Resveratrol trial for relief of pain in pseudoachondroplasia

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Protocol Identifying Number: HSC-MS-17-0573
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IND Sponsor-Investigator: Karen L. Posey, PhD
Funded by: NA
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Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
COMP	Cartilage Oligomeric Matrix Protein
DCC	Data Coordinating Center
DHHS	DHHS Department of Health and Human Services
DSMB	Data Safety Monitoring Board
FDA	FDA Food and Drug Administration
GCP	GCP Good Clinical Practice
GLP	GLP Good Laboratory Practices
HIPAA	HIPAA Health Insurance Portability and Accountability Act
IND	Investigational New Drug Application
IRB	Investigational Review Board
MOP	Manual of Procedures
NIH	NIH National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
PSACH	Pseudoachondroplasia
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
CI	Co Investigator

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following *(use applicable regulations depending on study location and sponsor requirements; examples follow):* United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812) ICH E6

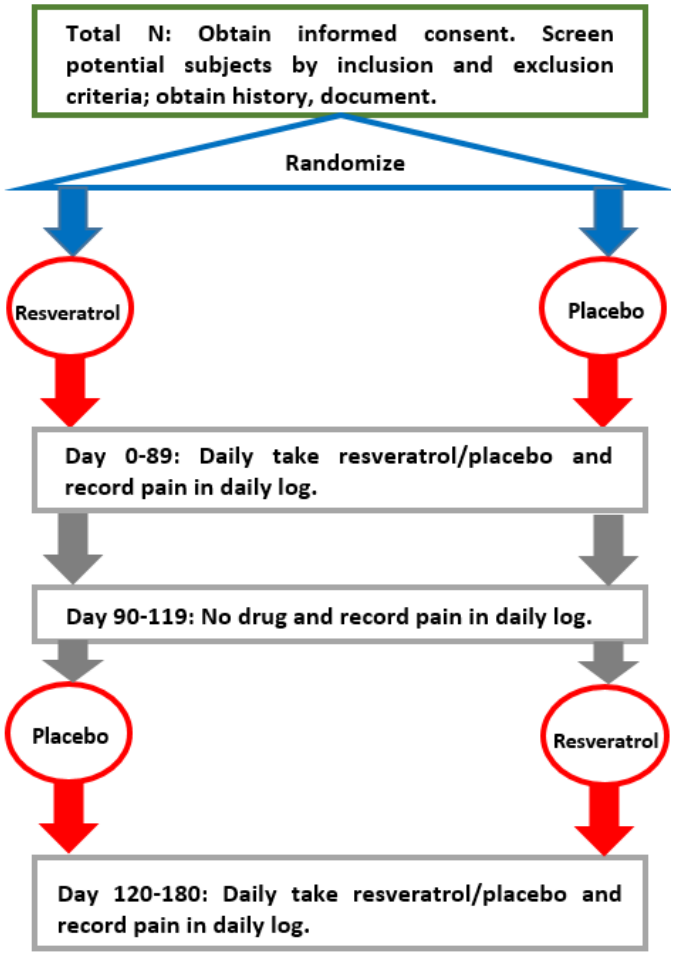
All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

PROTOCOL SUMMARY

Title:	Trial of Resveratrol for Pseudoachodroplasia Pain
Précis:	This is a cross over designed study to determine if self-administered oral resveratrol (90 days) can dampen joint pain for individuals with pseudoachondroplasia compared to placebo (90 days) as measured by daily pain logs.
Objectives:	To determine if resveratrol reserveage liquid lessens joint pain in individuals with pseudoachondroplasia.
Endpoint	Self-reported pain as ascertained by a 11-point pain scale from 0 to 10.
Population:	Pseudoachondroplasia patients aged 18 to 70 yrs (details below)
Phase:	IIA ("proof of concept" study)

Number of Sites enrolling participants:	1
Description of Study Agent :	Resveratrol Reserveage liquid super berry blend 225 mg + Pro-longevity factors blend 130 mg including **125 mg trans-resveratrol**
Study Duration:	5 yrs
Participant Duration:	210 days

SCHEMATIC OF STUDY DESIGN
1 KEY ROLES



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Pseudoachondroplasia (PSACH), a severe short-limb dwarfing condition, results from mutations that cause misfolding of the cartilage oligomeric matrix protein (COMP). Accumulated COMP in growth plate chondrocytes activates cellular stress that leads to inflammation and oxidative stress, ultimately causing chondrocyte death. The most debilitating features of the disorder is childhood joint pain and severe early-onset osteoarthritis. The only treatments for this pain are sporadic NASAID administration and joint replacement. We have shown that resveratrol dampens chondrocyte inflammation in a mouse model of the disorder. Given the lack of specific treatment for PSACH, the positive results with resveratrol in the mouse model and the low risk of resveratrol treatment, we propose to test resveratrol to treat joint pain in PSACH.

