



Adaptogens

CLINICAL STUDY

PROTOCOL NO. Protocol Adaptogen Study 001

A Pilot Double-Blind Crossover Study on the Effects of the Lera™ (also known as VR-3) Herbal Blend Intake on Acute and Chronic Stress and Their Biomarkers in Healthy Adults
Version: 1.0

Date: 3 September 2008

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Adaptogens

- Adaptogens are natural herb products that herbalists believe increase the body's resistance to stresses such as trauma, anxiety, and body fatigue.
- Use of adaptogens and their believed effects dates back thousands of years to ancient Indian (Ayurveda) and Traditional Chinese Medicine (TCM) practice.
- More scientific investigations did not begin until the 1940s, when Russian began a systematic classification and experimentation with these natural substances.

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Adaptogens

- Lazarev defined an Adaptogen as:
 - an agent that allows the body to resist or counteract the adverse effects of physical, chemical, or biological stressors by raising non-specific resistance towards such stress, thus allowing the person to “adapt” to stressful circumstances.

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Adaptogens

- Brekhman and Dardymov gave a formal definition to adaptogens: An adaptogen is
 1. non-toxic to the recipient,
 2. produces a nonspecific response in the body – increasing the power of resistance to multiple stressors including physical, chemical, and biological agents,
 3. has a normalizing influence on physiology, irrespective of the direction of change from physiological norms caused by the stressor

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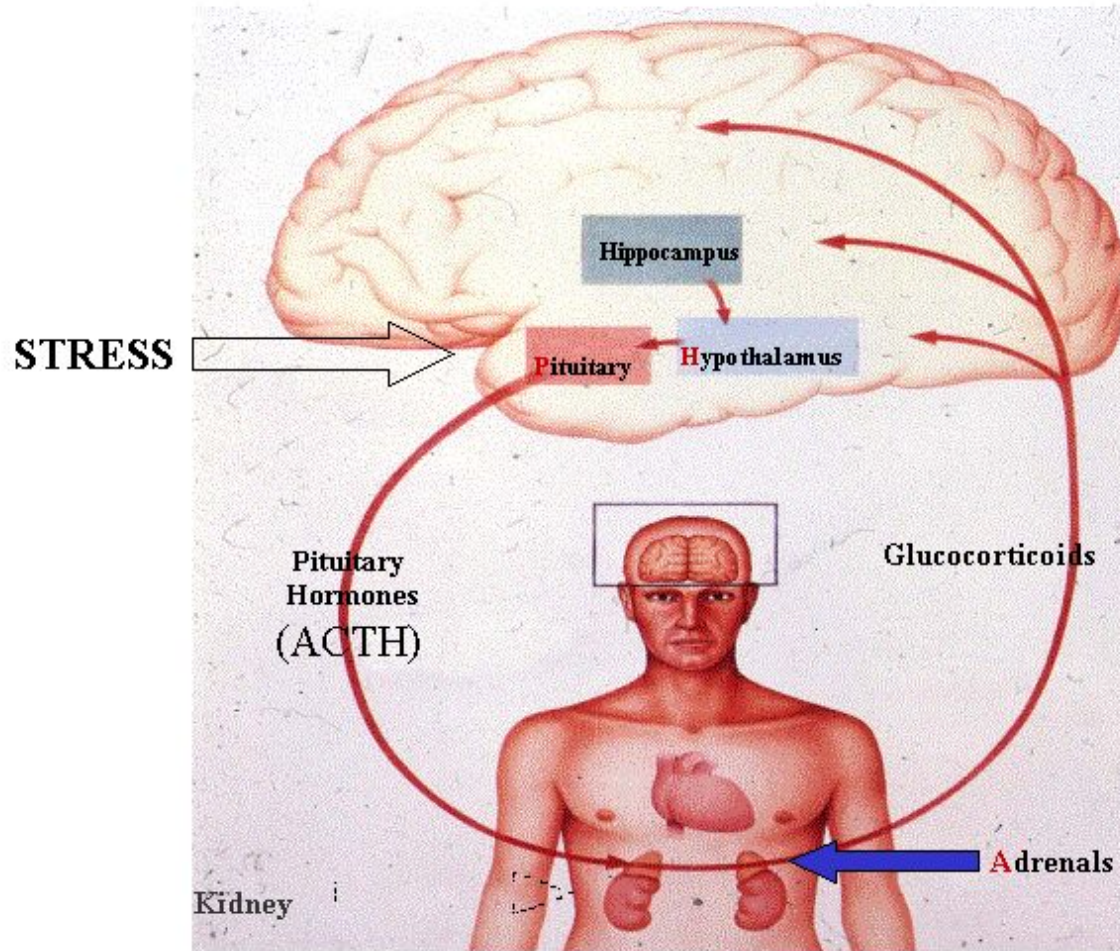
General Adaptation Syndrome (GAS)

