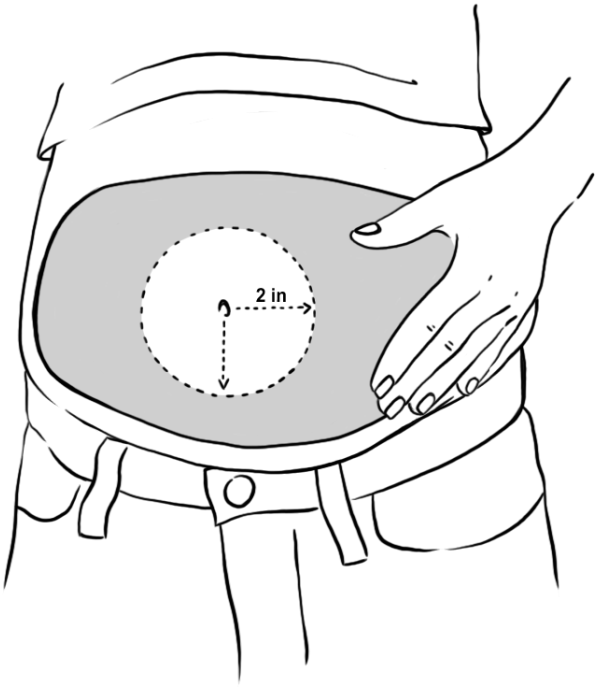

Figure P

How to inject your 1.4 mg dose of EGRIFTA SV

Do not remove the needle cap until you are ready to inject.

Step 1: Hold the syringe with the needle facing up. Pull the pink needle shield down away from the white protective needle cap.
Carefully remove the needle cap by pulling it straight off the needle. Do **not** twist the needle cap. (See Figure Q)
Do not touch the needle.

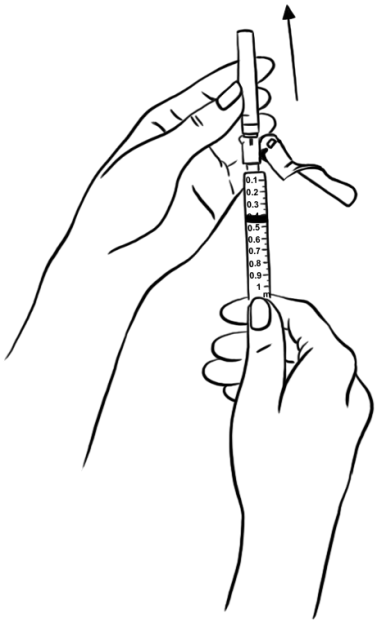

Figure Q

Step 2: Tap the syringe gently with your finger to force any air bubbles to rise to the top. Slowly push up on the plunger to remove any air and bubbles and until the medicine in the syringe is at the 0.35 mL mark of the syringe. (See Figure R)

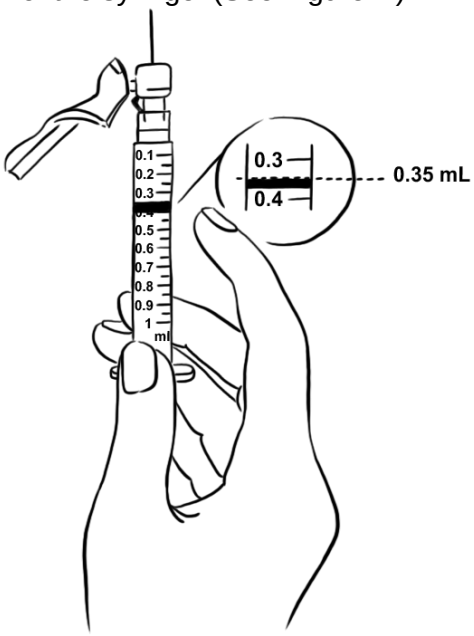

Figure R

Step 3: Clean the injection site you have selected with an alcohol pad and let it dry. Hold the syringe in one hand. With your other hand, gently pinch a fold of skin at your cleaned injection site. Hold the skin between your thumb and fingers. (See Figure S)

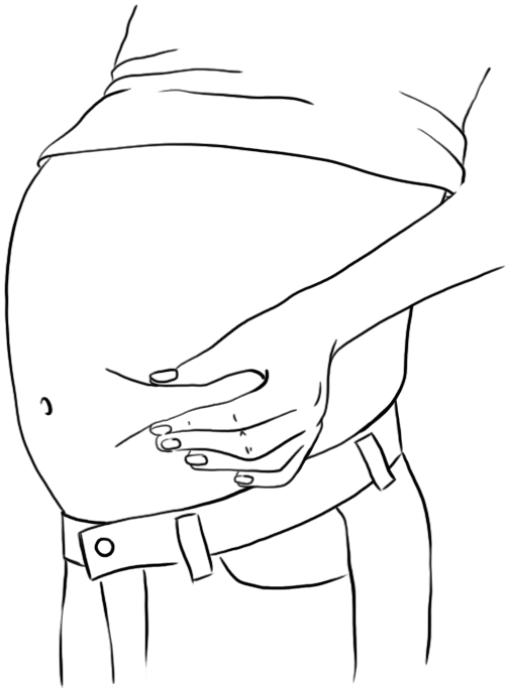

Figure S

Step 4: Hold the syringe at a 90 degree angle to the skin.
With a quick, dart-like motion, insert the needle straight into the skin. Most of the needle should go beneath the skin. (See Figure T)

