

AWARD NUMBER: W81XWH-14-1-0599

TITLE: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness

PRINCIPAL INVESTIGATOR: Giulio Maria Pasinetti MD., PhD

CONTRACTING ORGANIZATION:
Icahn School of Medicine at Mount Sinai
New York, NY 10029-6504

REPORT DATE: October 2015

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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT There are no treatments for Gulf War Illness (GWI) and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications, particularly chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems. Recent evidence from our group and from others revealed that certain dietary flavonoids may promote cognitive function and/or alleviate chronic fatigue. We hypothesized that dietary supplementation with a Flavonoid- Rich Preparation (FRP), a combination of Concord Grape Juice (CGJ) and Grape Seed Polyphenolic Extract (GSPE) may help alleviate clinical complications of GWI, particularly chronic fatigue and/or cognitive dysfunction. We propose to test the feasibility of dietary supplementation with FRP in Veterans with GWI, and to gather evidence supporting the efficacy of FRP in alleviating GWI-associated cognitive deficits and chronic fatigue. Purpose: to conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP in improving cognition function and alleviating chronic fatigue in Veterans with GWI. Scope: Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI. Progress: We obtained FDA IND approval (IND 123889) for using FRP comprised of Concord grape juice and grape seed polyphenol extract to treat veteran GWI subjects. We also submitted IRB applications to our local institutions: the Icahn School of medicine at Mount Sinai (ISMMS) in New York, NY, and the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS) at East Orange, New Jersey. Since submission of our initial IND and IRB documents, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with a FRP comprised of only Concord grape juice. This amendment does not change the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have amended the SOW to reflect this modification. We have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment. We submitted to FDA an amendment for using only Concord grape FRP for our proposed studies in veterans with GWI. The amendment was approved by the FDA. We also submitted our amended protocol, using FRP with only Concord grape juice to the ISMMS IRB and the DVANJHCS IRB. The proposed amended protocol received ISMMS and DVANJHCS IRB approval (see appendices).					
15. SUBJECT TERMS					
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	37	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4
4. Impact.....	5
5. Changes/Problems	6
6. Products.....	6
7. Participants & Other Collaborating Organizations.....	7
8. Special Reporting Requirements.....	7
9. Appendices.....	7

1. INTRODUCTION

An estimated 174,300 to 230,000 US military service members deployed to Iraq and Afghanistan are affected by Gulf War Illness (GWI). GWI is characterized by the persistent presentation of multiple functional symptoms involving a combination of diverse complaints centering on chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems that are not explained by established medical diagnoses. While the etiology of the GWI symptom complex is not known, GWI clinical complications typically persist over long-terms, cause significant pain and suffering, and interfere with the ability of affected Veterans to successfully integrate back into the civilian society. There are no treatments for GWI and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications. Recent evidence from our group and from others revealed/highlighted the potential value of flavonoids, a subclass of organic chemical called polyphenols that are abundantly found in some plants and common dietary preparations, may help alleviate chronic fatigue and preserve against cognitive functions. Based on this, our overall goal is to test the potential efficacy of dietary supplementation with a Flavonoid-Rich Preparation (FRP) to alleviate clinical complications in Veterans with GWI. In particular, we proposed to conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP (Concord grape juice) in improving cognition function and alleviating chronic fatigue in Veterans with GWI. Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI.

2. KEYWORDS

Gulf War Illness

Polyphenol

Flavonoids

Flavonoid-Rich Preparation

Chronic fatigue

Cognitive difficulties

Muscle pain

Mood disturbances

Sleep problems

3. ACCOMPLISHMENTS

- ***Major goals of the project***

Obtain IND/IRB approval (Year 0 to 0.5)

- obtain FDA IND approval
- Obtain local institutional IRB approval (from the Icahn School of Medicine at Mount Sinai and from the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS))
- Obtain approval from the U.S. Army Human Research Protection Office (HRPO)

Recruit 60 volunteers (Year 0.5 to 1.17)

- randomized volunteers into a treatment and a placebo arm, n=30 per arm
- complete baseline clinical assessments
- collect and bank baseline blood specimen

FRP treatment (Year 0.7 to 1.5)

- initial dose-escalation finding phase (6 weeks) followed by a stable treatment dose (18 weeks)
- complete clinical assessments during and post treatment
- collect and bank blood post treatment

Complete analysis of blood polyphenol contents (Year 0.5 to 1.7)

Complete data analysis and manuscript preparation (Year 1.8 to 2)

- ***Accomplishments under these goals***

We originally proposed to treat GWI subjects using a FRP comprised of combined Concord grape juice and a grape seed polyphenol extract. We obtained IND approval from the FDA (IND 123889) to conduct this trial using the FRP in veterans with GWI. Moreover, we submitted an IRB application to the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS) at East Orange, New Jersey for recruiting GWI cases for the study, treating and monitoring participant subjects, and collecting and banking de-identified plasma specimens from these subjects for subsequent biochemical analysis at by investigators at the Icahn School of Medicine (ISMMS). We also submitted an IRB application to ISMMS for conducting biochemical analysis of banked de-identified blood specimen that will be provided by DVANJHCS.

