A randomized, double-blinded and placebo-controlled study on super-oxygenated water

Protocol Number: Inhale-001

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SYNOPSIS

Oxygenated water is a functional water that contains higher levels of dissolved oxygen than found in normal drinking waters. Consumption of oxygenated water has become a growing trend that is believed to aid aerobic respiration and offer added health benefits apart from hydration. Several animal studies link drinking of oxygenated water to an elevated blood oxygen level, while clinical observations suggest a positive association with multitude of metabolic processes involving post-exercise recovery, stress endurance, alcohol detoxification, uric acid clearance, immune responses, and some benefits in patients with obesity, hypertension, and diabetes. Therapeutic delivery of additional oxygen to blood stream via hyperbaric and extracorporeal oxygenation are known to induce tissue repair, restore normal body functions and improve survival. The current prospective study will evaluate a non-invasive route for oxygen delivery through ingestion of super-oxygenated water in adult volunteers. The participants will be randomized 1:1 to two treatment arms viz. super-oxygenated water and placebo control with source and taste matched normal water. Both the participant and investigator will be blinded to the treatment assignment. Participants will drink 12 oz of their assigned water and at 1-minute post-ingestion blood oxygen saturation (SpO2) level and heart rate will be measured using a pulse oximeter. Response to super-oxygenated water will be evaluated in augmenting blood oxygen saturation (SpO2) level and reducing heart rate compared to their pre-ingestion levels.

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Section 1: STUDY SUMMARY

TITLE	A randomized, double-blinded and placebo-controlled study on super-oxygenated water
RATIONALE	Therapeutic effects of oxygen supplementation have been long known to improve health and wellness. In addition to the pulmonary gaseous exchange, oxygen has been shown to be absorbed from the gastric and intestinal surfaces. Oral delivery of dissolved oxygen with oxygenated beverage appears as a practical route to raise blood oxygen. This study will evaluate ingestion of water supersaturated with oxygen in comparison with normal water.
TARGET POPULATION	Adult volunteers
NUMBER OF PARTICIPANTS	60 divided into two treatment arms with 30 each
INTERVENTION	Subjects will drink 12oz of their assigned water (blinded)
PRIMARY OBJECTIVE	To demonstrate an improvement in blood oxygen saturation (SpO2) and reduction in heart rate following ingestion of super-oxygenated water
PRIMARY ENDPOINT	Pre- and post-ingestion SpO2 and heart rate will be measured using a pulse oximeter.
STUDY DESIGN	Randomized double blinded study with two treatment arms

Section 2: STUDY OBJECTIVE

To evaluate the efficacy of super-oxygenated water ingestion in augmenting blood Oxygen saturation (SpO2) level and reducing heart rate in adult volunteers.

Section 3: BACKGROUND AND RATIONALE

Gaseous oxygen remains central to aerobic metabolism that acts as the final electron acceptor in cellular respiration to generate energy[1]. Essentially, oxygen is an indispensable element for sustenance of aerobic life and is primarily acquired from the atmosphere. In terrestrial organisms, oxygen is made available to the tissues via three interdependent processes; 1) ventilation, the process by which air moves in and out of the lungs, 2) diffusion, the spontaneous exchange of gases across air-blood barrier between the air sacs or alveoli and the blood capillaries in the lungs, and 3) perfusion, the process by which the cardiovascular system pumps blood throughout the body. Oxygenated blood from lungs travels to peripheral tissues to deliver oxygen and returns to lungs as de-oxygenated blood to be re-oxygenated in their circulatory journey[2]. The oxygenation and de-oxygenation of blood are reversible processes facilitated by hemoglobin, an oxygen carrier protein in red blood cells. Hemoglobin chemically couples with oxygen during gaseous exchange in lungs and releases it in response to high levels of carbon dioxide prevalent in peripheral tissues. Cells have built-in oxygen sensors and any impairment in oxygen transport resulting in lower tissue oxygen levels induces cellular hypoxia that may lead a multitude of signaling events, cell injury and pathophysiologic outcomes[3,4].

Therapeutic benefits from oxygen supplementation have been long achieved. Hyperbaric oxygenation therapy that involves breathing of pure oxygen in a pressurized environment is a well-established treatment for decompression sickness, carbon dioxide poisoning, sepsis, hard to heal wounds, and COVID-19[5,6]. Delivery of supersaturated oxygen therapy via extra corporeal oxygenation is a recently approved treatment for acute myocardial infarction following percutaneous coronary intervention with stenting to reduce infarct size[7]. A long-term clinical benefit of supersaturated oxygen therapy has also been observed in an open-label study where patients who received intracoronary supersaturated oxygen therapy had an improved survival, lower rates of new-onset heart failure and hospitalization for the entire one year of follow-up study compared to those who did not receive the supersaturated oxygen therapy[8]. Despite clinical benefits, these interventions of oxygen supplementation are not amenable for everyday use and

are rather medically involved requiring specialized equipment including hyperbaric chambers, cardiac catheterization laboratory, and extracorporeal oxygenators.

