Bioavailability Study of COQUN ORAL FORMULATION (CoQ10) administered in Healthy Adults (CoQ10-01)

STUDY PROTOCOL

Study ID: VF-BAQ10/2018

Version Final – March 03, 2018

Sponsor: VISUFARMA SpA

Sponsor statement

The study will be conducted according to this protocol, the ICH-GCP, Good Clinical Practice guidelines, local laws and obligations and the World Medical Association Declaration of Helsinki.

Confidential

1 TITLE PAGE

STUDY PROTOCOL	
Title: Bioavailability Study of COQUN ORAL FORMULATION (CoQ10) administered in Healthy Adults (CoQ10-01)	Version number: Final
	Version date: March 03, 2018
	Study product: COQUN ORAL FORMULATION
Study/Protocol No.: VF-BAQ10/2018	Study phase: Bioavailability
EudraCT No.: NA	Intended use: Male & Female healthy volunteers
Principal Investigator: Dr. Delia Pintilei Reurean	
Sponsor: VISUFARMA SpA Via Canino, 21, 00191 Roma RM, Italia	
Contract Research Organization: 1MED SA Via Campagna 13 6982 Agno (CH)	
The information provided in this document is strictly confidential and is available for review to investigators, potential investigators, competent Ethics Committees and authorities only. No disclosure should be performed without the written authorization of Sponsor, except to the extent necessary to obtain Informed Consent from potential subjects.	

2 STUDY ADMINISTRATIVE STRUCTURE

Sponsor	VISUFARMA SpA Via Canino, 21, 00191 Roma RM, Italia
Drug safety officer	Anna Rita Bigioni, PhD VISUFARMA SpA
Principal Investigator	Dr. Delia Pintilei Reurean
CRO	1MED SA Via Campagna 13 6982 AGNO – CH
CRO Project Manager	Dr. Daniela Rotaru, 1MED
Statistician	Ilaria Speranza, 1MED
Analytical laboratory	SC LABORATOARELE BIOCLINICA SRL 30614 Bucuresti, Calea Calarasilor, Nr.161, Sector 3 Tel: 004 021 320 3311 Fax: 004 021 320 3100

SYNOPSIS AND FLOW CHART

3.1 Synopsis

Title:	Bioavailability Study of COQUN ORAL FORMULATION (CoQ10) administered in Healthy Adults (CoQ10-01)
Investigator:	Dr. Delia Pintilei Reurean
Study center:	Consult Med Iasi, 70, Calea Pacurari Str., bl 550, IASI, Iasi county, Romania
Study period:	Overall clinical duration of the study: 5 weeks Recruitment duration: 1 month Treatment duration: The study consists of 3 periods: 1. a *single-dose* phase, 1 day 2. a *wash-out period* of 7 days 3. a *multidose-dose* phase of 28 days The total duration of the study from the start of the first treatment period to the end of study visit is 35 days (5 weeks) per subject. Planned study start: June 2018 Planned study end: August 2018 Planned first subject in: July 2018 Planned last subject out: August 2018 Period per subject: 5 weeks
Study phase:	Bioavailability
Indication:	Male & Female Healthy Volunteers
Study Objective:	To evaluate the best dosage for COQUN ORAL FORMULATION in order to reach a level of plasma concentration which might assure its antioxidant effect if taken on a regular basis.
Outcome Measures:	- Area under the curve (microg/ml x h): ≥5 - Cmax: ≥0,8 - Tmax: ≥3 - elimination half-life (t 1/2)

Study type:	Interventional, Single-center, Single- and multi-dose Bioavailability Study of COQUN ORAL FORMULATION in Healthy Adults.	
Study description:	The study will include 24 healthy subjects who will test the CoQ10 formulation. All 24 subjects will test a single dose of 100mg CoQ10 in 1 day to assess bioavailability, which will be followed by a one week wash-out period and then by a 4 week period of continuous administration of COQUN ORAL FORMULATION in parallel groups (1:1): patients will be divided in the continuous treatment period into two groups, one group of 12 patients with intake of 100mg OD, the other one group of 12 patients with intake of 100mg BID, in order to assess multiple-dose profile of COQUN ORAL FORMULATION. Patients will have to fast the night before enrolment, for at least 10 hours. Patients will be requested to fill in a short diary in the multidose phase, on a daily basis, for confirming the product correct intake, and informing on any experienced adverse event and eventual medication taken for its solving.	
Number of subjects:	To be screened:	24
	To be divided in 2 parallel groups (1:1):	24
	Intention-to-treat (ITT):	This set contains all randomized subjects.
	Per protocol (PP):	This set consists of all subjects who meet all inclusion/exclusion criteria and who do not have any major protocol deviation.
Study population:	<u>Inclusion criteria:</u> • Subject Informed consent form (ICF) is singed • M & F Aged between 35-75 years at the time of the signature of ICF • A body mass index between 20 and 29 kg/m^2 • Fasting the night before enrolment, for at least 10 hours • Healthy, meaning absence of any prescribed medication for a month prior to the inclusion to the study and during the study • Willing to avoid a consumption of any food supplements except vitamin D and calcium at least 2 weeks before and during the study	