Since submission of our initial IND and IRB documents, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with a FRP comprised of only Concord grape juice. The range of Concord grape juice doses proposed is within the range of efficacy for improving cognitive function in the elderly, as we discussed in the application. This amendment does not change the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have amended the SOW to reflect this modification. A copy of the amended SOW, stating GWI veterans will be treated with Concord grape juice, is attached (file name: Appendix 1 - amended SOW). We have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment. Therefore, we submitted to FDA an amendment for using only Concord grape for our proposed studies in veterans with GWI. The amendment was approved by the FDA. We attached a copy of the notification from the FDA confirm IND approval for using a FRP comprised of Concord grape juice + grape seed polyphenol extract (file name: Appendix 2 - IND 123889 initial approval), and a copy of a subsequent communication from the FDA confirming we can treat veteran GWI subjects with a FRP comprised with only Concord grape juice (file name: Appendix 3 - IND 123889 amendment approval). We also submitted our amended protocol, using only Concord grape juice to the ISMMS IRB and the DVANJHCS IRB. The proposed amended protocol received ISMMS IRB approval. We attached a copy of the communication from the ISMMS IRB confirming IRB approval of the amended protocol (file name: Appendix 4 - ISMMS amended protocol approval). We received approval of the amended protocol from the DVANJHCS IRB (Appendix 5).

- ***Opportunities for training and professional development the project provided***

Nothing to Report

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

Nothing to Report

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

During the next reporting period, we aim to obtain HRPO approval to procure investigatory reagents and begin the initial subject recruitment. Enrolled subjects will be randomly assigned to the FRP or the control treatment arm. We will then collect baseline clinical assessment information and blood specimens from individual enrolled subjects and thereafter, proceed with FRP (or control) treatment.

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**

As we have noted above, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with a FRP comprised of only Concord grape juice. This amendment does not change the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment.

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

As we have noted above, initiation of the study was delayed by the followings: i) submission to the FDA of an amendment to the previously approved IND 123889, to seek FDA approval to treat GWI subjects with only Concord grape juice, ii) submission of local institutional IRB amendments to the ISMMS and the DVANJHCS, seeking IRB approval to treat GWI subjects with only Concord grape juice. As we have discussed above, we received approvals for our amended protocol from the FDA and from the ISMMS IRB and DVANJHCS IRB.

- **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**

Removing grape seed polyphenol extract from the FRP formulation. GWI subjects will be treated with FRP comprised of only Concord grape juice.

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

Removing grape seed polyphenol extract from the FRP formulation. GWI subjects will be treated with FRP comprised of only Concord grape juice.

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

Not applicable

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

Removing grape seed polyphenol extract from the FRP formulation. GWI subjects will be treated with FRP comprised of only Concord grape juice.

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.**

Presentation to the Gulf War Research Advisory Committee (Appendix 6)

Presenter: Dr. Drew A. Helmer

Date: September 29, 2015

Presentation Title: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness

- **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?**

Dr. Giulio Pasinetti (PI, ISMMS): no change

Dr. Drew Helmer (clinical PI, VA NJHCS): no change

Dr. Lap Ho (co-investigator, ISMMS): no change

- **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?**

Nothing to Report

8.SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS: N/A**

- **QUAD CHARTS: N/A**

9.APPENDICES

Appendix 1 - Amended SOW

Appendix 2 - IND 123889 initial approval

Appendix 3 - IND 123889 amendment approval

Appendix 4 - ISMMS IRB Approval

Appendix 5 - NJ VA IRB Approval

Appendix 6 - Presentation to the Gulf War Research Advisory Committee

STATEMENT OF WORK
PROPOSED START DATE 09/30/2014

A). Specific Aims of the proposal.

Specific Aim 1: Conduct a randomized, double-blind Phase I/IIA study to explore dose, compliance, safety, and tolerability of FRP over 6 months, and to assess the efficacy of FRP in improving cognitive function and alleviating chronic fatigue in Veterans with GWI.