2.2 RATIONALE

We have shown, in a mouse model of PSACH, that resveratrol reduces chondrocyte inflammation and improves the health and longevity of chondrocytes[1]. This work was the first and only therapeutic approach shown to mitigate both the chondrocyte and long-bone pathology of PSACH in a mouse model and suggests that reducing inflammation and oxidative stress early in the disease process with resveratrol may be a novel approach to treat this disorder. Additionally, other researchers have shown that resveratrol reduces joint damage in mouse models of arthritis[2-9]. Taken together these observations suggest that resveratrol may be beneficial for PSACH joint pain. In addition, resveratrol is available over the counter and has not been associated with major adverse events suggesting that the risk associated with resveratrol are low.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Four clinical trials have shown mild to moderate adverse gastrointestinal side effects associated with high levels of resveratrol 0.5- 5 g/day.[10-12]and Resveratrol for Alzheimer's disease at clinicaltrials.gov. The longest safety study was a 52 week phase II study of dosages up to 2 g/day for adults, the incidence of nausea and diarrhea were no different between placebo and resveratrol groups[13,14]. This phase II trial of 119 participants administered pure synthetic resveratrol 500 mg orally once daily with a dose escalation by 500-mg increments every 13 weeks until a final dose of 1000 mg twice daily was reached for the final 13 weeks concluded "Resveratrol (1) is detectable in cerebrospinal fluid (at low nanomolar levels), (2) **is safe and well tolerated**, (3) alters AD biomarker trajectories, (4) preserves blood–brain barrier integrity, and (5) modulates the CNS immune response [13,14]". **This 52 week safety trial shows that resveratrol is safe to use in humans for an extended period of time at dosages above those used in our study.** Additionally, resveratrol is available over the counter and has not been associated with major adverse events, suggesting that the risk associated with resveratrol is low. Previous studies in adults have used resveratrol dosages ranging from 40 mg - 5 g [10-12,15-31]. There are at least 100 resveratrol clinical trials and many studies did not show or discuss adverse events [15-31]. Four clinical trials showed mild to moderate adverse gastrointestinal side effects associated with high levels of resveratrol 0.5- 5 g per day [10-12] and (*https://clinicaltrials.gov/ct2/show/results/NCT01504854?term=resveratrol&cond=Alzheimer+Disease&rank=1&sect=X430156#othr*). Our study dosage at 125 mg/day for adults is far below this range

Category	Summary of findings	Reference
Common adverse events	- mild to moderate adverse gastrointestinal side effects [12,10,11] - In the largest (*n* = 119), longest (52 weeks), and highest-dose (ending with 2 g by mouth daily) human study of resveratrol to date, a total of 104 participants completed the phase II study[14]. Inclusion criteria individuals >49 years old with a diagnosis of mild-to-moderate dementia due to AD, with stable medications and medically stable. **No differences were found between the resveratrol and placebo-treated groups in terms of safety and tolerability**, with the only exception being weight loss in the resveratrol-treated group. The most common reported AEs were nausea and diarrhea, with 42% reported in the resveratrol group versus 33% in the placebo group. The difference between groups was not statistically significant different. The high background of gastrointestinal AEs is likely due to concomitant treatment with a cholinesterase	[12,10,11,14]

	inhibitor approved for Alzheimer disease. Weight loss in the resveratrol-treated group may be due to enhanced mitochondrial biogenesis mediated by SIRT1.	
Serious adverse events	- Renal failure with SRT501 (a micronized oral formulation of resveratrol) and bortezomid [12] - fever and bicytopenia [14]	12,14
Expected adverse events	- nausea and diarrhea	12,10,11,14
No adverse events discussed		15-31

Most studies did not show or discuss adverse events [15-31]. Our study dosage at 125 mg/day for adults are far below these levels of 0.5 to 5 g per day which were associated with gastrointestinal distress.

2.3.2 KNOWN POTENTIAL BENEFITS

Numerous *in vitro* and *in vivo* studies have shown antioxidant and anti-inflammatory properties are associated with resveratrol administration[32]. Since oxidative stress and inflammation play a important role in PSACH chondrocyte pathology, these antioxidant and anti-inflammatory properties may reduce join pain in PSACH.

3 OBJECTIVES AND PURPOSE

To determine whether resveratrol treatment is effective in reducing pain in PSACH.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

The study has a 2x2 crossover design. Participants will take either the placebo or resveratrol for 90 days followed by a 30 day washout period and the placebo or resveratrol for the last 90 days. 30 day washout period was choosen in order to eliminate any carry over from reseveratrol as it is recommended to avoid resveratrol 2 weeks prior to surgery suggesting that carry over could potentially be as long as 2 weeks (*http://www.webmd.com/vitamins-supplements/ingredientmono-307-resveratrol.aspx?activeingredientid=307*; http://ww5.komen.org/BreastCancer/Resveratrol.html). Participants will be mailed a 30 or 90 day (for international participants) supply of placebo or resveratrol which they will receive 5 days before the end of each 30 day period (not applicable for international participants). Participants will keep daily pain log of pain and activity levels during the entire 210 day study period. We recognize that this is a long period of time however this population is highly motivated because 1) their pain is not systematically treated, 2) currently available over the counter NSAIDs, frequently used to control pain, cause gastrointential issues when used for prolonged periods and 3) participants reached through Little People of America and the PSACH facebook page are actively seeking solutions to control pain. This is being co-ordinated by a single center and will enroll 30 PSACH individuals. Because this is a rare condition, participants from 18 years - to 70 years will be enrolled.

4.2.1 PRIMARY ENDPOINT

Self-reported pain will be obtained from all study subjects using the Numeric Pain Rating Scale to score the subject's pain on a 0 to 10 scale. This scale has been validated and widely used[33-38]. A pain level will be assessed with enrollment in order to assure the participant has pain. An additional assessment will take place at the first visit (day 0). Pain will then be ascertained daily (including during the "washout" period between the two intervention periods) through a daily pain log kept by participants. The pain logs will be requested from participants at each follow-up visit and at the end of each month in the treatment periods, and data from the pain logs will be compiled and analyzed

at the start and end of each of the two treatment periods (on days 0, 90, 120, and 210). Monthly pain averages will be compared to baseline.

The primary endpoint will be change in pain score between baseline and monthly average pain scores. The pain score on each day of month one will be averaged to obtain the average pain score for month one, and the same will be done for months two and three, and each of the monthly average scores for resveratrol and placebo periods will be compared to baseline.

4.2.2 SECONDARY ENDPOINTS

Monthly, health related quality of life scores (HRQoL) will be obtained and the 36-Item Short Form Health Survey (SF-36). These instruments have been validated. For the secondary outcome measure, baseline HRQoL will be compared to the 30, 60, and 90 day HRQoL scores.