- The combination of symptoms and changes that develop following exposure to an offending (stressful) stimulus.
- These responses are independent of the nature of the stressor. So physical (chemical, temperature, radiation etc.), mental, visceral (hunger, pain etc.) or emotional stresses are thought to elicit the same adaptive stress responses.
- GAS is thought to be in 3 phases

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Gas-1: Alarm Reaction(fight or flight)

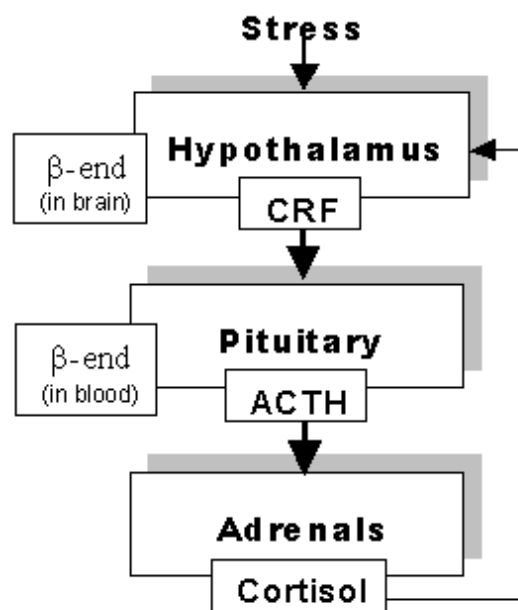
- Acutely mediated by the sympathetic nervous system to release adrenaline from the adrenal medulla to activate the emergency functions of the body (increased heart rate, raise systolic blood pressure, direct the blood supply to somatic muscles, slow down digestion etc.)
- This is followed by activation of the hypothalamic-pituitary-adrenocortical system (HPA), where cortisol is released from the adrenal cortex into the blood to help ready the body for the next phase of the GAS.

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HPA Axis Response



CRF - corticotropin-releasing factor;
ACTH - adrenocorticotropic hormone;
β-end - beta-endorphin

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Gas-2: The Resistance Phase

- Where the body attempt to maintain homeostasis in the face of the stressor. In this phase there is no sympathetic hyper activation, but cortisol levels are increased, and the cells are generally in a hyper metabolic state.
- Prolonged or very high intensity stimuli overpower the body's adaptability and lead to the last phase of the GAS.

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GAS- 3 The Exhaustion Phases:

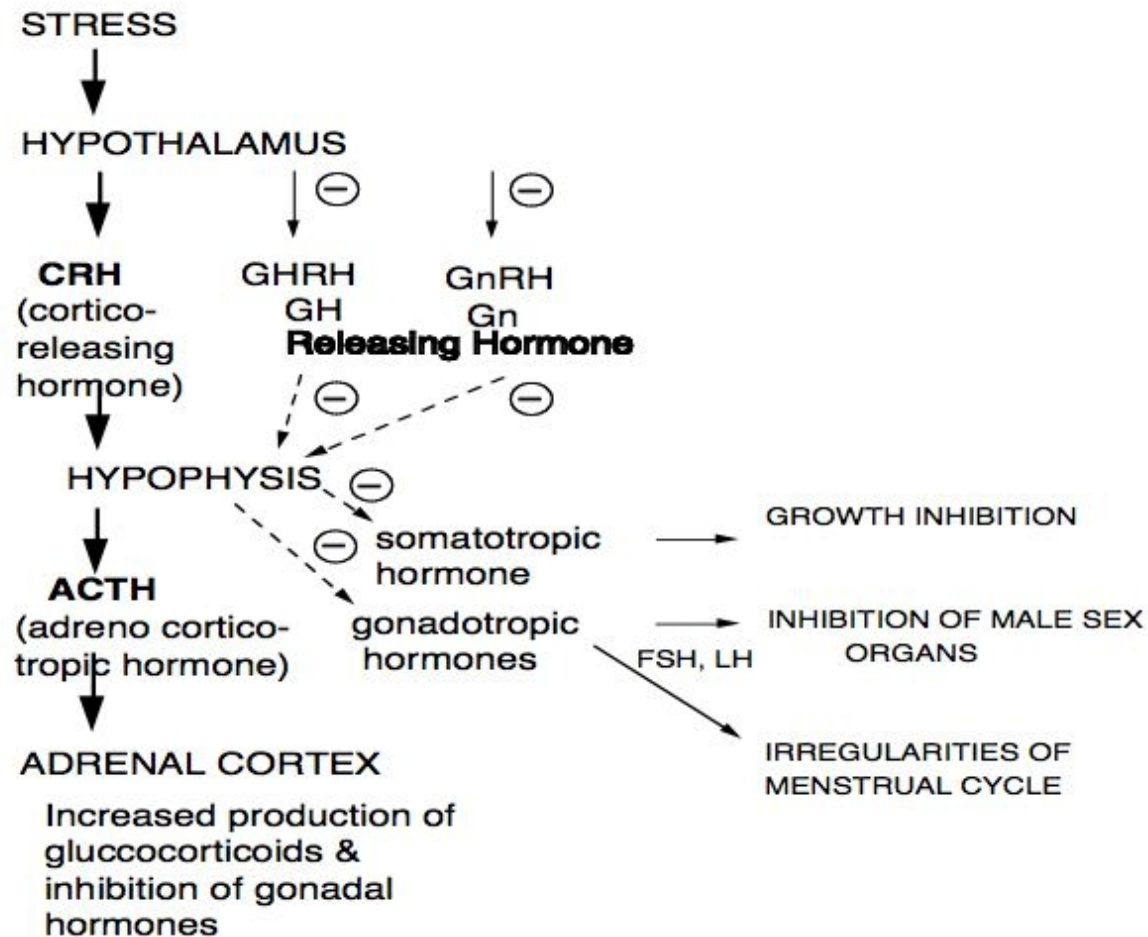
- Wherein the attempt to maintain the body's defense against the stressor comes at the expense of destruction of some of the vital structures.
- In this phase cortisol levels are still elevated, but antioxidant reserves, vital proteins etc., are depleted.
- This can lead to adrenal cortex hypertrophy, thymus, spleen and lymph node degeneration, and gastrointestinal ulceration (due to high cortisol levels).
- Eventually, if the stressor is strong or prolonged enough, death can ensue.