We propose to conduct a randomized, double-blind, placebo-controlled Phase I/IIA clinical proposal to test the feasibility/safety of treating veterans with Gulf War Illness with a Flavonoid-Rich Preparations [FRP; comprised a Concord grape juice (CGJ)], and to gather evidence supporting therapeutic efficacy in this population. This study will involve 2 groups, n=30 each for the FRP and the placebo arm. The overall study duration is 6 months. The study design is as follow: Subjects will initially be treated with a low dose of FRP/placebo (daily 4 oz. juice or an equivalent dose of placebo beverage) for two weeks (weeks 0-2). Based on absence of Adverse Events (AEs), subjects will be treated with the moderate dose of FRP/placebo (daily 8 oz. juice or an equivalent dose of placebo beverage) for two weeks (weeks 3-4). Pending on absence of AEs, subjects will be treated with the high dose of FRP/placebo (daily 16 oz. juice or an equivalent dose of placebo beverage) for 2 weeks (weeks 5-6). Based on outcome from these dose-finding studies, individual will be treated with the highest tolerated dose of juice /placebo for the remaining duration of the 6-month study (weeks 7-24).

B). Prime Study and Sub award site:

Prime Study Site

Research Institution Name: Icahn School of Medicine at Mount Sinai (MSSM)

Address: 1468 Madison Avenue,
Annenberg 20-02b,
New York, NY 10029

PI: Giulio Maria Pasinetti, M.D., Ph.D.

Subaward site

Research Institution Name: The Department of Veterans Affairs New Jersey Health Care System (DVANJHCS)

Address: War Related Illness and Injury Study Center
385 Tremont Avenue, Mail Stop 129
East Orange, NJ 07018-1095

Partnering PI: Drew A. Helmer M.D., M.S

Specific Aim 1(specified in proposal)	Timeline	Site 1	Site 2
Major Task 1 – IND / IRB approval	Months		
Subtask 1: IND submission	1-3		Dr. Helmer
Subtask 2: IRB submission (MSSM)	1-3		Dr. Helmer
Subtask 3: IRB submission (DVANJHCS)	1-3	Dr. Pasinetti	
Milestone(s) Achieved: complete IRB/IND submission	1-3	Dr. Pasinetti	Dr. Helmer
Local IRB/IACUC Approval	3		
Milestone Achieved: HRPO/ACURO Approval	6		
Major Task 2: Volunteer recruitment and baseline assessments			
Subtask 1: Procurement of intervention reagents (Concord grape juice) and corresponding placebos (placebo beverage)	6-8	Dr. Pasinetti	Dr. Helmer
Subtask 2: recruit 60 veterans with Gulf War Illness	6-14		Dr. Helmer
Subtask 3: baseline clinical assessments ⁽¹⁾	6-14		Dr. Helmer
Subtask 4: baseline blood collection	6-14		Dr. Helmer
Subtask 5: quantifying polyphenol contents in banked baseline plasma	6-16	Dr. Pasinetti	
Milestone(s) Achieved: complete baseline recruitment and baseline clinical evaluation	14		Dr. Helmer
Milestone(s) Achieved: complete identification and quantification of baseline polyphenol contents in plasma	16		Dr. Helmer
Major Task 3: short-term dose finding study			
Subtask 1: short-term treatments with three escalating FRP dose	8-16		Dr. Helmer
Subtask 2: safety monitoring at the end of each FRP dose	8-16		Dr. Helmer
Subtask 3: clinical assessments at weeks 12 and 24 ⁽²⁾	8-16		Dr. Helmer

Subtask 4: blood collection at weeks 12 and 24	8-16		Dr. Helmer
Subtask 5: quantifying blood polyphenol levels	12-20	Dr. Pasinetti	
Milestone(s) Achieved: Complete stable dose FRP study	16		Dr. Helmer
Milestone(s) Achieved: complete blood polyphenol assessments from 12 week and 24 week blood specimens	20	Dr. Pasinetti	
Major Task 4: data analysis and manuscryption			
Subtask 1: complete data analysis	20-22	Dr. Pasinetti	Dr. Helmer
Subtask 2: complete preparation of manuscript(s) for publication	22-24	Dr. Pasinetti	
Milestone(s) Achieved: completion of the study	24	Dr. Pasinetti	Dr. Helmer
Milestone(s) Achieved: completion publication of study results	24	Dr. Pasinetti	Dr. Helmer

(1,2) clinical assessments at baseline, 12 months and 24 months: Brief Symptom Inventory, Neuropsychological Battery, Chalder Fatigue Scale Questionnaire, Alcohol, Smoking And Substance Use Screening, Pittsburgh Sleep Quality Index, Post-traumatic Stress disorder, Patient Health Questionnaire

If human subjects are involved in the proposed study, please provide the projected quarterly enrollment in the following table.