4.2.3 EXPLORATORY ENDPOINTS

NA

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. The diagnosis of PSACH is based on clinical assessment either in person or by photographic review by skeletal dysplasia specialist (JTH),
2. Healthy beyond PSACH associated complications,
3. Age at enrollment between 18 years to 70 years.
4. Baseline pain level of 2 or higher on 10 point scale.

5.2 PARTICIPANT EXCLUSION CRITERIA

1. Current use of resveratrol
2. Current use of blood thinners, lovastatin, ketoconazole, itraconazole, fexofenadine and triazolam.
3. Other non-PSACH realted health conditions, e.g. cancers.
4. Pregnancy or breastfeeding.
5. Women of childbearing age not using adequate contraception methods known to prevent pregnancy during the study.
6. Participation in another clinical study and/or using investigational agents.
7. Use of NSAIDs or aspirin.
8. Current use of Alfentanil, Cyclosporine, Dihydroergotamine, Dofetilide, Ergotamine, Fentanyl, Flibanserin, Oxycodone, Pimavanserin, Pimozide, Quinidine, Saquinavir, Sirolimus, Tacrolimus, Temsirolimus, Theophylline, Tizanidine, Thioridazine, Fosphenytoin, Phenytoin or Warfarin.
9. Age 17 years or less.
10. Platelet count below 50,000 per µl on baseline CBC.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will be conducted at Little People of America convention (n=300 PSACH members) and the PSACH blog (Facebook page: “Pseudoachondroplasia Dwarfish – and growing!!!” Closed group with 211 members). We will be recruiting International participants that contact us with interest in the study or that international colleagues refer to us. This recruitment strategy reaches out to the most active population in order to recruit motivated participants

that will complete the 7 month study. Monthly calls to participants to assess compliance and record keeping as well as any adverse events will be done to increase retention.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from the study at any time upon notification to the PI or study coordinator via phone or written request via email or postal mail An investigator may terminate participation in the study if:

a. Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
b. The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Participants who choose to withdraw or are withdrawn due to an AE or exclusion critera must return the unused portion of study materials to the study coordinator. **All mailing/communication costs will be paid by the study.**

All participants withdrawn/discontinued will be followed for 1 month to make sure that no AEs have developed after withdrawal from the study. If a participant was withdrawn due to AEs, they will be advised to seek medical help with their primary care physician. Those costs are not covered by this study.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the study PI to IND sponsor. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination of futility.

A suspended study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB and/or FDA

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Resveratrol liquid manufactured by Reserveage Nutrition will be purchased by the study. Placebo formulated by John Yoo, Pharmacist at The Compounding Shop (*http://mycompoundingshop.com/)* will be purchased.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Resveratrol liquid manufactured by Reserveage Nutrition will be tinted to match placebo color and repackaged in standard amber plastic bottle and relabeled so that the study participants will not know whether the compound is placebo or resveratrol. Placebo formulated to taste similar to the resveratrol liquid and be similar in appearance will be packaged in standard amber plastic bottle and labeled so that the study participants will not know whether the compound is placebo or resveratrol. Bottles will be labeled with particiapants name. This work will be performed by The Compounding Shop at 11851 Wilcrest Dr, Houston, TX 77031; Phone: 281-495-2230; Fax: 281- 495-2232.

6.1.3 PRODUCT STORAGE AND STABILITY

Resveratrol and placebo are stable at room temperature for extended periods of time but the manufacturer recommends storage in the refrigerator after opening. The participants will be instructed to store the opened supplement in the refrigerator.

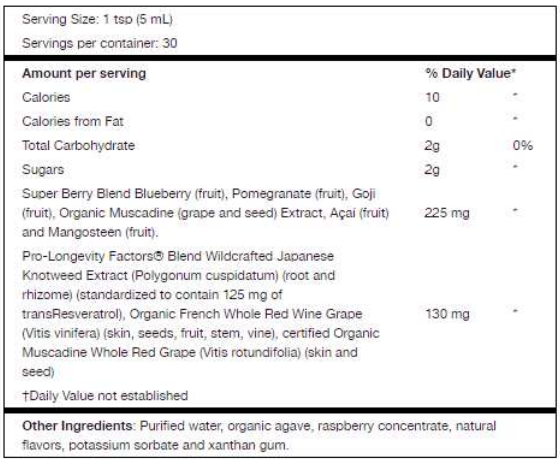
6.1.4 PREPARATION

As mentioned in section 6.1.2, resveratrol liquid will be tinted to match placebo color prior to repackaging. The packaged supplement and placebo are ready to be administered as is when supplied to the participants and do not require any futher preparation or dilution.

6.1.5 DOSING AND ADMINISTRATION

Based on the manufacturer's recommendation, the adult dosage is 125 mg/day or 5 ml of resveratrol reserveage liquid (http://reserveage.com/product/resveratrol-cellular-age-defying-tonic/). Four clinical trials have shown mild to moderate adverse gastrointestinal side effects associated with high levels of resveratrol 0.5- 5 g/day.[10-12,15-31] and Resveratrol for Alzheimer's disease at clinicaltrials.gov. While at least many other studies did not show or discuss adverse events [15-31]. Our study dosages at 125 mg/day for adults are far below these levels.

Self aministration for participants. Participants should take study medication 30 min prior to breakfast.