	• Consumption of dairy and cereal products (standardized breakfast will include low lactose dairy and bread) • Willing to follow all study procedures, including attending all site visits (including sessions during which a venous line will be inserted for blood sampling), and keeping a diary for the time of multiple-dose study (to follow their compliance and palatability) <u>Exclusion criteria:</u> • Intake of any prescribed medication within 2 weeks of the beginning of the study • Intake of any food supplements within 2 weeks of the beginning of the study, except vitamin D and calcium • Hypotension • Any clinically significant history of serious digestive tract, liver, kidney, cardiovascular or hematological disease, diabetes • Gastrointestinal disorders or other serious acute or chronic diseases • Known lactose/gluten intolerances/ food allergies (limitation for standardization of meals) • Inadequate veins (in the opinion of the investigator) or known contraindication to placement of a dedicated peripheral line for venous blood withdrawal • Known drug and/or alcohol abuse • Using any form of nicotine or tobacco • Mental incapacity that precludes adequate understanding or cooperation • Participation in another investigational study or blood donation within 3 months prior to or during this study
Sample size	The simple size for this study is not based on any power calculation. 24 subjects (12 for each arm) have been considered sufficient to obtain reliable results for the exploratory purposes of the study.
Duration of treatment:	1. *single-dose* phase of 1 day: 24 adult healthy subjects will be given a single dose of 100 mg of COQUN ORAL FORMULATION 2. a *wash-out period* of 7 days (no treatment) 3. a *multidose-dose* phase of 28 days: 12 adult healthy subjects will be given OD 100mg of COQUN ORAL FORMULATION, after dinner (group A), while the other group of 12 adult healthy subjects will be given BID a dose of 100 mg of COQUN ORAL FORMULATION, after lunch and after dinner (group B)

Investigational Product:	Study product:	COQUN ORAL FORMULATION (Coenzyme Q10 Miniactive Retard 100mg capsules)
	Dose/dosage:	Single-dose of 100 mg Multi-dose: 100mg OD (one group) vs 100mg BID (second group)
	Administration:	Single-dose of 100 mg Multi-dose: 100mg OD (one group) vs 100mg BID (second group)
	Dose/dosage:	Coenzyme Q10 Miniactive Retard 100mg capsules, in a vegetable case containing 30 capsules
	Administration:	po (oral formulation)
Criteria for evaluation:		
COQUN ORAL FORMULATION level of plasma concentration:	- *single-dose* phase; 24 adult healthy subjects will be given a dose of 100 mg of COQUN ORAL FORMULATION and plasma coenzyme Q10 will be measured over the next 12 hours: at 1, 2, 4, 8 and 12 hours after intake. Pharmacokinetic properties including area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax) and elimination half-life (t 1/2) will be measured - *multidose-dose* phase; 12 adult healthy subjects will be given OD 100mg of COQUN ORAL FORMULATION, after dinner (group A), while the other group of 12 adult healthy subjects will be given BID a dose of 100 mg of COQUN ORAL FORMULATION, after lunch and after dinner (group B); plasma coenzyme Q10 will be measured over the next 4 weeks. Pharmacokinetic properties including area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax) and elimination half-life (t 1/2) will be measured.	
Safety:	Safety will be monitored through vital signs, physical exams, clinical laboratory tests (hematology, serum chemistry), and adverse events including assessment of relationship to the IP.	

Statistical methods:	Due to the explorative aim of the study, descriptive statistics and confidence intervals at 90% level will be provided. In particular, continuous variables will be presented as arithmetic mean values ± standard deviation (SD) and median values with interquartile range; geometric means will be provided as well; for categorical variables absolute and percentage frequencies will be provided.