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Shift in HPA secretory priorities during stress



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Quantitatively Measurements Stress.

- Various biochemical surrogates/markers have been studied in an effort to quantify and more easily measure the stress response.
- Serum catecholamine and cortisol levels correlate with the phases of the GAS.
- Catecholamine levels increase during the Alarm Phase and correlate with increased heart rate, systolic blood pressure and other physiological measures of stress.
- Serum cortisol levels increase during the Alarm and Resistance Phases to various stressors.

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Salivary Cortisol Measurements

- Have gained wide acceptance as a non-invasive correlate of serum cortisol measurements.
- Many studies have shown a correlation of increased salivary cortisol to serum cortisol under a variety of stressors.
- Measurement of cortisol levels has become standardized and is easily quantified.
- The increased cortisol levels mark the activation of the HPA axis of the stress response.

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Why not measure Catecholamines

- At least two (2) systems are activated during the acute phase of the stress response, the sympathetic/adrenergic phase and the HPA axis response.
- The sympathetic response usually precedes the HPA phase.
- Catecholamines are not stable in saliva and have shown not to reflect serum adrenergic activation or the Alarm Phase of stress.

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The Utility of Measuring Salivary Amylase

- Salivary alpha amylase is a biomarker for the sympathetic axis of the stress response.
- Many human studies have shown that salivary alpha amylase (SAA) is increased during periods of acute stress.
- Moreover, the SAA changes correlate with salivary cortisol levels in many of the studies, and the levels of serum catecholamines as well.

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Proposition

- Given the literature support and the potential benefits of the Adaptogens, it would be enormously useful to test the stress reducing effects of *Eleutherococcus senticosus* and other adaptogenic herbal supplements on human subjects and evaluate the physiological effects (heart rate and systolic blood pressure) and biomarkers (salivary cortisol and alpha amylase) of the stress response.

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Protocol Team

- NEMA Research Inc. (www.nema.net)
 - Clinical Research Implementation
Organization with over 150 combined years of drug discovery and clinical research experienced
 - Turn-key operations: Bench-top to Bedside
 - Global operations
 - Research Headquarters located in Naples, FL

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Lera™ Team

- Key Players (see attached CV's)
 - Ismail Shalaby M.D., PhD.
 - Unv. Chicago, Johns Hopkins, Pfizer
 - Protocol Design
 - Joseph Pergolizzi, Jr., M.D.
 - Johns Hopkins, Georgetown, DIA, AAPP
 - Medical Monitor, Principal Investigator
 - Charlotte Richmond, M.D.
 - Unv. Texas, FIU, J. MED
 - Study Management and Site Monitoring, SAE Monitor
 - Duolao Wang, PhD.
 - Unv. London, Oxford
 - Biostatistics