Serving Size: 1 tsp (5 mL)
Servings per container: 30

Amount per serving	% Daily Value*
Calories	10 *
Calories from Fat	0 *
Total Carbohydrate	2g 0%
Sugars	2g *
Super Berry Blend Blueberry (fruit), Pomegranate (fruit), Goji (fruit), Organic Muscadine (grape and seed) Extract, Açai (fruit) and Mangosteen (fruit).	225 mg *
Pro-Longevity Factors® Blend Wildcrafted Japanese Knotweed Extract (Polygonum cuspidatum) (root and rhizome) (standardized to contain 125 mg of transResveratrol), Organic French Whole Red Wine Grape (Vitis vinifera) (skin, seeds, fruit, stem, vine), certified Organic Muscadine Whole Red Grape (Vitis rotundifolia) (skin and seed)	130 mg *

†Daily Value not established

Other Ingredients: Purified water, organic agave, raspberry concentrate, natural flavors, potassium sorbate and xanthan gum.

6.1.6 ROUTE OF ADMINISTRATION

Oral liquid

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

N/A

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

N/A

6.1.9 DURATION OF THERAPY

90 days each of either placebo or resveratrol, with a month (30 days) of no medication in between the crossover administration.

6.1.10 TRACKING OF DOSE

Doses are administered by the participants with 30 day supply mailed out monthly or 90 day supply for international participants.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

N/A

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Resveratrol and placebo will be received by the study team from The Compounding Shop at 11851 Wilcrest Dr., Houston, TX 77031; Phone: 281-495-2230; Fax: 281-495-2232 and stored at room temperature in a secure location. Study coordinator will be responsible for mailing resveratrol and placebo to participants based on their randomized arm and a log will be kept recording drug/placebo identifier and to whom it is mailed. Study coordinator will be responsible for collecting the unused supplement and placebo from participants.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

- All potential participants will submit photos to confirm their PSACH diagnosis either by directly depositing photos into a secured encrypted server or via US mail (to be scanned and put into our secure data base and subsequently shredded.
- Medical history will be obtained by interview to confirm diagnosis of PSACH and to exclude those taking exclusion medications resveratrol, blood thinners, lovastatin, ketoconazole, itraconazole, fexofenadine, triazolam, Alfentanil, Cyclosporine, Dihydroergotamine, Dofetilide, Ergotamine, Fentanyl, Flibanserin, Oxycodone, Pimavanserin, Pimozide, Quinidine, Saquinavir, Sirolimus, Tacrolimus, Temsirolimus, Theophylline, Tizanidine, Thioridazine, Fosphenytoin, Phenytoin, or Warfarin. This information will be ascertained by the study staff over the phone and the participants will be asked to read the names of the medications and the dosages off the medicine containers. Information on medications will be collected for All medications the participant is on (both prescription and OTC). Exclusions will be made if any of the medications mentioned above are being used.
- Pain will be assessed to ensure that participants have pain to enroll in the study.
- For this 2X2 crossover design with two periods, patients will be randomized to one of two sequences, resveratrol/placebo or placebo/resveratrol. Those randomized to resveratrol/placebo will be given resveratrol in the first period and placebo in the second and vice versa for those randomized to to the placebo/resveratrol sequence. Randomization will be carried out by our biostatistician so that investigators evaluating outcomes, along with participants, are blinded.
- Once enrolled into the study and randomized, a parcel will be mailed to the participants including all study materials including first month's study drug supply, study forms and pain logs.
- Monthly phone calls will be used to assess of adherence to protocol and will be logged into the study logbook by study staff. These phone calls will also include ascertainment of any changes to medications and diagnosis of any new health condition or pregnancy.
- Patient-reported daily pain logs will be mailed or emailed to study co-ordinator on a monthly basis.
- Platelet count below 50,000 per µl will result in exlusion from the study as this increases risk of bleeding with injury. A normal platelet count is around 140,000 to 450,000 platelets per microliter (µl) of blood. When the number of platelets is low, this concentration reduces. Women normally experience a platelet count that varies slightly during the menstrual cycle and can fall near the end of pregnancy. The risk of bleeding increases as the platelet count drops, but bleeding problems are unlikely unless the count is less than 80,000-100,000 platelets per µl.

The following platelet counts carry the risk of serious bleeding:
Between 20,000 and 50,000 per µl: There is more risk of bleeding when injured.
Less than 20,000 per µl: Bleeding happens even without injury.
Below 10,000 platelets per µl: Spontaneous bleeding can be severe and a risk to life.

7.1.2 STANDARD OF CARE STUDY PROCEDURES
N/A

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS
NA

7.2.2 OTHER ASSAYS OR PROCEDURES
NA

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE
NA

7.2.4 SPECIMEN SHIPMENT
NA

7.3 STUDY SCHEDULE

7.3.1 SCREENING/ENROLLMENT (VISIT 0)
- Review medical photos to confirm diagnosis of PSACH.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Review urine pregnancy test to determine eligibility based on inclusion/exclusion criteria.
- Obtain written informed consent from participants which can be scanned/photographed and emailed to Maria.E.Serna@uth.tmc.edu.
- Inform participants of eligibility and enrollment into the study.
- Provide participants with specific instructions needed to participate in the study.
- Schedule phone visits for eligible participants for the duration of the study.

7.3.2 ENROLLMENT/BASELINE
Baseline Phone call (Visit 1, Day 0)
- Patient will be contacted after receipt of initial study package via postal mail (including medications and information for blood draw to assess kidney function, liver function and blood cell count). The complete metabolic panel includes analysis of renal function [blood urea nitrogen (BUN), creatinine*]*, liver function [total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP)*,* and aspartate aminotransferase (AST*)*], glucose, electrolytes [calcium, sodium, potassium, carbon dioxide (bicarbonate), chloride], protein [albumin, total protein]. The complete blood count (CBC) includes analysis of red blood count, hemoglobin, hematocrit, white blood cell count, platelet count. Platelet count below 50,000 per µl in CBC which indicates increased bleeding risk will result in exclusion.
- For Participants in the United States they will be asked to complete blood draw to the closest LabCorp or from their local facility at our cost. For the International participants blood need to be draw from a local facility an mailed to us for analysis at the local labcorp lab.