3.2 Flow Chart

	V1 Screening & treatment start						V2	V3	V4	V5 (EOS)
	Day -7						Day 0	Day 7	Day 14	Day 28
	moment 0	h 1	h 2	h 4	h 8	h 12				
ICF	x									
Incusion/Exclusion criteria check	x									
Vital signs	x	x	x	x	x	x	x	x	x	x
Physical examination	x						x	x	x	x
Medical history	x									
Concomitant medication	x						x	x	x	x
Blood sampling	x	x	x	x	x	x	x	x	x	x
CoQ10 intake	x						AB	AB	AB	AB
Pharmacokinetics		x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x

4 TABLE OF CONTENTS

5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Events
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Aea under the concentration-time curve
AUC_{0-t}	Area under the serum concentration versus time curve to the last measurable concentration (t)
AUC_{0-inf}	Area under the serum concentration versus time curve to infinity
C_{max}	Maximum measured serum concentration
C_{min}	Concentration at the end of a dosing interval
CFR	Code of Federal Regulations
°C	Degrees Celsius
CRO	Contract Research Organization
CTR	Clinical Study Report
CRF	Case Report Form
ECG	Electrocardiogram
e.g.	Exempligratia, for example
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
i.e.	Id est, that is
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-treat
kg	Kilogram
MedDRA	Medical Dictionary or Regulatory Activities
mg	Milligram
ug/ml	Microgram/Milliliter
PD	Pharmacodynamic
PK	Pharmacokinetic
QA	Quality assurance
QC	Quality control
PP	Per Protocol
SAE	Serious Adverse Event
SAS	Statistical Analysis System (SAS®)
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Apparent terminal elimination half-life
t_{max}	Time of the maximum measured serum concentration
TMF	Study Master File

6 INTRODUCTION

6.1 Background

Coenzyme Q10 (CoQ10) is a substance similar to a vitamin. It is found in every cell of the body. The body produces CoQ10, and the cells use it to produce energy for the body needs for cell growth and maintenance. It also functions as an antioxidant, which protects the body from damage caused by harmful molecules. CoQ10 is naturally present in small amounts in a wide variety of foods, but levels are particularly high in organ meats such as heart, liver, and kidney, as well as beef, soy oil, sardines, mackerel, and peanuts.

The Coenzyme Q10, also known as ubiquinone, is an endogenous molecule, synthesized by our body and essential for the proper functioning of the mitochondria, or the cellular units responsible for the production of energy in the body.

In organisms it participates in redox reactions and, depending on the state of oxidation, it can be present in three forms: an oxidized, a semi-quinone intermediate and a reduced form. The side chains make it very lipophilic, in fact it is present in biological membranes, especially mitochondrial ones.

Higher levels of Q10 could improve the efficiency of the electron transport chain, increasing the available energy.

Rebalancing the function of the mitochondria, which are in practice the "lungs" of every single cell, means allowing the cell to restore its original energy potential, and, in a certain sense, to "rejuvenate" allowing it to "breathe" and use the available energy correctly.

If coenzyme Q is reduced by acquiring an electron it forms a radical called ubisemichinone (QH.). For further reduction the compound becomes a ubiquinol (QH2).

The concentration of coenzyme Q10 tends to decrease with aging; low levels are also recorded in the presence of particular chronic diseases, such as those resulting from heart problems, Parkinson's disease, muscular dystrophy, diabetes, cancer and AIDS. Certain drugs, such as statins used in the control of hypercholesterolemia, can also lower Coenzyme Q10 levels.

Coenzyme Q10 has been shown to have beneficial effects on some patients with migraine and is a major component of the myth cocktail used in the treatment of mitochondrial myopathy and other metabolic disorders.

Taking 100 mg a day or more of CoQ10 has caused mild insomnia in some people. And research has detected elevated levels of liver enzymes in people taking doses of 300 mg per day for long periods of time. Liver toxicity has not been reported.

Other reported side effects include rashes, nausea, upper abdominal pain, dizziness, sensitivity to light, irritability, headache, heartburn, and fatigue.

Medicines for high cholesterol (statins) and medicines that lower blood sugar cause a decrease of CoQ10 levels and reduce the effects of CoQ10 supplements. CoQ10 can reduce

the body's response to the blood thinner (anticoagulant) medicine warfarin (Coumadin) and can decrease insulin requirements in people with diabetes.

Many factors can affect the Q10 blood level of people who are not taking a Q10 supplement: age, diet, disease, medications (for example, statin medications).
Q10 levels in the blood from the body's own synthesis of the substance increase after (0.20 ug/ml) birth until about the age of 21. Thereafter, the body's synthesis of Q10 gradually decreases.
It is expected that supplementing regularly with Q10 to raise the Q10 blood level, but much depends on the way in which the Q10 product has been prepared and much depends on the dosage. It was demonstrated that taking 30 milligrams or 50 milligrams of Q10 daily will not raise the Q10 level as much as taking 100 mg of Q10 daily will do, while taking 100 milligrams of Q10 twice daily will yield even greater gains in Q10 blood levels.