	Year 1				Year 2			
Target Enrollment (per quarter)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Site 1			18	18	18	6 (Q2: 4 th month only)		
Site 2								
Site 3								
Target Enrollment (cumulative)			18	36	54	60		



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123889

STUDY MAY PROCEED

Attention: Drew A. Helmer, MD
WRIISC, Department of Veterans Affairs
New Jersey Health Care System
385 Tremont Ave., Mail Stop 129
East Orange, NJ 07018-1095

Dear Dr. Helmer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mega Natural BP Grape seed Extract 150mg & 300mg Capsules, Concord Grape Juice.

We have completed our 30-day, safety review of your application and as communicated to you in an email from Teresa Wheelous of this Division of September 25, 2014, have concluded that you may proceed with your proposed clinical investigation for the treatment of cognitive deficits and chronic fatigue in veterans with Gulf War Illness.

In addition, we have the following comments for your consideration:

CLINICAL

1. Please provide the number of subjects in each cohort who will receive FRP or placebo during the initial dose-finding phase, and the number of subjects who will receive FRP or placebo during the stable-dose treatment phase.
2. Please provide the symptom checklist that will be used during safety monitoring.
3. Please provide details of the instructions given to the subjects for reporting AEs. Subjects should be monitored for all AEs throughout the study duration.
4. Please provide the list of blood parameters that will be monitored.

Please include these items in the appropriate sections of the protocol and submit an amended protocol.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all

submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

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 and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
10/16/2014

Amended FDA Approval (removing Grape seed Polyphenol Extract from the Study)

Ho, Lap

Subject: FW: Lap Ho. Mount Sinai School of Medicine - question RE FDA IND #123889

From: Wheelous, Teresa A [<mailto:Teresa.Wheelous@fda.hhs.gov>]

Sent: Thursday, October 22, 2015 5:29 PM

To: Helmer, Drew A.; Ho, Lap

Cc: Pasinetti, Giulio; Kishore, Vandna N; Fobler, Malusha M.

Subject: RE: Lap Ho. Mount Sinai School of Medicine - question RE FDA IND #123889

Dr. Drew,

A may proceed letter was mailed to you on Oct. 16, 2014, stating that your IND is now active.

Once an IND is allowed to proceed there are no additional review clocks for subsequent submissions. Ordinarily, we would not contact you regarding subsequent submissions unless there are some concerns. At this time, there are no concerns with the 7/15/15 submission.

I will forward your email to the team to confirm that there are no comments.

Again, I will only contact you if there are concerns regarding the 7/15/15 submission.

Regards,

Teresa

From: Helmer, Drew A. [<mailto:Drew.Helmer@va.gov>]

Sent: Thursday, October 22, 2015 4:41 PM

To: 'Ho, Lap'; Wheelous, Teresa A

Cc: Pasinetti, Giulio; Kishore, Vandna N; Fobler, Malusha M.

Subject: RE: Lap Ho. Mount Sinai School of Medicine - question RE FDA IND #123889

Hello again, Dr. Wheelous.

Our coordinator, Ms. Fobler, received verbal confirmation that there were no issues with our amendment request. Can we receive confirmation of that by email reply or some other enduring documentation?

Thanks in advance,
drew

Drew A. Helmer, MD, MS
Director- War Related Illness and Injury Study Center
VA- New Jersey Health Care System
East Orange, NJ
908-202-4382

From: Ho, Lap [<mailto:lap.ho@mssm.edu>]

Sent: Tuesday, August 11, 2015 11:45 AM

To: 'Wheelous, Teresa A'

Cc: Helmer, Drew A.; Pasinetti, Giulio; Kishore, Vandna N

Subject: [EXTERNAL] RE: Lap Ho. Mount Sinai School of Medicine - question RE FDA IND #123889

Dear Teresa:

I am writing to you on behalf of Dr. Drew Helmer, who is Sponsor of FDA IND #123889 entitled: "Development of dietary polyphenol preparations for treating Veterans with Gulf War illness". We have receive IND approval to proceed with the protocol. More recently, we decided to slightly modify protocol #123889. I wrote to Ms. Vandna Kishore for her advice on how best to seek IND approval for this modification. Based on Ms. Kishore's recommendations, we submit the updated protocol as an amendment, noting the changes made to the existing IND, and submitting hard copies of the amended protocol to the Central Document Room. The documents was sent to and received by the mail room on July 14, 2015. Since then, we have not receive any information regarding the status of application. Would it be possible for you to give us some idea when we should expect an decision from the FDA?


Thank you for your help in this matter.