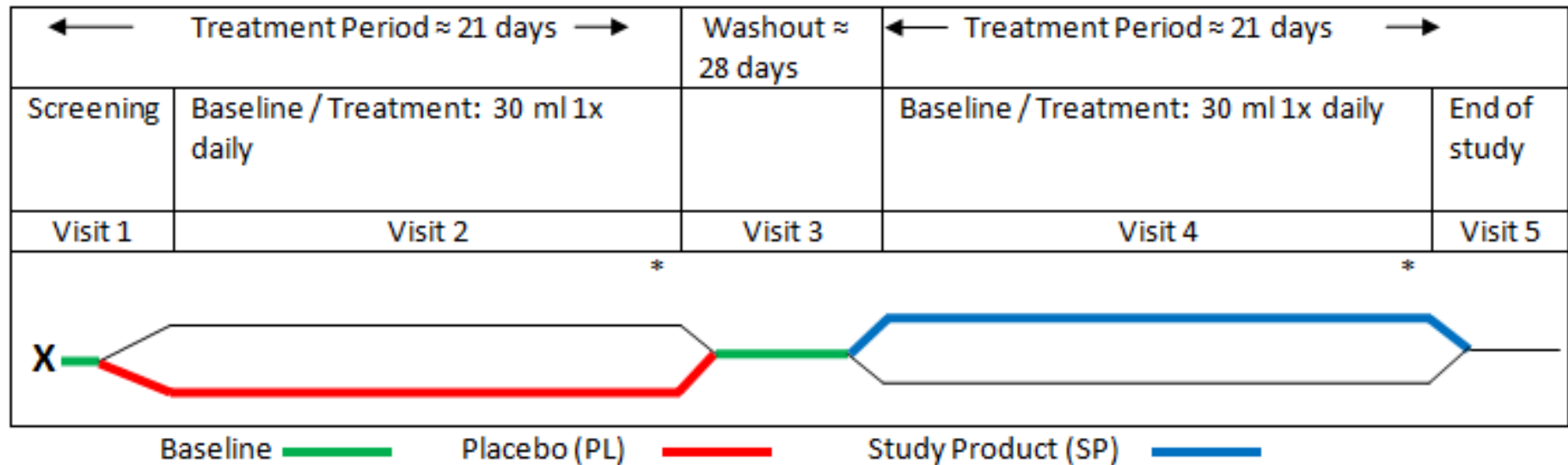
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Effects of Lera™ Herbal Blend Intake on Acute and Chronic Stress and Their Biomarkers in Healthy Adults: Pilot Study Objectives and Design

- Objective: To determine the safety and efficacy of Lera™ Herbal Blend and its effects on acute and chronic stress responses.
- Design: Pilot Double-Blind, Randomized, Placebo Controlled Crossover study in Healthy Volunteers



*Primary outcome assessments.

Data on file, NEMA Research Inc., Naples, FL.

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Inclusion Criteria

- Healthy men and women between the ages of 35-45.
- No concerns that would confound the study as determined by study physicians.
- Women must not be pregnant or become pregnant for the duration of the study.