From the literature it is known that a well-absorbed Q10 supplement should over time raise the blood level to about 2.5 micrograms per milliliter if the individual is taking a 100-milligram dosage once a day, while if taken the same Q10 supplement in a dosage of 100 milligrams twice a day, its blood level should, over time, raise the steady-state Q10 blood level to somewhere in the area of 3.5 micrograms per milliliter. But, the attainable levels will vary from individual to individual, beside depending on the product itself as formulation.

Recent studies have shown how the antioxidant effects of the enzyme Q10 can have benefits on the body and on the brain. Some of these studies indicate that coenzyme Q10 can protect the brain from neurodegenerative diseases, such as Parkinson's disease, as well as damage that causes ischemia (stroke) to the brain. Other recent studies show a benefit regarding the possibility of survival, after cardiac arrest, if coenzyme Q10 is given concurrently to a cooling of body temperature (between 32-34 degrees Celsius).

The endogenous concentrations of Coenzyme Q10 tend to reduce also in the presence of some chronic neurodegenerative diseases, such as Glaucoma.
Numerous scientific studies have shown that the axons of retinal ganglion cells are rich in mitochondria necessary to produce energy for nerve conduction. The reduction in energy production and the increase in the production of mitochondrial free radicals of ganglion cells is to be considered a key mechanism in the etiopathogenesis of glaucoma, which predisposes to the death of such cells and their axons.

Recent studies have also shown that CoQ10 ameliorates oxidative stress in ischemic retina, promotes retinal ganglion cell (RGC) survival in ischemic retina induced by intraocular pressure elevation and apoptotic cell death by decreasing Bax or by increasing pBad protein expression in ischemic retina, providing a promising therapeutic potential for ameliorating oxidative stress-mediated mitochondrial dysfunction in ischemic retinal injury.

Also, topical CoQ10 appears an effective therapy preventing RGC apoptosis and loss in glaucoma-related models.

6.2 Rationale of the Study

Many studies showed the beneficial proprieties of CoQ10 on the body and on the brain especially if taken on a daily basis, as well as its properties to ameliorate oxidative stress in ischemic retina, providing a promising therapeutic potential for ameliorating oxidative stress-mediated mitochondrial dysfunction in ischemic retinal injury and for preventing RGC apoptosis and loss in glaucoma-related models.

It is expected that supplementing regularly with Q10 will raise the Q10 blood level, but much depends on the way in which the Q10 product has been prepared and much depends on the dosage. It was demonstrated that taking 30 milligrams or 50 milligrams of Q10 daily will not raise the Q10 level as much as taking 100 mg of Q10 daily will do, while taking 100 milligrams of Q10 twice daily will yield even greater gains in Q10 blood levels.

From the literature it is known that a well-absorbed Q10 supplement should over time raise the blood level to about 2.5 micrograms per milliliter if the individual is taking a 100-milligram dosage once a day, while if taken the same Q10 supplement in a dosage of 100 milligrams twice a day, its blood level should, over time, raise the steady-state Q10 blood level to somewhere in the area of 3.5 micrograms per milliliter. But, the attainable levels will vary from individual to individual, beside depending on the product itself as formulation.

Therefore, this bioavailability study is intended to be performed in order to evaluate the best dosage for COQUN ORAL FORMULATION, with its innovative technology based on the modified release of active principles at certain time intervals, in order to reach a level of plasma concentration which might assure its antioxidant effect if taken on a regular daily basis.

6.3 Risk/Benefit Consideration

Taking 100 mg a day or more of CoQ10 has caused mild insomnia in some people and research has detected elevated levels of liver enzymes in people taking doses of 300 mg per day for long periods of time. Liver toxicity has not been reported.
Other reported side effects include rashes, nausea, upper abdominal pain, dizziness, sensitivity to light, irritability, headache, heartburn, and fatigue.
Medicines for high cholesterol (statins) and medicines that lower blood sugar cause a decrease of CoQ10 levels and reduce the effects of CoQ10 supplements. CoQ10 can reduce the body's response to the blood thinner (anticoagulant) medicine warfarin (Coumadin) and can decrease insulin requirements in people with diabetes.
Many factors can affect the Q10 blood level of people who are not taking a Q10 supplement: age, diet, disease, medications (for example, statin medications).

For this study, the subjects will be screened in order to be healthy, with no concomitant diseases, who will receive 100mg or 200mg of COQUN ORAL FORMULATION for 1 moth and will be treated appropriately and constantly monitored so that benefits outweigh potential risks for the subjects.