- Query participants about any changes in inclusion/exclusion criteria.
- Patients will be asked to start taking study medication on the next day.
- Admininister HRQoL instrument.

7.3.3 FOLLOW-UP

Follow-up Phone call (Visits 2, 3, 5, 6 and 7: Days 30, 60, 120, 150 and 180 -/+ 5 working days)

- Record adverse events as reported by participant to study co-ordinator. Study coordinator will ask about gastrointestinal health, any bleeding events and unusual bruising. PI will follow up with participant to assess the adverse events and determine whether to terminate participation.
- Record participant's adherence to treatment protocol.
- Inquire about any medication and health condition changes.
- Admininister HRQoL instrument.
- Self-reported will be obtained from all study subjects using the Numeric Pain Rating Scale to score the subject's pain on a 0 to 10 scale. This scale has been validated and widely used[33-38]. Pain will be ascertained daily (including during the "washout" period between the two intervention periods) through a daily pain log kept by participants. The pain logs will be requested from participants at each follow-up visit and at the end of each month in the treatment periods, and data from the pain logs will be compiled and analyzed at the start and end of each of the two treatment periods (on days 0, 90, 120, and 210).
- Request participant to mail back or email their pain log and a photo of the empty bottle at end of the month
- Inform participant to start on their next 30 days aliquot of study drug.

Follow-up Visit (Visit 4, Day 90 -/+ 5 working days)

- Inform patient that they are supposed to not take any study medication for the next 30 days but should continue their pain logs.
- Record adverse events as reported by participant to study co-ordinator. Study coordinator will ask about gastrointestinal health, any bleeding events and unusual bruising. PI will follow up with participant to assess the adverse events and determine whether to terminate participation.
- Record participant's adherence to treatment protocol.
- Inquire about any medication and health condition changes.
- Admininister HRQoL instrument.
- Request participant to mail back or email their pain log and mail back any unused medication or email a photo of the empty bottle. The data from the pain logs will be compiled and analyzed at the start and end of each two treatment periods (on days 0, 90, 120, and 210).
- Ask participants about which medication, reserveratrol or placebo, they think they were taking during the last 90 day period (evaluation of the success of blinding).
- Female participants in the United States will be asked to take a urine pregnanacy test at local labcorp or local lab. Email a photo of self administered pregnancy test supplied by us for female international participants within 30 days prior to next medication mail out.
- Participants will be asked to complete blood draw to the closest LabCorp or from their local facility at our cost. For the International participants omplete blood draw to the closes local facilityblood and mailed to us for analysis at local Labcorp lab.
- The complete metabolic panel includes analysis of renal function [blood urea nitrogen (BUN), creatinine], liver function [total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST)], glucose, electrolytes [calcium, sodium, potassium, carbon dioxide (bicarbonate), chloride], protein [albumin, total protein]. The complete blood count (CBC) includes analysis of red blood count, hemoglobin, hematocrit, white blood cell count, platelet count. Platelet count below 50,000 per μl in CBC which indicates increased bleeding risk will result in removal from the study.

7.3.4 FINAL STUDY VISIT

Final Study Visit (Visit 8, Day 210 +/- 5 working days)

- Inform patient that they have completed the study.
- Record adverse events as reported by participant to study co-ordinator. Study coordinator will ask about gastrointestinal health, any bleeding events and unusual bruising. PI will follow up with participant to assess the adverse events and determine whether to terminate participation.
- Record participant's adherence to treatment protocol.
- Inquire about any medication and health condition changes.
- Participants will be asked to complete blood draw from their local facility at our cost to assess kidney function, liver function and blood cell count. The complete metabolic panel includes analysis of renal function [blood urea nitrogen (BUN), creatinine*]*, liver function [total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP)*,* and aspartate aminotransferase (AST*)*], glucose, electrolytes [calcium, sodium, potassium, carbon dioxide (bicarbonate), chloride], protein [albumin, total protein]. The complete blood count (CBC) includes analysis of red blood count, hemoglobin, hematocrit, white blood cell count, platelet count. Platelet count below 50,000 per μl in CBC which indicates increased bleeding risk will result in removal from the study.
- Adminiinister HRQoL instrument.
- Request participant to mail back or email their pain log and mail back any unused medication or email a photo of the empty bottle. The data from the pain logs will be compiled and analyzed at the start and end of the two treatment periods (on days 0, 90, 120, and 210).
- Ask participants about which medication, resveratrol or placebo, they think they were taking during the last 90 day period (evaluation of the success of blinding).

Post Study Visit (Visit 9, Day 240 +/- 5 working days)

- Participants will be queried regarding any AE/SAE.

7.3.5 EARLY TERMINATION VISIT

If the study terminates early, the participants will be called and notified of study termination. In addition, the call will include the following:

- Information will be collected on any adverse events that the subjects may have experienced during their participation in the study. If the participant reports any adverse events, especially if they were the reason for early termination, the participant will be advised to seek medical assistance from their primary care physician.
- Participants will be asked to mail back any unused medication or email a photo of the empty bottle. Participants will be asked to mail back or email their pain log.
- HRQoL will be administered.
- Partipants will be informed that they will be re-contacted 30 days post-termination visit to assess any AE/SAE.