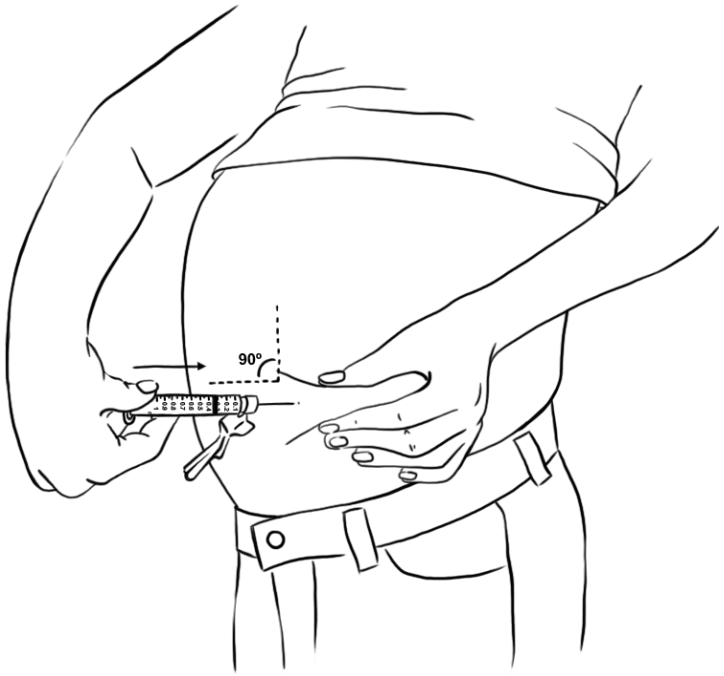

Figure T

Step 5: Remove your hand from the pinched area of skin after the needle is inserted. Be careful not to remove the needle from the skin.

Step 6: Slowly push the plunger of the syringe all the way down until all of the medicine in the syringe has been injected. (See Figure U)

Figure U

Pull the needle out of your skin. Be careful to pull the needle out at the same angle as it was inserted.

Step 7: While holding the syringe in one hand, gently press the pink needle shield against a hard, flat surface until you hear a “click” and the injection needle is covered by the pink needle shield. (See Figure V)

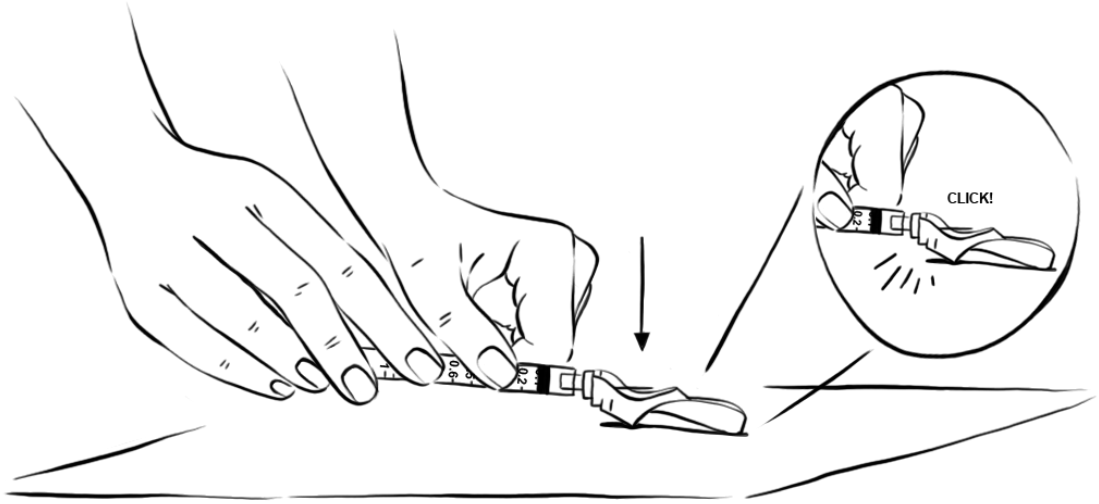

Figure V

- Apply pressure to the injection site with gauze for 30 seconds. If there is bleeding, apply an adhesive bandage to the site.
- Throw away the syringe. (See **“How should I dispose of the used syringes, needles, bottles and vials?”**)

How should I dispose of the used syringes, needles, bottles and vials?

- **Do not** recap the needle or remove the needle from the syringe after you inject EGRIFTA SV.
- Put your used EGRIFTA SV needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.
- If another person receives a needle stick with a used needle, that person should be told to contact a healthcare provider right away.
- Keep the sharps container away from children and pets.

If you have any questions, call your healthcare provider.
You can call THERA patient support™ toll-free at 1-833-23THERA (1-833-238-4372) or visit the EGRIFTA SV website at www.EGRIFTASV.com for more information.

How should I store EGRIFTA SV 2 mg vials, Sterile Water for Injection, syringes and needles?

- You will be given 2 boxes from the pharmacy when you get your prescription of EGRIFTA SV:
  - Store the 2 mg EGRIFTA SV vials in the Medication Box they come in, at room temperature between 68°F to 77°F (20°C to 25°C).
  - Store the Sterile Water for Injection, syringes and needles that come in the Injection Box at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep EGRIFTA SV vials out of the light.
- After mixing, use EGRIFTA SV **right away**. Throw away any unused EGRIFTA SV after mixing.
- **Do not** store, freeze or refrigerate EGRIFTA SV after it has been mixed with the Sterile Water.
- Throw away any Sterile Water for Injection left in the bottle after use.
- Do not use EGRIFTA SV after the expiration date (EXP) printed on the carton and vial labels.

Keep EGRIFTA SV and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

THERA technologies

Distributed by: Theratechnologies Inc., Montréal, Québec, Canada H3A 1T8

Revised: 07/2019

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

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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
05/16/2019 03:21:59 PM