7 STUDY OBJECTIVES AND VARIABLES

7.1 OBJECTIVES

Primary objective:

The primary objective of this study is to evaluate the best dosage between 100mg OD or 100mg BID for COQUN ORAL FORMULATION in order to reach a level of plasma concentration which might assure its antioxidant effect if taken on a regular basis.

Secondary Objectives:

Secondary objectives of this study are:

- To evaluate the safety and tolerability COQUN ORAL FORMULATION following single dose of 100mg
- To evaluate the safety and tolerability of COQUN ORAL FORMULATION during the 1 month daily dose

7.2 VARIABLES

Primary Variable

Pharmacokinetic properties:

- Area under the curve (microg/ml x h): ≥5
- Cmax: ≥0,8
- Tmax: ≥3
- elimination half-life (t 1/2)

Secondary Variable(s)

The secondary variables are the ones regarding safety which will be monitored through vital signs, physical exams, ECGs, clinical laboratory tests and adverse events, as follows:

- following a single oral dose of 100mg COQUN ORAL FORMULATION
- in 1 month period of daily oral intake of 100mg OD or BID COQUN ORAL FORMULATION

Symptoms and signs like mild insomnia, elevated levels of liver enzymes, rash, nausea, upper abdominal pain, dizziness, sensitivity to light, irritability, headache, heartburn, and fatigue will be closely monitored.

8 SUBJECT POPULATION

8.1 Subject Population

In order to participate in this study, each subject must meet all of the following inclusion and none of the exclusion criteria at screening and at check-in.
24 subjects will be screened in order to receive a single dose of 100mg COQUN ORAL FORMULATION, while after 1 week of wash-out period, the subjects will be divided in two equal groups of 12 subjects each in order to enter the 1 month multidose phase: group A (12 subjects) will receive 100mg OD of COQUN ORAL FORMULATION, while the group B (12 subjects) will receive 100mg BID of COQUN ORAL FORMULATION.

8.2 Inclusion Criteria

Subjects will only be included in the study if they meet all of the following criteria:

- Subject Informed consent form (ICF) is singed
- M & F Aged between 35-75 years at the time of the signature of ICF
- A body mass index between 20 and 29 kg/m^2
- Fasting the night before enrolment, for at least 10 hours
- Healthy, meaning absence of any prescribed medication for a month prior to the inclusion to the study and during the study
- Willing to avoid a consumption of any food supplements except vitamin D and calcium at least 2 weeks before and during the study
- Consumption of dairy and cereal products (standardized breakfast will include low lactose dairy and bread)
- Willing to follow all study procedures, including attending all site visits (including sessions during which a venous line will be inserted for blood sampling), and keeping a diary for the time of multiple-dose study (to follow their compliance and palatability)

8.3 Exclusion Criteria

Subjects will not be included in the study if any of the following criteria applies:

- Intake of any prescribed medication within 2 weeks of the beginning of the study
- Intake of any food supplements within 2 weeks of the beginning of the study, except vitamin D and calcium
- Hypotension
- Any clinically significant history of serious digestive tract, liver, kidney, cardiovascular or hematological disease, diabetes
- Gastrointestinal disorders or other serious acute or chronic diseases
- Known lactose/gluten intolerances/ food allergies (limitation for standardization of meals)
- Inadequate veins (in the opinion of the investigator) or known contraindication to placement of a dedicated peripheral line for venous blood withdrawal
- Known drug and/or alcohol abuse
- Using any form of nicotine or tobacco
- Mental incapacity that precludes adequate understanding or cooperation
- Participation in another investigational study or blood donation within 3 months prior to or during this study

8.4 Premature Discontinuation

Any subject who discontinued the study before the scheduled completion of the study procedures will be considered as prematurely discontinuation, regardless of the reason for discontinuation.

Upon discontinuation, the final study visit should be performed. For safety reasons, reasonable attempt should be made to contact withdrawn subjects in due time post the discontinuation to gather information on adverse events and long-term outcome measures, i.e. laboratory measurements. Information collected as a result should be recorded on the appropriate CRF pages.

Drop-outs, if any, will be replaced only if the per-protocol number of subjects will not be reached in order to have the per-protocol number of subjects.

8.4.1 Premature Discontinuation due to an Adverse Event

Adverse events resulting premature discontinuation of a subject must be assessed, documented, and reported by the investigator as per protocol (see section 11.1.6). Subjects that are withdrawn due to an adverse event not resolved by end of study visit should be followed up until the event or its sequel resolves or stabilizes at a level acceptable to the investigator and the sponsor.

8.4.2 Premature Discontinuation by the Subject

Subjects may discontinue the study at any time without giving reasons and without any disadvantageous consequences for their subsequent medical care.