7.3.7 SCHEDULE OF EVENTS TABLE

Visit type	**Screen-ing**	**Start 1st arm**	**Follow-up**	**Follow-up**	**End 1st arm**	**Wash out period**	**Start 2nd arm**	**Follow-up**	**Follow-up**	**End of study**	**Post-study**
Visit Number	**0**	**1**	**2**	**3**	**4**		**5**	**6**	**7**	**8**	**9**
Day		**0**	**30**	**60**	**90**		**120**	**150**	**180**	**210**	**240**

Procedures											
Check I/E criteria	X										
Obtain HIPAA clearance	X										
Informed Consent	X										
Obtain medical/medication history	X										
Urine pregnancy test	X					X					
Blood test	X					X				X	
HRQoL assessment		X	X	X	X		X	X	X	X	
Request pain logs			X	X	X		X	X	X	X	
Pain assessment (compile and analyze pain monthly average from pain logs)		X			X		X			X	
Request unused mediction or photo of empty bottle			X	X	X			X	X	X	
SE/AE/SAE ascertainment			X	X	X		X	X	X	X	X
Query change in medications		X	X	X	X		X	X	X	X	
Query change in health status		X	X	X	X		X	X	X	X	
Blinding success evaluation					x					x	
Asked to start next month's dose		X	X	X			X	X	X		
Asked to stop taking all study drugs					X					X	

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

NA

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

None

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

None

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Current use of resveratrol at time of study start (Day 0). Use of NSAIDs or aspirin. Blood thinners, lovastatin, ketoconazole, itraconazole, fexofenadine and triazolam. Alfentanil, Cyclosporine, Dihydroergotamine, Dofetilide, Ergotamine, Fentanyl, Flibanserin, Oxycodone, Pimavanserin, Pimozide, Quinidine, Saquinavir, Sirolimus, Tacrolimus, Temsirolimus, Theophylline, Tizanidine, Thioridazine, Fosphenytoin, Phenytoin or Warfarin.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

None

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

The participants pain medications can be taken during the study and the use of pain medication will be recorded to determine if resveratrol reduces use of pain medication and/or self reported pain. Non-NSAID pain relievers such

as Tylenol can be used to control pain. If the rescue pain med(s) can't sufficiently control the pain, then the participant will be taken off the study.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Since resveratrol reserveage is an over-the-counter supplement, patients will have full access to product after study concludes.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or co-investigator or DSMB, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems involve risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the Office for Human Research Protections (OHRP) definition of UP.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The AE grading system used is based on NIH National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.
  A Semi-colon indicates 'or' within the description of the grade.
  A single dash (-) indicates a Grade is not available.
  Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

	Grade of Adverse Event (CTCAE version 5.0)				
Adverse Events	1	2	3	4	5
Kidney Function					
Creatinine increased	>ULN-1.5x ULN	>1.5-3.0x baseline; >1.5-3.0x ULN	>3.0 baseline; >3.0-6.0x ULN	>6.0x ULN	-
Acute Kidney Injury	-	-	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Hyperkalemia (*A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.*)	>ULN-5.5 mmol/L	>5.5-6.0 mmol/L	>6.0-7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Liver Function					
Alanine aminotransferase increased	>ULN-3.0x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0-5.0x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0-20.0x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Alkaline phosphatase increased	>ULN-2.5x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5-5.0x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0-20.0x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Aspartate aminotransferase increased	>ULN-3.0x ULN if baseline was normal; 1.5 - 3.0 x	>3.0-5.0x ULN if baseline was normal; >3.0 - 5.0 x baseline if	>5.0-20.0x ULN if baseline was normal; >5.0 - 20.0 x baseline if	>20.0x ULN if baseline was normal; >20.0 x baseline if	-

	baseline if baseline was abnormal	baseline was abnormal	baseline was abnormal	baseline was abnormal	
Blood bilirubin increased	>ULN-1.5x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5-3.0x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0-10.0x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Gastrointestinal Disorders					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Platelet count decreased	<LLN-75,000/mm3; <LLN -75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0- 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0- 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9/L	-
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 -4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death

8.2.2 RELATIONSHIP TO STUDY AGENT

The clinician's assessment of an AE's relationship to study agent (supplement) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 EXPECTEDNESS

The DSMB will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study phone interviews with the study participants or upon review by the DSMB. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report forms. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately in the database regardless of relationship. All AEs will be followed to adequate resolution.

Any PSACH-related medical issue present at the time the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unanticipated problems will be recorded in the data collection system throughout the study. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the study staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The study coordinator will ask about gastrointestinal health any bleeding events and unusual bruising and fill out the AE forms as events are noted. The DSMB will be informed of all AEs.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DSMB within 24 hours of site awareness.
- Other SAEs regardless of relationship, will be submitted to the DSMB within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DSMB and should be provided as soon as possible. The PI will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.4.3 UNANTICIPATED PROBLEM REPORTING

None

8.4.4 EVENTS OF SPECIAL INTEREST

None

8.4.5 REPORTING OF PREGNANCY

Although resveratrol is likely to not have any untoward effect during pregnancy either to the mother or the fetus, there is no definitive data on the safety of the supplement during pregnancy. Therefore, pregnancy is considered an exclusion criteria in this study. During enrollment, female participants will be asked about their intention to get pregnant in the next few months. Additionally, female participants of child-bearing age will be asked to practice adequate contraception methods known to prevent pregnancy. They will be asked to notify the study team when they become pregnant and to stop study medication if such an event occurs. A urine pregnancy test will verify potential participants are not pregnant prior to test medication being mailed. A urine pregnancy test will be administered for particiapants in United States and Interantional participants will self administer urine preganancy test at the end of first 90 day period of placebo or resveratrol or during the 30 day washout period.

8.5 STUDY HALTING RULES

Administration of study agent will be halted study-wide when any of the following occur and are reported to the DSMB:

- three grade 3 AEs
- three grade 1 or grade 2 AEs of the same type
- three grade 1 or grade 2 AEs related to liver function
- one grade 4 or 5 AE

The research coordinator will notify the principal investigators and co-investigator immediately when the the study stopping criteria are met and enrollment screens will stop accepting new study participants. The principal investigator will inform the Data and Safety Monitoring Board (DSMB) members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the principal investigator. The principal investigator will inform the FDA of the temporary halt and the disposition of the study.
An individual participant will be asked to discontinue study medication if any of the following occur:

- one grade 3, 4, or 5 AE
- three grade 2 AEs
- five grade 1 AEs

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including gastroenterology, infectious diseases and hematology The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to PI.

