STUDY TITLE: OPEN LABEL POSTMARKET EVALUATION OF ORALLY DOSED ALMEGA PL® ON CHOLESTEROL AND CARDIO-METABOLIC PARAMETERS.

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Clinical Trial Protocol

1. Study Title: Open label post-market evaluation of orally dosed Almega PL on cholesterol and cardio-metabolic parameters.

2. Short title: AlmegaPL CV Health Open Label Study

3. Protocol ID #: ALM-CVH-22

4. **Version #**: V1 March 4th 2022

5. Investigators: Dr Eneko Ganuza[1] (Principal Investigator), Eghogho H. Etomi[1] (Study Director).

6. Sponsors: [1]Qualitas Health (Texas, USA)

7. Study site: 2800 Post Oak Blvd, Suite 5858 Houston, TX 77056.

8. Introduction

8.1 Study Rational

Cardiovascular disease is one of the leading causes of mortality in the United States hence, there is an increasing demand for supplements to lower atherogenic lipid levels.

8.2 Investigational Product

The investigational product iwi/Cholesterol is a commercially available capsule-form herbal (algae) supplement containing Almega®PL, a *Nannochloropsis* algae-derived extract rich in eicosapentaenoic acid (EPA). EPA is a type of omega-3 essential fatty acid known to play a beneficial role in protection against cardiovascular disease. Iwi/Cholesterol is the only source of long chain omega-3 that does not contain the DHA that is present in other omega-3 sources (fish oil, krill oil, other algal oils). Almega®PL was registered at the Food and Drug Administration (FDA) as a New Dietary Ingredient (NDIN) in 2014.

8.3 Background

AlmegaPl was previously studies in a double-blind, placebo-controlled, randomized three-month clinical trial (Rao et al., 2020 *Nutrients*, 12, 1869) that showed that this product decreases total cholesterol and VLDL-cholesterol.

8.3 Risk Benefit Assessment

8.3.1 Known Potential Risks

The safety of Almega®PL has already been reviewed by the FDA as part of the New Dietary Ingredient notified in 2014. AlmegaPl is a commercial rather than an investigational product with more than 5 years of history of use, where no major adverse events have been reported. In the above-mentioned clinical trial (Rao et al., 2020 *Nutrients*, 12, 1869) three participants in each group (placebo and Almega®PL) reported adverse effects (nausea, abdominal cramping and diarrhea) which was likely associated to the nocebo effect.

8.3.2 Known Potential Benefits

- Almega®PL decreases total and VLDL-cholesterol (Rao eta al., 2020)
- AlmegaPL increases your omega-3 index (Rao et al., 2020).
- Higher bioavailability than other omega-3 forms (Kagan et al., 2013 *Lipids Health Dis*, 12, 1)
- No fishy aftertaste.
- More sustainable than fish oil.
- Provides each participant with their lipid panel information they could monitor during the study.
- Increase consumer awareness and engagement towards Almega®PL and their health benefits.

8.3.3 Assessment of potential risk and benefits Potential Risks

As a final remark we would like to add that the current study will be targeting new customers that will be taking the Almega®PL regardless of their participation of this study. Therefore, the study is not exposing the participants to the risks (and benefits) of taking the supplement but rather monitoring the population that is already taking the supplements. From that point of view, this is not strictly an interventional study, but a cohort study in which a population is being monitored.

8.3 Objectives and Endpoints

The aim of this study is to assess the effectiveness of Almega®PL on improving blood markers associated with heart health of iwi customers. Specifically, we would like to confirm the decrease in cholesterol observed in our previous trial (Rao et al., 2020) while assessing the capacity to decrease also triglycerides (primary outcome).As a secondary objective we would like to understand if EPA, precursor of signalling molecules involved in the inflamatiory response, could help decrease the inflammatory marker hs-CRP.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Can Almega®PL supplement decrease triacylglycerides in a generally healthy population?	Triglyceride change from baseline over 6-month period.	*Triglyceride levels is an atherogenic lipid and an important risk factor in Cardiovascular Disease*
Secondary		
Can Almega®PL supplement replicate the decrease in VLDL and total cholesterol we observed in our previous clinical trial (Rao et al., 2020)? *Will the results from a controlled population translate to the iwi costumers?* *Can Almega®PL supplement decrease the age-related inflammatory marker hs-CRP in a generally healthy population?*	Total Cholesterol change from baseline over 6-month period. VLDL-Cholesterol change from baseline over 6-month period. LDL-Cholesterol change from baseline over 6-month period. HDL-Cholesterol change from baseline over 6-month period. hs-CRP change from baseline over 6-month period. Fasting glucose change from baseline over 6-month period. HbA1c change from baseline over 6-month period.	*Cholesterol in plasma levels is atherogenic and a risk factor in Cardiovascular Disease.* *Hs-CRP is an age related inflammatory market. Omega-3 help regulate the inflammatory response.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS

9. Study Design:

EPA is a type of omega-3 essential fatty acid known to play a beneficial role in protection against cardiovascular disease. Almega®PL is the only natural source containing EPA as sole n-3 HUFA that is available over the counter for human consumption. We **hypothesized** that AlmegaPL supplementation improves blood markers associated with heart health and inflammation. This post-market open label single armed trial involving 200-300 male and female participants, that will be monitored during the first 6 months following their subscription to Almega®PL.

As part of the **screening procedure**, participants will complete a short questionnaire to make sure they are new iwi users. Any participant who is already using iwi will not be considered in the study. Any participant that has a serious condition (including but not limited to kidney, neurological, immunological, liver, and gastrointestinal disease, any heart condition, or diabetes) will also be disqualified for the program and directed to their doctor. Any participant attempting conception, pregnant or breastfeeding will also be disqualified. All other participants will be accepted into the limited study based on their time of application until the quota is completed. Participation in this study is purely voluntary and participants can withdraw at any point without prejudice.

Participants will be asked to take the allocated product according to the **dose** prescribed (2 capsules per day containing 1000-1100 mg Almega®PL) and adherence to the protocol will be evaluated with a follow up email. Participants will be asked to maintain their usual level of physical activity and diet for the duration of the study. The dose used in this trial is in agreement with the commercial dose communicated to the FDA and comparable to doses previously used in our clinical trials.

Along with the fist supplement order shipped to the new subscriptions, participants will receive the baseline hearth health test kit from Imaware™. Participants will be contacted 3 and 6 months after and they will be sent subsequent kits once the confirmed adherence to the supplement. The test kits will monitor blood lipid levels across a supplementation period (baseline, month 3 and month 6) thanks to a finger prick blood drawing system. The age, height, weight, gender, fasting total cholesterol, LDL-cholesterol, HDL-cholesterol, calculated VLDL-cholesterol, triglycerides, as well as hs-CRP inflammatory marker, and glucose and HbA1c as diabetes indicator of each participant will be recorded over the study period. **Qualitas Health** will receive the aggregated data of the participants only for statistical analyses at their headquarter in Houston and store it in the company share drive with access restricted to those involved in the study. There will be no cost incurred for this analytical assessment to the participant.

Results for the per protocol (PP) population will be first tested for normality before any other test will be conducted and baseline data was compared again month 3 and month 6 data. Based on the distribution of data, Welch two-sample unequal variance t-tests and Wilcoxon Ranks sum tests were used to compare two-tailed differences between groups. Differences will be considered statistically significant at a p value < 0.05. Intervention effect will also test using an analysis of covariance model (ANCOVA) adjusting for baseline parameters.

10. Study Procedures:

10.1 Treatment Schedule

Study Stage	**Specific Timing**	**Activity**
Planning 2 Months	N/A	• Approval of protocol • Independent peer-review

		● Logistical arrangements ● Recruitment
Pre-Study 1 Month	Upon approval and completion of recruitment	● Preliminary screening against inclusion and exclusion criteria ● Pre-study interview: ○ Information email and gain informed consent from the participant ○ Enrolled participants purchase the product and receive the testing kits along with instruction regarding the study requirements.
Study Week 0-24	Baseline data collection	First test kit will be shipped to imaware
	Trial Period	● Participant takes product as instructed ● Participant will receive and send the test kits on month 3 and 6
Trial Months 0-6 (Period begins at trial week 2) End-Study Month 3	Trial end interview	● Participant completes end-trial blood test. ● Participants exit email or phone interview to address adherence.
Post-Study	N/A	● Data verification and statistical analysis ● Report drafting and approval ● Study debrief and review

***** Please note that enrolment in the trial to receive product will only occur after all inclusion criteria have been met.

10.2 Length of Treatment Time

In total, participants will be required to send the test kits 3 times throughout the total trial time of 6 months.

At the completion of month 6, participants will repeat the baseline measures including a final blood test and a required exit interview.