8.4.3 Premature Discontinuation of a Subject by the Investigator

The investigator may withdraw a subject from the study at any time in case of intercurrent illness, adverse event, and therapeutic procedure or as a general rule if further participation in the study is believed to be to the subject's detriment.

The investigator must immediately withdraw any subject from the study who is found not to be eligible for the study based on the inclusion and exclusion criteria. This can occur, for example, in the case of alarming examination results or strikingly abnormal laboratory values. In these cases, no investigational product is to be administered and no protocol procedures are to be performed any more.

8.4.4 Reporting of Premature Discontinuation

The investigator must notify the Sponsor/CRO of any premature discontinuation of a subject and complete the CRF end of study page.

9 TREATMENTS

9.1 General

The sponsor will provide the investigational site with adequate supplies of the IP. The IP will be produced, packed, and labeled according to national drug laws and GMP. IP shipped to the investigational site will be documented on an appropriate shipment form.
The IP administered to the subjects will be documented on a drug accountability form and in the CRF.
Storage conditions as specified on the drug labels shall apply; the IP shall be kept at temperatures below 25°C, in a dry and cool place and out of reach of children.

9.2 Treatments Administered

The investigator will use the IP only for subjects included in the study. It is prohibited to use the IP for any other purpose. Unused IP will be collected and returned to the sponsor at the end of the study.
Each subject who completes the study screening assessments and meets all the eligibility criteria will be assigned a unique screening number and will receive the corresponding IP according to the dosage scheme. The treatment will be assigned after the Investigator had entered by hand on the IP label the subject screening number.

9.3 Identity of Investigational Product

9.3.1 Investigational Product

Name:	COQUN ORAL FORMULATION
Description:	COQUN ORAL FORMULATION is a food supplement based on Coenzyme Q10 MINIACTIVES®
Ingredients:	Coenzyme Q10, Sucrose, Corn starch, Shellac (E904), Polysorbate 80 (E433), Hydroxypropylmethylcellulose Coloring: Titanium dioxide
Dose/dosage	100 mg CoQ10 / 1 caps
Pharmaceutical company responsible for the product:	VISUfarma Spa
Batch No.:	to be defined in the certificate of analysis
Packaging, labeling, and release of IP:	Sponsor

COQUN ORAL FORMULATION will be supplied in boxes containing e blisters each of 10 capsules (total 30 capsules) produced in Italy by VISUfarma.

9.3.2 Rescue Treatment/Medication

No rescue medication is foreseen; subjects will be recommended to respect the daily dose and intake time, as well as the storage conditions.
Subjects will be requested to inform the investigator on any adverse event experienced in the multidose phase of the study in order to allow the investigator to take the best safety decision for the subject.

9.4 Dosage Regimen and Intake

Subjects should be fasted for at least 10 h prior to enrolment. The IP capsules will be administered orally, always after food intake and at specific moments during the day, according to the OD or BID intake:
- group A: 100mg OD, after dinner
- group B: 100mg BID after lunch and after dinner

9.5 Start of Treatment and Instruction of Subjects

The administration of IP will have to be documented in the corresponding section in the CRF, as well on the specific forms filed in the ISF.
The investigator has to inform the subject in detail how and when the IP shall be administrated.

9.6 Methods of Assigning Subjects to Treatment Groups

Subjects who are eligible for the study will first be thoroughly informed about the aims and details of the study and in case the subject accepts to participate, the signed Informed Consent will be obtained, and the patient will receive the lowest screening number available.
If all required criteria for admitting a subject to the study are fulfilled, the investigator will proceed with the study procedures of the Screening visit (V1) and with the single dose administration of IP.
After the screening visit, subjects will have one week of wash-out period, then will be requested to return to the site for V2, during which Subjects will be randomly assigned to one of the two groups:
- group A: 12 adult healthy subjects will be given OD 100mg of COQUN ORAL FORMULATION, to be taken after dinner
- group B: the other 12 adult healthy subjects will be given BID a dose of 100 mg of COQUN ORAL FORMULATION, to be taken after lunch and after dinner

9.7 Drug Accountability and Compliance

The site will be provided with IP shipment and accountability forms to maintain accurate written documentation of all IP transfer processes between the sponsor, the investigator, and the subject. The IP shipment form will be used to document when and the IP quantity delivered to the study site. The accountability form will be used to document when and how much IP is dispensed to the subject. The investigator will document the IP administration to subjects in the source documents.

The accountability form must show how much of the IP was used and unused at the end of the study. The monitor will collect the remaining IP, the packages, and the corresponding documentation forms after study completion. The used and unused amount of the IP will be assessed by the monitor by counting. All remaining IP and packages will be returned to the sponsor at the end of the study.