Enteric delivery of gaseous oxygen has been demonstrated to raise blood oxygen level experimentally in cats and rats as well as clinically in humans[9-11]. It was observed that administration of enteral oxygen in patients undergoing upper abdominal operations showed nearly 20% increase in oxygen saturation of the portal blood[11]. In another preclinical experiment oxygenated water was administered into stomach of anesthetized rabbits[12]. Following the intragastric delivery, an elevated oxygen content was noted in the abdominal cavity as well as in the portal vein indicating enteric absorption of the dissolved oxygen. Notably, effective oxygen absorption was noticeable when the level of dissolved oxygen was at least 45 mg/L. Till today numerous animal studies have been conducted that link drinking of oxygenated water to improved metabolism, stress responses and protective immunity. In a placebo-controlled study with rats, pretreatment with oxygenated water for four weeks or longer prevented hyperuricemia and significantly attenuated experimental hyperuricemia induction in a dose dependent manner[13]. Drinking of oxygenated water for 25 days induced greater cellular and humoral immune responses in pigs to an experimental infection by Salmonella producing significantly higher levels of white blood cells, lymphocytes and cytokines compared to control pigs who drank tap water[14]. Benefits of drinking oxygenated water has also been reported in broiler chickens where an increased level of serum lysozyme, a potent anti-bacterial component, and greater infection-fighting peripheral blood mononuclear cell proliferation were observed compared to control chickens who drank tap water[15]. In the same study, chickens experimentally infected with Salmonella showed a marked alleviation in disease symptoms and registered an increased survival of over 20% over the control by drinking oxygenated water. Additional effects of oxygenated water ingestion have been noted to accelerate alcohol detoxification in monkeys[16], and protect rats from epileptic seizures[17].

Given that an adult human body is composed of 50-70% of water, the U.S. National Academies of Sciences, Engineering, and Medicine determined that necessary daily fluid intake is approximately 2.7 liters (91 ounces) for women and approximately 3.7 liters (125 ounces) for men to maintain adequate hydration. The daily fluid requirement is generally higher for physically active individuals, and those living in warmer climate and with other physiologic needs such as breast-

feeding. Nearly 80% of the daily fluid requirement is met by ingestion of water or beverages. In this context, targeting drinking water as a vehicle for oxygen supplementation emerges as a practical route.

Normal drinking waters contains low amounts of dissolved oxygen (5-7 mg/L) whereas commercially available oxygen-enriched drinking waters may contain 30 mg to 120 mg of dissolved oxygen per liter[13]. Ingestion of oxygenated water showed a faster recovery from an intense exercise regimen[18]. The placebo-controlled study evaluated male collegiate distance runners that were given oxygen-supplemented water before, during and after a 5000-meter treadmill run where serum lactate clearance was significantly higher in runners receiving oxygen-supplemented water compared to those receiving taste matched control water. In another double-blind placebo-controlled diabetes study, patients with type 2 diabetes ingested 21L of water stably enriched with oxygen every fortnight for 24 weeks[19]. Remarkably, the glycosylated hemoglobin level in patients on oxygen enriched water was significantly lower at weeks 6 and 12 with respect to their baseline values whereas no such reduction was noted in glycosylated hemoglobin in placebo drinking water. Dissolved oxygen has been shown to reduce blood alcohol levels[20]. Alcoholic drinks that had greater dissolved oxygen content (20, and 25 mg/L) had a faster elimination from the body evidenced by lower blood alcohol level compared to alcohol drink that had normal level of dissolved oxygen (8 mg/L). In a related study, oxygen enriched water was supplemented with alcoholic drinks that had varied levels of dissolved oxygen[21]. Even after consuming a large amount of alcohol, the blood alcohol concentration was markedly lower in group that received the oxygenated alcohol drink along with oxygenated water.

From the review of available anecdotal reports and controlled studies, drinking of oxygenated waters appear beneficial even though deciphering these findings is an arduous task due to lack of a defined study endpoint, lack of understanding of an optimal oral dose of dissolved oxygen and multitude of commercially available products with unique chemistry and varied dissolved oxygen levels. The functional water that encompasses oxygenated water is an emerging concept whose market size for year 2022 was valued at $4.2 billion US dollars. Due to the inherent variability with the manufacturing process and oxygen content, it is imperative that each oxygenated water product is evaluated for the benefit claim.