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Exclusion Criteria

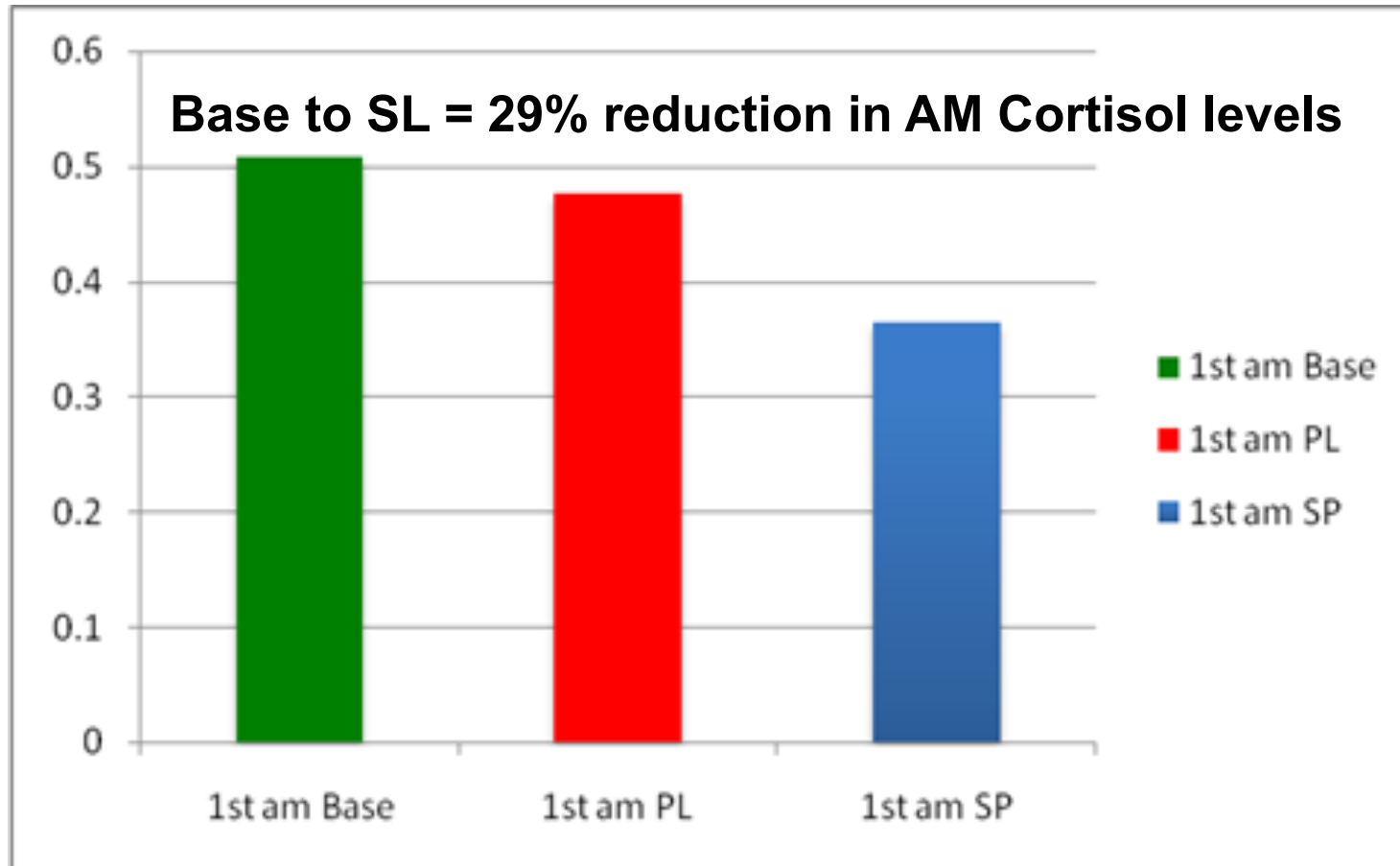
- The subject has a history of hypersensitivity to any of the compounds used in the study
- The subject is pregnant or a lactating female.
- History of Psychiatric Illness or Chronic Stress or Anxiety
- Hypertension, cardiovascular disease, liver, or kidney disease or other health concerns at the study physician feels may confound study results 5.
- Allergy or sensitivity to test product or ingredients
- Individuals who are cognitively impaired or who are not able to give informed consent
- Any routine prescription medication or nutraceutical intake
- Previous participation in a clinical research trial within 30 days prior to randomization
- The subject has an ongoing abuse of illicit substances, alcohol, or actively smoking marijuana.
- The subject is actively engaging in the use of Herbal Medicine, Traditional Chinese Medicine, Ancient Indian Medicine, Yoga, or Ayurveda

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Interim analysis (IA) Preliminary Report: Primary Endpoint AM Cortisol



The means for all samples were determined and then compared.
NB: Due to the small sample size of the IA statistical significance was not determined but shall be done at the end of the study.

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Next Steps

- Study is due to be completed by April 3, 2009
- Statistical synopsis is projected by May 1, 2009
- Final study report synopsis is projected by May 10, 2009
- Creation of abstract and submission for presentation at Pan Week in September 2009
- Submission to Journal of Medicine by Q4 09
- Open label trial and larger trial to be considered

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Summary

- Lera™ Blend reduced Morning (AM) Cortisol levels (a known marker for chronic stress) approximately 29% from baseline.
- Morning cortisol levels are predictive of Chronic Stress
- Many studies have shown a correlation of increased salivary cortisol to serum cortisol under a variety of stressors.
- Please note that the sample size for the IA is small (only seven patients) and therefore the conclusions might change when the total study population is examined.
- Notwithstanding the trend is very encouraging.

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Contacts

- **SUNRISE GLOBAL TRADING, LLC**
 - Michael Dowling, Managing Member
 - (407) 582-9424
 - mikedowling@sunriseglobaltrading.com
- **NEMA Research Inc.**
 - Joseph Pergolizzi, Jr., M.D.
 - (239) 597-3662
 - nemaresearch@aol.com

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