9.8 Previous and Concomitant Medication

Any medication taken in parallel with the IP is defined as concomitant medication and will be carefully documented in the CRF including the previous medication administered within the last 2 months prior to the start of the study.
Except for medication which may be required to treat AEs (see below), no medication will be allowed during the entire study duration, in concomitance with the IP until after the end-of-study evaluation.
The investigator will instruct the subject to notify the study site about any new medications or significant non-drug therapies (including physical therapy and blood transfusions) administered after the start of the IP. All such medications and non-drug therapies will be documented in the CRF and may require the subject to be withdrawn.
Whenever possible, administration of concomitant medication should be avoided with special attention to PK and PD sampling and may require the subject to be withdrawn.
For previous and concomitant medication/therapy the following information will be recorded in the CRF:

- Brand name or generic name (preferred)
- Indication
- Total daily dose and units
- Route of administration
- Time/duration of treatment.

9.9 Overdose

The daily recommended dose should be respected, in order to avoid side effects possibly generated by a higher daily dose than the recommended one.
In case succeeds, the subject will be instructed to inform immediately its investigator.

9.10 Packaging, Labeling, and Storage

Packaging and labeling will be performed by the sponsor.
The investigational product is available as Coenzyme Q10 Miniactive Retard 100mg capsules, in a vegetable case containing 30 capsules, packaged in 3 blisters (10 capsules each); for each enrolled subject, 2 boxes containing 30 capsules will be supplied, with 1 box as reserve.
Investigational products will be packed and labeled according to national requirements and GMP.

Labels text:

Single dose phase

Secondary packages:

For the, 100mg COQUN OS x 1 for 1 day (for 24 healthy subjects)

SINGLE DOSE PHASE
VISUFARMA S.p.A.
Via Canino, 21, 00191 Roma RM, Italia
Phone: 0039-06-89765262, Anna Rita Bigioni
ONLY FOR CLINICAL INVESTIGATION
Bioavailability Study: **VF-BAQ10/2018**
30 capsules food supplement of COQUN, 100mg/caps
3 blisters each of 10 capsules
only for Day -7

Dosage: 1 capsule once
Investigator**:** _____
Site # 01
STORAGE: Keep at temperatures below 25°C, in a dry and cool place
WARNINGS: Keep out of reach of children

Lot: _____ Expiry: MM/YYYY

Multidose phase

Secondary packages:

group A: 100MG COQUN OS x 1 / day

MULTIDOSE PHASE
VISUFARMA S.p.A.
Via Canino, 21, 00191 Roma RM, Italia
Phone: 0039-06-89765262, Anna Rita Bigioni
ONLY FOR CLINICAL INVESTIGATION
Bioavailability Study: **VF-BAQ10/2018**
30 capsules food supplement of COQUN, 100mg/caps
3 blisters each of 10 capsules
To be released at V2

Dosage: 1 capsule once daily (after dinner)
Investigator**:** _____
Site # 01
STORAGE: Keep at temperatures below 25°C, in a dry and cool place
WARNINGS: Keep out of reach of children

Lot: _____ Expiry: MM/YYYY
Patient Number: 0 1 I__II__I

group B: 100MG COQUN os x 2 / day

MULTIDOSE PHASE
VISUFARMA S.p.A.
Via Canino, 21, 00191 Roma RM, Italia
Phone: 0039-06-89765262, Anna Rita Bigioni
ONLY FOR CLINICAL INVESTIGATION
Bioavailability Study: **VF-BAQ10/2018**
30 capsules food supplement of COQUN, 100mg/caps
3 blisters each of 10 capsules

To be released at V2

Dosage: 1 capsule twice daily (after lunch and after dinner)
Investigator**:** _____
Site # 01
STORAGE: Keep at temperatures below 25°C, in a dry and cool place
WARNINGS: Keep out of reach of children

Lot: _____ Expiry: MM/YYYY
Patient Number: 0 1 I__II__I

Study medication must be stored at temperatures below 25°C, in a dry and cool place, out of reach of children. This temperature range should be closely maintained until administration to the subjects, while subjects shall continue to respect the storage conditions at their home in the multidose phase. To be stored in original package in order to protect from light.
The product should not be used, and must be discarded if the blisters are broken, not completely sealed.

10 DESIGN, METHODS, AND CONDUCT OF THE STUDY

10.1 Study Design

This is an interventional, single-center, single- and multi-dose bioavailability study of COQUN ORAL FORMULATION in Healthy Adults.
The primary objective of the study is to evaluate the best dosage for COQUN ORAL FORMULATION in order to reach a level of plasma concentration which might assure its antioxidant effect if taken on a regular basis.
24 healthy subjects will be chosen for the study population.
Each subject who completes the study screening assessments and meets all the eligibility criteria will be assigned to one of the two groups and will receive the corresponding IP dose.