Section 4: STUDY DESIGN

The study will be conducted by Dr Dawn DeSylvia at the provider's clinic/office and/or at surrounding business locations in Westlake Village, CA. A total of 60 adult volunteers will be enrolled who will provide written informed consent on the IRB approved form before study participation.

The study subjects will sign informed consent form and will be randomized at 1:1 ratio between two study arms to receive either INHALE super-oxygenated water or a source and taste-matched normal water by a randomization software (Randomizer, https://www.randomizer.at/). This is a double blinded study where neither the subject nor the investigator will know the assigned treatment arm. An unblinded research staff will perform the randomizations and prepare the blinded waters for use by blinded investigator. The randomized subjects will be stratified based on the gender (Male or Female) to ensure proportionate participation. Water in both treatment arms will be served chilled (4°C) to the study subjects.

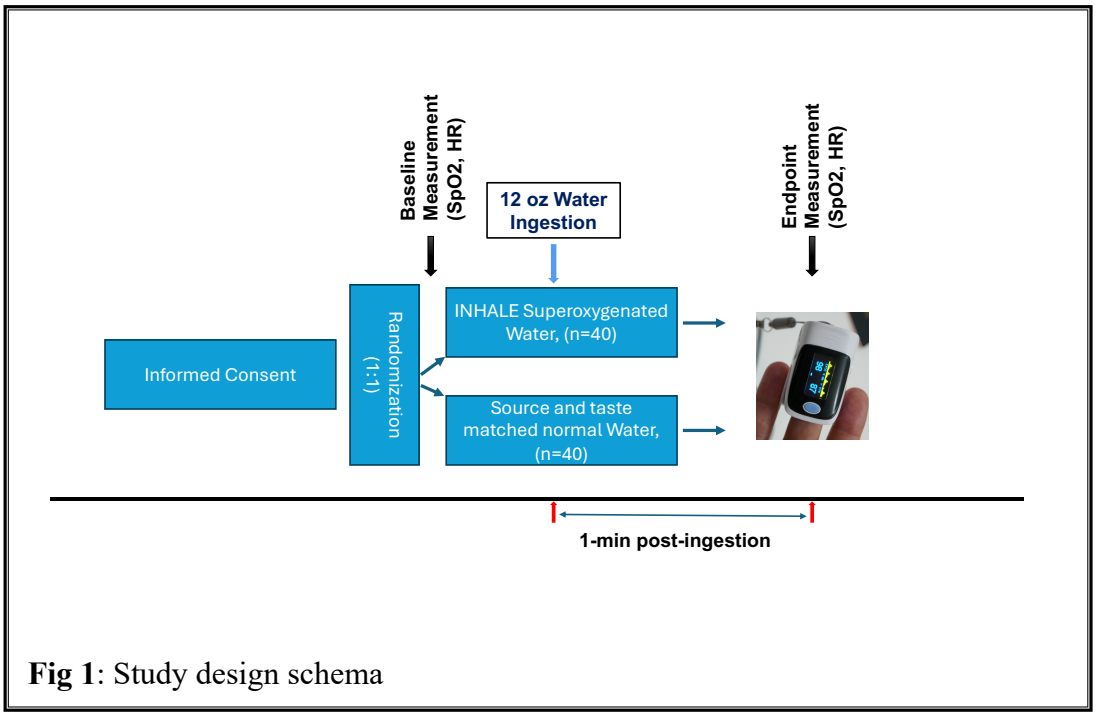

Fig 1: Study design schema

The study will evaluate ingestion of 12 oz of water (about 10% of daily fluid intake and is similar to an average beverage size) in one administration. The test article, INHALE super-oxygenated water contains dissolved oxygen at ~56 mg/L without any added sodium, sugar, protein or fat (Table 1, Fig 2).

The test articles INHALE super-oxygenated water, and a taste matched normal water will be provided at no cost to the subjects by the research team. The preparation, supply, storage and handling of the waters will be according to the manufacturer's guidelines.

Only one dose (12 oz) of water will be ingested. This amount is based upon available literature which is a reasonable amount to drink and not to cause any dilution effect on blood oxygen saturation. No overdose is expected since there is only one serving size per container. Subjects will not be allowed to crossover from one arm to the other.

Subjects receiving medications and supportive therapies necessary to maintain general health are allowed other those listed in the exclusion criteria.