Best regards,

Lap

From: Eshikena, Marilyn
Sent: Thursday, October 08, 2015 4:21 PM
To: Pasinetti, Giulio
Cc: Gursahai, Susan
Subject: UPDATED APPROVAL OF RESEARCH GCO# 13-1398

Importance: High



Icahn School
of Medicine at
Mount
Sinai

Institutional Review Board
Program for the Protection of Human Subjects

The Mount Sinai Medical Center
One Gustave L. Levy Place, Box 1081
New York, NY 10029-6574
T 212-824-8200
F 212-876-6789
icahn.mssm.edu/pphs

APPROVAL OF RESEARCH

Date: 10/8/2015

To: Giulio Maria Pasinetti, MD, PhD (giulio.pasinetti@mssm.edu)

On **10/7/2015**, an Institutional Review Board of the Mount Sinai School of Medicine, in accordance with Mount Sinai’s Federal Wide Assurances (FWA#00005656, FWA#00005651) to the Department of Health and Human Services approved the following human subject research from **10/7/2015** until **2/2/2016** inclusive:

Type of Review:	Modification Request for Approval
Project Title:	Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness
Investigator:	Giulio Maria Pasinetti, MD, PhD (Dept: PS - Psychiatry)
Project Information:	HS#: 14-01091 GCO#1: 13-1398(0001) Department Of The Army/Department of Defense
Sites:	VA
IND or IDE (if any):	IND# 123889; No IDEs;
Submission Details (if any):	Requesting modification to remove grape seed polyphenol extract from the study and to treat veteran GWI subjects with only Concord grape juice.

Between **12/17/2015** and **12/22/2015**, or within 30 days prior to study close, whichever is earlier, you are to submit a completed FORM HRP-212: Continuing/Final Review Progress Report and required attachments, in order to request continuing IRB approval or study closure. If IRB continuing review approval is not granted before the expiration date of **2/2/2016**, IRB approval of this research expires on that date.

- The IRB has determined that this research involves no greater than MINIMAL RISK. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45CFR.46.102; 21CFR50.3k).

In conducting this research you are required to follow the requirements listed in the **Investigator Manual**. If stamped approved consent forms are attached, use copies of these forms to document consent. IRB approval does not constitute or imply institutional support for the conduct of this research. Additionally, all required local committee approvals at each **research affiliate** site must be obtained prior to initiation.

cc: Study Contact(s): Susan Gursahai (susan.gursahai@mssm.edu)

Human Studies Subcommittee (IRB)

VA New Jersey Healthcare System

DVA New Jersey Health Care System • 385 Tremont Avenue • East Orange, NJ 07018 • Fax: 973-395-7184

IRB APPROVAL - DeNovo Resubmission

Date: November 3, 2015

From: Phil J. Whang, MD, Chairperson

Investigator: Drew A. Helmer, MD, MS

Protocol: Development of dietary polyphenol preparations for treating Veterans with Gulf War Illness

ID: 01327 Prom#: N/A Protocol#: N/A

The following items were reviewed at the 10/05/2015 meeting:

- Data Use Agreement - NJHCS and Icahn School of Medicine at Mount (08/19/2015; 10/05/2015)
- Request to Review Research Proposal/Project (09/12/2015; 10/05/2015)
- Abstract (09/15/2015; 10/05/2015)
- Research Protocol - Version 9/1/15 (09/01/2015; 10/05/2015)
- Advertisement - Recruitment Poster (09/15/2015; 10/05/2015)
- Budget Page (09/15/2015; 10/05/2015)
- Consent Form - Version 2 - 8/18/15 (08/18/2015; 10/05/2015)
- Consent Form - Version 2 - 8/18/15 (08/18/2015; 10/05/2015)
- Financial Disclosure Form - Giulio M. Pasinetti, MD, PhD (08/25/2015; 10/05/2015)
- Financial Disclosure Form - Hap Lo, PhD (08/25/2015; 10/05/2015)
- Financial Disclosure Form - Drew A Helmer, MD., MS (10/17/2014; 10/05/2015)
- Financial Disclosure Form - Omowunmi Osinubi (10/17/2014; 10/05/2015)
- HIPAA Authorization (08/18/2015; 10/05/2015)
- HIPAA Waiver Request - Partial Waiver for recruitment/screening purposes (08/18/2015; 10/05/2015)
- Recruitment Letter (09/15/2015; 10/05/2015)
- Revocation of Authorization for Use & Release (09/15/2015; 10/05/2015)
- ISO Checklist (09/01/2015; 10/05/2015)
- Privacy Checklist (09/01/2015; 10/05/2015)
- VANJHCS Research Application (08/18/2015; 10/05/2015)
- VANJHCS Research Application (08/18/2015; 10/05/2015)
- Waiver of Consent - Partial Waiver (08/18/2015; 10/05/2015)
- Welch's Letter of Support from Dr. Wightman (07/23/2015; 10/05/2015)
- Preliminary Screening and Recruitment Script (11/14/2014; 10/05/2015)
- Questionnaire / Survey - PCL; BTBIS; Food Frequency Questionnaire; BSI; (09/15/2015; 10/05/2015)

The following items were Approved at the 10/05/2015 meeting:

- Request to Review Research Proposal/Project (09/12/2015; 10/05/2015)
- Abstract (09/15/2015; 10/05/2015)
- Research Protocol - Version 9/1/15 (09/01/2015; 10/05/2015)
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Page 1 of 2

FWA00001281: The East Orange VAMC IRB & R&D is not connected with, has no authority over, and is not responsible for human research conducted at any other institution, except where a Memorandum of Understanding specifies otherwise. Separate consent forms, initial reviews, continuing reviews, amendments, and reporting of serious adverse events are required if the same study is conducted at multiple institutions.