9 CLINICAL MONITORING

None

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

The primary outcome (change in pain between baseline and monthly pain average score) will be scored using the the Numeric Pain Rating Scale. Based on prior studies that utilized these scales, a difference of at least 2 units on the 11-point scale are considered to be a reflection of a true change in pain[39,40]. Median and mean monthly pain will be compared. The pain score on each day of month one will be averaged to obtain the average pain score for month one, and the same will be done for months two and three, and each of the monthly average scores will be compared to baseline. For the secondary outcome measure, baseline HRQoL will be compared to the 30, 60, and 90 day HRQoL scores.

Data from the daily pain logs and the monthly HRQoL assessments will be used to evaluate changes in outcomes within each intervention period stratified by study drug. The analysis will be performed within the framework of the 2x2 crossover study design. Baseline charachteristics (demographic and clinical) will be tabulated. Exploratory analyses will be performed to assess differences in outcomes as stated above after further stratification by gender.

10.2 STATISTICAL HYPOTHESES

The primary hypothesis is that patients' report of pain (and/or use of pain medication) will be 2.8 points lower on the pain scale (0-10) while on the resveratrol than while on placebo.

The secondary hypothesis for this study states that the change in self-reported HRQoL from the start of the study period to the end will be different in PSACH patients during the period they are on resveratrol compared to when they are on placebo.

10.3 ANALYSIS DATASETS

The dataset analyzed will be comprise of demographic and clinical information obtained from the patient, the pain scores obtained from the pain and HRQoL instruments described above. The database will be maintained by the study coordinator and will be password-protected and stored on the secure and HIPAA-compliant University of Texas Health Science Center's zone 100 network. It will be accessible only to the study staff.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Multilevel mixed-effects models will be utilized to assess the data while accounting for the lack of independence of data obtained from multiple time-points while considering the initial (baseline) outcome scores, type of intervention (placebo vs. resveratrol) and the sequence of intervention (placebo first, then resveratrol, or vice versa). This analysis wil be performed using STATA (v.14, College Station, TX). Exploratory analyses after stratification by subject's gender will also be performed.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

A baseline pain assessment will take place at the first visit (day 0). Pain will then be ascertained daily (including during the "washout" period between the two intervention periods) through a daily pain log kept by participants. The pain logs will be requested from participants at each follow-up visit and at the end of each month in the treatment periods, and data from the pain logs will be compiled and analyzed at the start and end of each of the two treatment periods (on days 0, 90, 120, and 210). Each of these scores will then be entered as raw values for each subject if the parameter distribution is non-normal, ranked values will be used as units of analysis.

The primary endpoint will be change in pain score between baseline and monthly average pain score. The pain score on each day of month one will averaged to obtain the average pain score for month one, and the same will be done

for months two and three, and each of the monthly average scores for resveratrol and placebo periods will be compared to baseline.
In an extreme condition, if a sufficiently large proportion (>30%) of the study subjects experience no pain (a score of 0), zero-inflated negative binomial models will be utilized to analyze the data while considering the individuals that report no pain.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The data from the HRQoL instruments will be ascertained for each subject at the following time-points – prior to the start of the first period (first intervention), at 30 days after the start of the first period, at 60 days after the start of the first period, and at the end of the first period (90 days), at the start of the second period (second intervention) after the "washout" time of 30 days has passed, at 30 days after the start of the second period, at 60 days after the start of the second period, and finally at the end of the second period. These normalized scores will then be used in generalized mixed models as stated above. Baseline HRQoL will be compared to the 30, 60, 90 day HRQoL scores.

10.4.4 SAFETY ANALYSES

The study DSMB will meet after every 10 patients have successfully completed the full study and all study data has been completed. The DSMB will be presented with all study-duration events (signs/symptioms/co-morbidities) that have been ascertained from all the patients that have completed their participation in the study and will be classified as study-related vs. incidental. The crude rate of the study-related event(s) will be tabulated with one-sided 95% confidence intervals[41]. Additionally, for study-related events that occur in more than 5 patients will be be further analyzed to incorporate duration of exposure to study drug.

10.4.5 ADHERENCE AND RETENTION ANALYSES

At the end of each intervention period, subjects will be asked to complete two questions on adherence. The first question will incorporate a visual analog scale (VAS) as a means to calculate self-reported adherence to study medication use. The second question will inquire about reasons for their non-compliance if any. These scales will be assessed after successful completion of every 10 patients so that any issues with adherence may be identified early and rectified for subsequent study participants.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will be presented for demographic and clinical information for each patient. These will be tabulated and described as frequencies and percentages (for categorical data) and mean and standard deviations or median and inter-quartile ranges (for normally distributed and non-normally distrubted continuous data, respectively). No statistical comparisons will be performed between the two as this is a randomized clinical trial.

10.4.7 PLANNED INTERIM ANALYSES

None

10.4.7.1 SAFETY REVIEW

The study DSMB will meet after every 10 patients have successfully completed the full study and all study data has been completed. Nonblinded information on all study-duration events (signs/symptioms/co-morbidities) that have been ascertained from all the patients will be classified as study-related vs. incidental.