Table 1: Nutrition facts for INHALE super-oxygenated water

Ingredients: Water	
Serving Size 12 fl oz	
1 Serving per container	
Amount per serving	
Calories	0
	% Daily Value*
Total Fat, 0g	0%
Sodium, 0g	0%
Total Carbohydrate, 0g	0%
Total Sugars, 0g	
Includes 0g Added Sugars	0%
Protein 0g	

* The % Daily Value tells you how much a nutrient in a serving of food contributes to a daily diet. 2000 calories a day is used for general nutrition advice.

Fig 2: Test article, INHALE Superoxygenated water

Section 5: SUBJECT SELCTION AND ENROLLMENT

Subject eligibility must be reviewed and documented by the Investigator before study enrolment. Sponsor may be consulted for an eligibility review on a case-by-case basis. No exceptions to the subject eligibility requirements set in the protocol will be granted by the Sponsor.

Inclusion Criteria

1. Legally adult (≥18 years) and either gender (Male or Female) will qualify
2. Subject must be willing to review and provide an informed consent to participation
3. Subject must agree to the study procedures including water ingestion, and SPO2 and heart rate measurements

Exclusion Criteria

1. Any active and life-threatening medical condition involving hepatic, renal, cardiac, respiratory, endocrinal, or gastrointestinal systems, or any blood disorder in view of the Principal Investigator to confound the study
2. Female subjects those are pregnant, nursing or planning to become pregnant
3. Subjects receiving any experimental medications or have undergone a major surgical procedure in last 30 days

4. Subjects are excluded if they have previously utilized the test article (INHALE super-oxygenated water) within the last 24 hours, have undergone bariatric surgery or have received weight-loss medication
5. Subjects with known anemia, hemoglobinopathies or other comorbidities necessitating fluid restriction would be excluded

Section 6: STUDY ASSESSMENTS AND PROCEDURE

Voluntary, written, dated, and signed IRB-approved informed consent form must be obtained from the subject before any study specific procedures are performed. Participants not with active life-threatening medical conditions and not on medications interfering with oxygen metabolism are eligible for enrollment. The subjects will complete a demographics and brief medical history form (Appendix 1).

As this is a randomized study with two (2) treatment arms, the subjects will be assigned their treatment group using Randomizer, (https://www.randomizer.at/). Neither the subject nor the investigator will know the treatment assignment (as they are blinded in the study) and an unblinded study staff will perform the randomization and dispense the blinded water for the subject.

The subjects will provide an Energy level and Brain clarity assessment (Appendix 2) at pre-dose. Pre-ingestion or baseline measurements of blood oxygen saturation (SpO2) and heart rate will be measured with a pulse oximeter attached to index or middle finger of either hand. The subjects are expected to ingest their assigned water within 30 sec. At 1-minute post ingestion, SpO2 and heart rate will be recorded. Subjects will again provide the Energy level and Brain clarity assessment (Appendix 2) at post-dose. Super-oxygenated water is marketed as functional water and is generally considered safe for human consumption. The sponsor is not aware of any health events related to drinking of super-oxygenated water. The production cycle of INHALE super-oxygenated water encompasses a closed and aseptic cycle that ensures consistency and sterility of the product.

The study treatment would require only one session/visit and no follow-up visits will be necessary. The participants will be asked for an optional 30-min post-ingestion observation. Patients may discontinue from study treatment at any time at their own request, or they may be discontinued at

any time at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol or procedures.

Section 7: STUDY ENDPOINTS AND CLINICAL OUTCOMES

Primary efficacy endpoint for the study will be an increase in blood oxygen saturation and decrease in heart rate at post-ingestion compared with that at pre-ingestion baseline. A medical grade pulse oximeter will be utilized in the measurement.

Section 8: ADVERSE EVENT REPORTING

An adverse event (AE) is any reaction, side effect or other unfavorable medical event that occurs during participation in a clinical trial regardless of treatment group or suspected causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease in the enrolled subjects. All AEs that occur prior to the study treatment are considered as medical history unless the AE develops or worsens during or after the study treatment. Assessment of AEs will include type, incidence, severity, timing, seriousness, and relatedness to study treatment. A treatment emergent AE (TEAE) is an AE that occurs after the first dose of any study treatment or any preexisting condition that increases in severity should be reported as AEs. The AE is classified as a serious adverse event (SAE) when the untoward medical occurrence results in death, becomes life threatening, causes persistent/significant disability or results inpatient hospitalization.