Clinical interviews will be undertaken by email or phone. The trial will be completed once the last participants complete the exit interview.

10.3. Risks and Discomforts

As in the case of taking any treatment, we cannot guarantee that participants will not experience any uncomfortable effects during this study. The treatment includes the following ingredients: Almega PL.

There are 4 reported causes of adverse effects of orally dosed supplements containing EPA reported on the TGA database. Specifically, diarrhoea, dry skin, enteritis infection (inflammation of the small intestine) and nephrolithiasis (kidney stones). These events are 4 out of several thousands of participants. A 2011 study using a similar EPA based product and involving 229 participants found the product to be well tolerated.

There is also a risk of discomfort that may be experienced because of the blood draws with finger prick. Blood sampling can cause pain, bleeding, bruising, and/or swelling at the site of needle penetration (risk less than 1 in 50). Fainting may occur (risk less than 1 in 100), and infection rarely occurs (risk less than 1 in 1000).

Should participants experience any of these or other mild adverse effects or have other concerns about the treatment, blood collection, or data collection please contact the investigators (24 hours a day). Our contact details are found in the Contacts section of this document and the 24-hour contact mobile number is also on the product label.

10.4. Voluntary Participation/Right to Refuse or Withdraw

There is no obligation for participants to be involved in this study. If participants decide to participate in the study and later feel they no longer wish to be part of it, participants may withdraw from the study at any time without prejudice to any current or future involvement in clinical studies held by the study investigators or sponsor. If participants withdraw their consent, all data collected up until that time will be used in the analysis of the data.

All communications will be performed by a trained iwi Qualitas employee (Study Director) or the Principal Investigator Dr. Ganuza. In the event that Dr. Ganuza does not screen the participant, Dr Ganuza will review case files before participants are enrolled. Any participant that presents a response or result (e.g. blood test) that is outside of normal range will be directed by Imaware^{TM} to medically trained professionals with their results.

10.5. Confidentiality

The study investigator will gather certain personal information about participants. This information will be held by Qualitas/iwi as aggregated data. Data will be identifiable via study number allocated at enrolment but not by participant name. All publicly shared data or data used in publications will be in a non-identifiable form.

Consent is sought for extended use of the data, which means it may be used in future research—for example, an extension of the current study and/or related studies conducted by Qualitas/iwi. Furthermore, data may be used for subsequent statistical analysis, which may be published in peer-reviewed journals; however, no identifiable personal details will be published or used.

Participant data will be stored in the company share drive with access restricted to the researchers involved in the study at the head office of Qualitas Health for a period of 15 years and will be accessed by Trial Co-Investigator and trial contact. At the end of this storage period participant data will be disposed of in a confidential manner.

Unless required by law, only the participants and their authorised representatives, will have access to data which identifies participants by name or from which participant identity is otherwise apparent or can be reasonably ascertained.

All personal information will be used only for the purpose of administering participation in this study and in accordance with the laws governing the protection and privacy of personal information under USA privacy legislation.

By signing the attached consent form, participants authorize the release of/or access to this confidential information in an aggregated non-identifiable form to the relevant study personnel and regulatory authorities as noted above.

Participants have the right to access personal information collected from them in connection with the study and request corrections of any such personal information that is incorrect.

10.6. Termination of the Study

This research project may be stopped for a variety of reasons.

During the trial, any participant that records out-of-range analytical levels will be referred to their GP for assessment of suitability/safety for continuation in the trial.

At the discretion of the GP the participant will either be placed on standard care of cholesterol-lowering medication (and removed from the trial) or continue in the trial on the supplementation.

The participant also has the option to stop supplementation at any point.

11. Investigator Benefits

The investigators are being remunerated to conduct this study. They will not allow a conflict of interest to compromise their position or this research study.

12. Consent

The Principal Investigator, Dr Eneko Ganuza, is required to provide participants with all information regarding the nature and purpose of the research study, risks/benefits, and the possibility of alternative treatment; participants should be given the opportunity to discuss these. It must be stated that participants are free to withdraw anytime and that if participants do not participate, they will not suffer any prejudice.

13. Advice and Information – Contact Details

If participants have any further questions regarding this study, please do not hesitate to contact:

Eneko Ganuza –Trial Contact
Ph: +1 832 850 2022
24hr mobile: +1 480 519 5342

If unwarranted side effects occur, please don't hesitate to contact a doctor and the study representative.
In the case of an emergency please dial 911.