- Consent Form - Version 2 - 8/18/15 (08/18/2015; 10/05/2015)
- Financial Disclosure Form - Giulio M. Pasinetti, MD, PhD (08/25/2015; 10/05/2015)
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The following items were Acknowledged (but do not require Approval) at the 10/05/2015 meeting:

- Data Use Agreement - NJHCS and Icahn School of Medicine at Mount (08/19/2015; 10/05/2015)
- Budget Page (09/15/2015; 10/05/2015)
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- Privacy Checklist (09/01/2015; 10/05/2015)

Approval is granted for a period of 12 months and will expire on 10/04/2016. Your Continuing Review is scheduled for 09/12/2016, and the requirements are attached.

The protocol was determined to have the following level of risk:
Greater than Minimal Risk

The protocol was determined to have the following level of benefit to participants:
No prospect for direct benefit to participants, but likely to yield generalizable knowledge

The protocol was approved for a maximum of 100 human subjects.

**A Partial Waiver for recruitment/screening purposes is Granted.
A Partial Waiver of consent is Granted.**

Investigator files must be retained for 6 years after the study closure date. Such records include: research records maintained by the investigator that span the entire lifecycle of the project and the records required by regulations such as the investigator's regulatory file.

Development of dietary polyphenol preparations for treating Veterans with Gulf War Illness

Presentation to the Gulf War Research
Advisory Committee

Tuesday, September 29, 2015

Drew A. Helmer, MD, MS

Presented by the **VA War Related Illness and Injury Study Center (WRIISC)**

Disclosures

- Department of Defense, Congressionally Directed Medical Research Program- GW130070
- Principal Investigator- Giulio Pasinetti, MD, PhD
- Co-Investigator- Lap Ho, PhD
- *"The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government."*
- *"This material is the result of work supported with resources and the use of facilities at the War Related Illness and Injury Study Center at VA-New Jersey Health Care System, East Orange, NJ and VA Office of Public Health."*

Rationale

- No established treatment for Gulf War Illness
- Flavonoids, a subclass of polyphenols, may help alleviate fatigue and cognitive dysfunction
- Innovative Treatment Evaluation Award
 - DoD CDMRP
 - Phase 1/2a randomized controlled trial

Pathophysiology

- Alterations in brain connectivity (3)
- Alterations in brain metabolism (4)
- Dysfunction in the cholinergic autonomic system (5)
- Dysfunction in dopamine/glutamatergic neurotransmission (6)
- Inflammatory responses (7, 17, 18).

Polyphenols

- Two or more benzene rings that each having at least one hydroxyl group (OH)
- abundant in fruits, vegetables, berries, tea, grapes and other plant sources
- potential health benefits, including
 - cancer prevention (8)
 - reducing the risk of heart disease (9)
 - protection against neurodegenerative disorders (10)

Cognition

■ Preclinical

- Flavonoid subclass Concord purple grape juice (CGJ) effectively promote neuronal plasticity mechanisms that play a major role in learning and memory functions (11;12).
- Bioavailable, bioactive, brain-penetrating

■ Clinical

- 16-weeks of dietary supplementation with CGJ (15 - 21 oz. per day) improved cognitive function of older adults with mild cognitive impairment (14)