Every AE will be assessed by the investigator with regard to evaluation of its Severity (Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe], Grade 4 [life-threatening] and Grade 5 [death]; Causality (Related- when there is a reasonable chance that the AE is connected to or is caused by the water ingestion, Not related- when there is a reasonable chance that the AE is connected to or is caused by something else other than the water ingestion); and Outcome (Recovered/Resolved, Recovered/Resolved with sequelae, Ongoing, Fatal/results in death).

The active reporting period for SAEs begins from the time that the patient provides informed consent and until completion of the study (post-ingestion endpoint measurement). All SAEs must be reported to the sponsor (emailed or faxed) within 24 hours of Investigator being aware about occurrence about the event. Sponsor will report the collected SAE events to the IRB following their reporting guidelines.

Section 9: DATA MANAGEMENT AND STATISTICS

Privacy of research subjects and confidentiality of their personal information will be maintained to the maximum limit possible under applicable regulations and international guidelines. Subjects will be assigned with anonymized identifiers to minimize such risks. A detailed methodology for summary and statistical analyses of the collected data will be developed and maintained by the Sponsor. Each eligible subject will be assigned with a unique combination of alphanumeric characters. Initials for First and Last names of the subject and gender and a sequence number will be assigned to each subject. For example, subject 1, Jane Doe will be denoted as JDW-001. Similarly subject 2, John Doe, will be denoted as JDM-002. These subject number will be utilized in randomization for treatment assignment. At no time, the protected health information (PHI) will be collected, shared or stored during the study.

The hypothesis being tested here is that INHALE super-oxygenated water will significantly increase SpO2 levels and decrease heart rate following a single ingestion. The study aims to enroll 30 subjects per treatment arm that will further be stratified between male and female. The sample size is selected to support analysis for an expected <1% increase in SpO2 and an anticipated 1% decrease in heart rate as continuous measures in the experimental group with an alpha level of 0.05 powered at 80%. Statistical analysis of this study will be the responsibility of the Sponsor and Investigators. All tests of treatment effects will be conducted at a 2-sided, unless otherwise stated. Continuous variables will be summarized using descriptive statistics (i.e., number of participants, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

At study conclusion all datasets will be utilized to construct a comparative analysis. The data will be analyzed by JMP Pro and GraphPad Prism software for statistical comparisons. Principles of intent-to-treat analysis will be applied where every piece of collected data will be processed without any bias or selection and no enrolled subjects will be excluded from the analysis.

Section 10: DATA COLLECTION AND QUALITY ASSURANCE

All data entries will be conducted by the study investigator or trained study staff. No PHI data will be utilized as subject identifier, and every subject will be assigned an anonymized alphanumeric

character described in **Section 9**. All study personnel and sub-investigators will be trained by the Principal Investigator with regard to study protocol and subsequent data collection.

Section 11: OPERATIONAL CONSIDERATION

This study will be conducted in accordance with International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences), Guidelines for Good Clinical Practice (GCP) (International Council for Harmonization [ICH] 1996), ICH E6 (R2) and concepts that have their origin in the Declaration of Helsinki. The study will be conducted under a protocol reviewed and approved by an Institutional Review Board (IRB) and the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written informed consent before any protocol-driven procedures or evaluations are performed.

The Investigator or designee is responsible for informing the subject of all available information relevant to his/her safety and obtaining signed, written consent from all participating subjects. Additionally, the Investigator is responsible for monitoring subject safety and providing periodic and requested reports to the IRB/EC. The Investigator is responsible for the accuracy and completeness of all study records including source documents and/or case report forms (CRFs).

Section 12: PUBLICATION

Results from this study may be considered for publication in an appropriate scientific platform upon study completion.

Section 13: REFERENCES

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Section 14: APPENDICES

APPENDIX 1:

Demographics and Brief Medical History

Subject #:_____ **Date:**_____
(dd -Mmm- yyyy)

1. Age (Years):_____

2. Gender (Choose one):

- ☐ **Male**
- ☐ **Female**
- ☐ **Not Reported**

3. Medical History:

#	Condition/Disease (one item per line)	Start Date (dd/Mmm/yyyy)	Status
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved
			☐ Current ☐ Resolved

APPENDIX 2:

Energy Level and Brain Clarity Assessment

Subject #:_____ ☐ **Before Dosing** ☐ **After Dosing**

(Choose one)

1. How would you score your Energy Level?

10= Very High, 1= Very Low

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10	**9**	**8**	**7**	**6**	**5**	**4**	**3**	**2**	**1**
Very High									Very Low

2. How would you score your Brain Clarity?

10= Very High, 1= Very Low

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10	**9**	**8**	**7**	**6**	**5**	**4**	**3**	**2**	**1**
Very High									Very Low