10.4.7.2 EFFICACY REVIEW

There will be no interim analysis to assess efficacy performed for this study as this is a rare condition and there are a finite number of patients available for recruitment into the study. Adjusting the Type I error rate and recruiting additional patients is not achieveable. However, safety assessments will be ongoing by the DSMB as described in section 8.6

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

None

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

The design incorporates repeated measurements. The statistical models will account for that.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

Tabulation of indidivual response data for regulatory bodies will be provided as needed. The data included per patient will be dependent on the study report being presented. If needed all repeated measurements from every study subject will be presented in the appropriate tables.

10.4.11 EXPLORATORY ANALYSES

None

10.5 SAMPLE SIZE

Although studies haven't quantified pain variability in PSACH, other studies have utilized a pain VAS and have reported standard deviation (SD) of the difference between scores for the same patient of about 10-15 on a 1-100 scale. In addition, previous research by one of the investigators has suggested that a strong placebo effect can be present in studies using the pain VAS at a magnitude of about 20 on a 1-100 scale. Assuming a similar degree of variability in our study population and considering the placebo effect as reported, with a sample size of 30 participants at a Type I error rate of 5%, the minimal detectable difference would be 2.8 units at a SD of 10 and power of 80%, 4.25 at a SD of 15 and power of 80%, 3.3 at a SD of 10 and power of 90%, and 4.9 at a SD of 15 and power of 90%. Considering that there are about 300 potential patients that can be approached through the "Little People of America" support group and the Facebook PSACH group, we should be able to recruit into the study at least half of those highly motivated and invested individuals. We should be able to achieve our sample size of 30 patients for this study, even assuming a considerably high 33% attrition rate. We will screen 60 to enroll 30.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

One hundred individuals with PSACH will enrolled in the study and then randomized to receiving resveratrol or placebo first based on randomization assignment by biostatistician. We will not replace enrollees that drop out as we have statistical power to lose 10% of the cohort ad still determine whether the supplement provides relief of pain. All study participants will be blinded to the study drug. All study investigators and analysts will be blinded to the study drug with the exception of the study coordinator who will be responsible for mailing out the study medications.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

At the end of each study period, all study subjects will be asked to respond to a single question asking them to identify if they were on the study drug or placebo during the previous intervention period. This data will be analyzed after 20, 40 and all subjects have completed the study to evaluate the success of blinding.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

The study blind/participant code will be broken only in the case of an AE or SAE if the DSMB deems it important for appropriate assessment of the event. In this scenario, the study coordinator will communicate with the DSMB regarding the randomization arm of the particular participant. Other study team members will remain blinded.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

All study documents and data will be kept securely by the study coordinator. All electronic data will be password-protected and stored on HIPAA compliant NAS servers at the McGovern Medical School University of Texas Health Science Center at Houston. All hard-copies of the ICFs, CRFs, consent forms, pain logs, HRQoL assessments and other data collected from patients will be stored in a locked filing cabinet on the premises of the McGovern Medical School at the University of Texas Health Science Center at Houston. Access to all these records will be limited to the study coordinator. The coordinator will tabulate and aggregate information for consumption by the DSMB, study team and IRB if applicable.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented by the study-coordinator to monitor all study documentation for completeness and accuracy. Any missing data or data anomalies will be communicated to the principal investigator for clarification/resolution.
The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by any local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigators will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.]

13.2 INSTITUTIONAL REVIEW BOARD

Committee for the Protection of Human Subjects
University of Texas Health Science Center at Houston 6410 Fannin, Suite 1100, Houston, Texas 77030; Phone 713-500-7943; Fax 713-500-7951, Email *cphs@uth.tmc.edu*

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to ascertaining diagnostic information and/or starting intervention/administering study product. The following consent materials are submitted with this protocol : 1) adult consent form.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Study participants and/or their family members will be informed of risks and possible benefits of participation in this study. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator/study corrdinator will explain the research study to the participant and answer any questions that may arise. All participants must be able to communicate in English and they will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form, discuss with other family members and ask questions prior to signing. The participant will sign the informed consent document prior to any participation in the study and mail the consent form to the study coordinator in a provided self-addressed stamped envelope or scan/photograph and email to study coordinator. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records or if the participant has they original they will retain this copy for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

Representatives of the IRB may inspect all documents and records required to be maintained by the principal investigator, for the participants in this study. The clinical study site will permit access to all records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for 10 years.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES,SPECIMENS OR DATA

No human samples or specimens will be collected during this study

Data collected will be analyzed to determine if resveratrol has any benefit for pain in PSACH.

Storage: Access to stored data will be limited using password electronic protection and locked file cabinets. Data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

13.5 FUTURE USE OF STORED SPECIMENS

N/A.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Pain logs will be mailed or emailed to the the study coordinator. The study coordinator will also be responsible for the data collection and storage of the documents in a secured location.

14.2 STUDY RECORDS RETENTION

All study documentation will be kept in a secure location for 10 years and then destroyed.

14.3 PROTOCOL DEVIATIONS

As a result of any protocol deviation, corrective actions will be developed by the PI and implemented promptly. The study IRB will be notified of any protocol deviation within 10 working days of the deviation. The deviations will also be logged in a "Protocol Deviation Log" which will be part of the study quality monitoring plan.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

14.4 PUBLICATION AND DATA SHARING POLICY

This study is not funded. We will submit a manuscript with the findings to a peer-reviewed journal. In addition, the clinical trial be registered with *clinicaltrials.gov*.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Steering Committee, composed of Drs. Hecht and Posey, who are the PIs, will govern the conduct of the study. The Steering Committee meets on a weekly basis. Study progress, including recruitment rates protocol deviations, quality monitoring and DSMB reports will be assessed by the Steering Committee on an annual basis.

16 CONFLICT OF INTEREST POLICY

This project is independent of any actual or perceived influence, such from the pharmaceutical industry. We are using an over the counter supplement that is purchased and there is no financial contribution from the manufacturer.

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APPENDIX

Version	Date	Significant Revisions