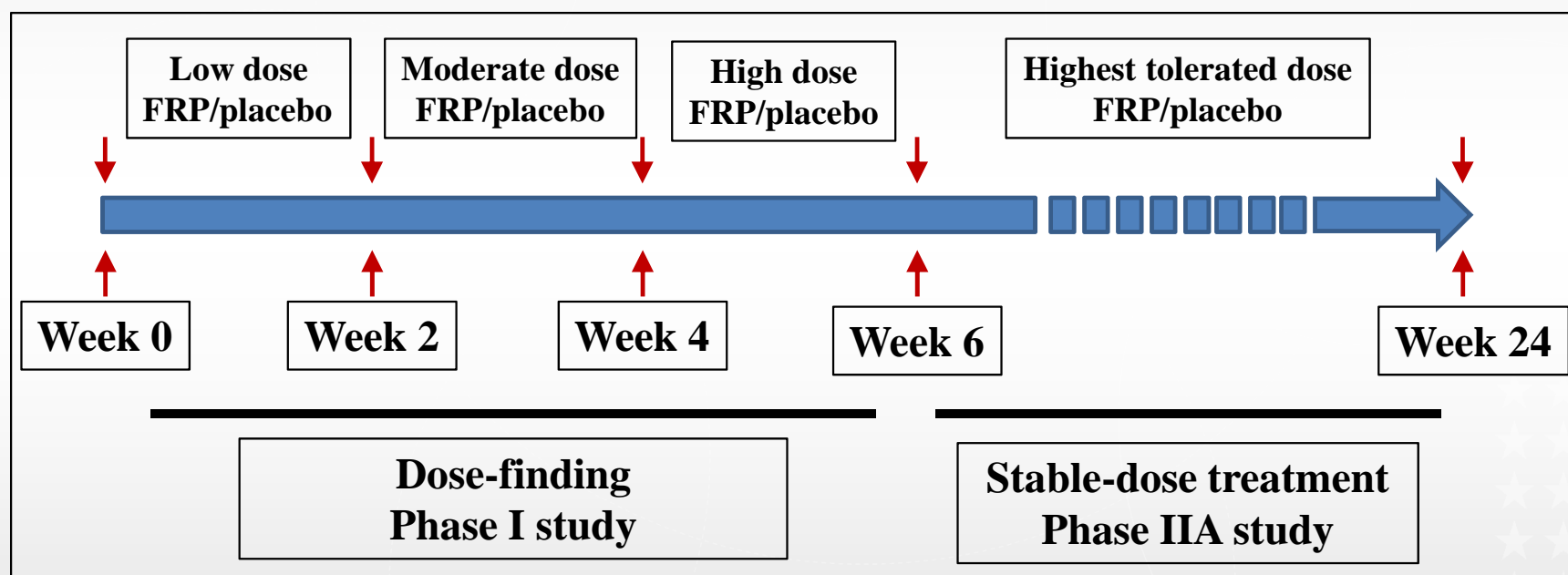
Fatigue & Inflammation

- Chocolate, which contains a high quantity of many flavonoids found in CGJ, significantly reduced subjects' self-reports of fatigue (15).
- Flavonoids are potent anti-inflammatory reagents (16).

Safety and Tolerability

- Two human studies (Krikorian (14)) and Novotney (unpublished) demonstrate no adverse effects of 16 oz CGJ daily.
- In both studies, the CGJ was well tolerated.

Study Design



Presented by the **VA War Related Illness and Injury Study Center (WRIISC)**

Primary Outcomes

- Compliance to CGJ/placebo treatment that will be monitored based on tabulation of returned unused juice.
- Safety/tolerance to CGJ/placebo treatment that will be monitored using a symptom checklist.
- Changes in cognitive functions based on assessments of neuropsychological battery (NPB).
- Changes in fatigue assessed using the self-report Chalder Fatigue Scale questionnaire.
- Plasma flavonoid profiles.

Population- Inclusion Criteria

- Gulf War Veterans deployed to the Persian Gulf theatre between August 1990 and August 1991.
- GWI will be defined according to Steele et al. (27).
 - 6 symptom domains
 - Requires endorsement of moderately severe and multiple symptoms in at least 3 of those domains.
 - Each symptom first became problematic during or after the Gulf War.

Population- Exclusion Criteria

- Conditions that might interfere with ability to report symptoms (e.g., drug use)
- Conditions that may explain the symptoms of GWI (e.g., diabetes, heart disease, among others)
- Significant current (e.g., suicidal or homicidal ideation) or lifetime psychiatric diagnoses (e.g., schizophrenia or bipolar disorder)
- Regular consumption of high levels of dietary polyphenol

Sample Size

- 30 participants in each arm (randomized in blocks of four).
- Sample size determined based on need for feasibility/pilot data for larger study.
- Sample size (n=60) produces 80% power to detect a rare adverse event (incidence 2.5%) and 80% power to detect a 20% difference in the change in reaction time on the NES.

Study Timeline

Week	0	2	4	6	8	12	16	20	24
Recruitment	x								
Informed consent	x								
Dispense FRP/placebo	x	x	x	x	x	x	x	x	x
Collect empty bottle/log sheets	x	x	x	x	x	x	x	x	x
Food frequency questionnaire	x	x	x	x	x	x	x	x	x
Brief Symptom Inventory	x	x	x	x	x	x	x	x	x
Patient Health Questionnaire- 15	x	x	x	x	x	x	x	x	x
Neuropsychological Battery	x					x			x
Chalder Fatigue Scale Questionnaire	x					x			x
Alcohol, Smoking and substance use involvement screening test	x					x			x
Pittsburgh Sleep Quality Index	x					x			x
Post-Traumatic Stress Disorder	x					x			x
Patient Health Questionnaire – 8	x					x			x
Blood collection	x					x			x

Presented by the **VA War Related Illness and Injury Study Center (WRIISC)**

Neuropsychological Tests

- Attention, concentration & information processing
 - NES simple reaction time
 - NES symbol-digit substitution
 - NES serial digit learning
 - Paced Auditory Serial Addition Test (PASAT)
 - Wechsler Adult Intelligence Scale (WAIS-IV) digit span subtest
- Abstraction and conceptualization
 - Trail Making test
 - Halstead Category Test Short Form

Presented by the **VA War Related Illness and Injury Study Center (WRIISC)**

Data Analysis

- Summary of new/exacerbated symptoms(safety)
- Summary of adherence (tolerability)
- linear regression $\Delta Y \sim \beta_0 + \beta_1 \text{Group} + \beta_2 X$
 - ΔY is the change before and after treatment
 - Group denotes the treated/placebo status
 - X is the covariate vector, such as compliance, dose, blood flavonoid content, age, gender and dietary polyphenol intake outside of the therapy

Impact

- Gather key information for a larger efficacy study of CGJ
 - Safety/tolerability
 - Dose
 - Outcomes
 - Covariates
- Explore efficacy
 - Few rigorous human studies of polyphenols
 - No accepted treatments for GWI

References

3. Rayhan RU, Stevens BW, Timbol CR, Adewuyi O, Walitt B, VanMeter JW, Baraniuk JN. Increased brain white matter axial diffusivity associated with fatigue, pain and hyperalgesia in Gulf War illness. *PLoS One* 2013;8(3):e58493.
4. Rayhan RU, Raksit MP, Timbol CR, Adewuyi O, VanMeter JW, Baraniuk JN. Prefrontal lactate predicts exercise-induced cognitive dysfunction in Gulf War Illness. *Am J Transl. Res* 2013;5(2):212-23.
5. Haley RW, Charuvastra E, Shell WE, Buhner DM, Marshall WW, Biggs MM, Hopkins SC, Wolfe GI, Vernino S. Cholinergic autonomic dysfunction in veterans with Gulf War illness: confirmation in a population-based sample. *JAMA Neurol* 2013 Feb;70(2):191-200.
6. Torres-Altoro MI, Mathur BN, Drerup JM, Thomas R, Lovinger DM, O'Callaghan JP, Bibb JA. Organophosphates dysregulate dopamine signaling, glutamatergic neurotransmission, and induce neuronal injury markers in striatum. *J Neurochem* 2011 Oct;119(2):303-13.
7. Broderick G, Fletcher MA, Gallagher M, Barnes Z, Vernon SD, Klimas NG. Exploring the diagnostic potential of immune biomarker coexpression in Gulf War Illness. *Methods Mol Biol* 2012;934:145-64.
8. Chen AY, Chen YC. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. *Food. Chem* 2013 Jun 15;138(4):2099-107.
9. Jiang F, Chang CW, Dusting GJ. Cytoprotection by natural and synthetic polyphenols in the heart: novel mechanisms and perspectives. *Curr Pharm. Des.* 2010;16(37):4103-12.
10. Pasinetti GM. Novel role of red wine-derived polyphenols in the prevention of Alzheimer's disease dementia and brain pathology: experimental approaches and clinical implications. *Planta. Med* 2012 Oct;78(15):1614-9.
11. Ho L, Ferruzzi MG, Janle EM, Wang J, Gong B, Chen TY, Lobo J, Cooper B, Wu QL, Talcott ST, et al. Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease. *FASEB J* 2013 Feb;27(2):769-81.
12. Wang J, Ferruzzi MG, Ho L, Blount J, Janle EM, Gong B, Pan Y, Gowda GA, Raftery D, rrieta-Cruz I, et al. Brain-targeted proanthocyanidin metabolites for Alzheimer's disease treatment. *J Neurosci* 2012 Apr 11;32(15):5144-50.
14. Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. *Br J Nutr.* 2010 Mar;103(5):730-4.
15. Sathyapalan T, Beckett S, Rigby AS, Mellor DD, Atkin SL. High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. *Nutr. J* 2010;9:55.
16. Kumar GP, Khanum F. Neuroprotective potential of phytochemicals. *Pharmacogn. Rev* 2012 Jul;6(12):81-90.
27. Steele L, Sastre A, Gerkovich MM, Cook MR. Complex factors in the etiology of Gulf War illness: wartime exposures and risk factors in veteran subgroups. *Environ. Health. Perspect.* 2012 Jan;120(1):112-8.