10.2 Study Duration

Recruitment period is estimated to be 1 month.
Once a subject has signed the informed consent form, will enter the single dose phase of 1 day, after which will follow a 1 week washout period, then will enter the 1 month multidose treatment phase.

Planned study start is June 2018 (submission phase) and planned study end is September 2018 (clinical study report).

10.3 Study Schedule

Healthy volunteer subjects who meet the inclusion/exclusion criteria at screening will start the IP administration as follows:

1. a *single-dose* phase; 24 adult healthy subjects will be given a dose of 100 mg of COQUN ORAL FORMULATION and plasma coenzyme Q10 will be measured over the next 12 hours: at 1, 2, 4, 8 and 12 hours after intake. Pharmacokinetic properties including area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax) and elimination half-life (t 1/2) will be measured.

2. a *wash-out period* of 1 week

3. a *multidose-dose* phase; 12 adult healthy subjects will be given OD 100mg of COQUN ORAL FORMULATION, after dinner (group A), while the other group of 12 adult healthy subjects will be given BID a dose of 100 mg of COQUN ORAL FORMULATION, after lunch and after dinner (group B); plasma coenzyme Q10 will be measured over the next 4 weeks. Pharmacokinetic properties including area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax) and elimination half-life (t 1/2) will be measured.

Subjects will be requested to fill in a short diary in the multidose phase, on a daily basis, for confirming the product correct intake, and informing on any experienced adverse event and eventual medication taken for its solving.
Subjects will have to fast the night before enrolment, for at least 10 hours, then should be seen for all visits on the designated day.
Subjects will be requested to fill in a short diary in the multidose phase, on a daily basis, for confirming the product correct intake, and informing on any experienced adverse event and eventual medication taken for its solving.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations and adverse event (AE) monitoring.

10.4 Methods

10.4.1 Subject Information and Informed Consent

The investigator must obtain written Informed Consent from each subject prior any study related procedure. The Informed Consent Form must be personally dated and signed by both, the investigator and the subject (please refer to chapter 15.4 'Informed Consent Form and Subject Information').

By dating and signing the Informed Consent Form, the subject is enrolled into the study and CRF must be filled in.

10.4.2 Methods for Assessment of Pharmacokinetic Variables

Samples will be analyzed for serum CoQ10 using an immunosorbent assay (ELISA;enzyme-linked immunosorbent assay) validated at the analitycal laboratory.

10.4.3 Methods for Assessment of Pharmacodynamic Variables

Red blood cells and reticulocytes will be assessed using flowcitometry method and Hemoglobin will be assessed using spectrophotometry method. Hematocrit will be calculated from MCV value and total number of red blood cells.

10.4.4 Methods for Assessment of Safety Variables

Safety will be monitored through vital signs, physical exams, ECGs, clinical laboratory tests and adverse events including assessment of relationship to the IP.

10.4.5 Methods for Assessment of other Variables

Following Demographic information will be recorded: date of birth, race and gender. Medical history will be recorded with the following data: disease, date of onset, date of resolution or status, treatment.
Concomitant medication will be recorded as follows: all medication-treatments within the last 2 months prior to screening, date of start, date of stop or status, dosage, route of administration, frequency of administration.

10.4.6 Appropriateness of Measurements

All measurements will be performed, and all data will be collected according to medical standard procedures. The laboratory involved in the laboratory investigations is a certified one.

10.5 Conduct of the Study

10.5.1 Screening visit & treatment start (V1, Day -7, single dose phase)

Screening visit will be performed once the subject signed the informed consent form and the following procedures will be performed:

- subject information and informed consent
- demographic data and medical history recording
- physical examination
- vital signs (blood pressure, heart rate, temperature and respiratory rate)
- body measurements (height and weight)
- 12 lead ECG
- safety laboratory analysis
- concomitant medication recording

- assessment of inclusion/exclusion criteria

Once the subjects are considered eligible for the study, all 24 adult healthy subjects will enter the single dose treatment phase and will be given a dose of 100 mg of COQUN ORAL FORMULATION and plasma coenzyme Q10 will be measured over the next 12 hours: at 1, 2, 4, 8 and 12 hours after intake. Pharmacokinetic properties including area under the curve (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax) and elimination half-life (t 1/2) will be measured.
Safety parameters will be monitored during the whole day.

The subjects will be requested to fasten for at least 10 hours before IP intake; when will arrive at the study center subjects will be hospitalized for at least 12 hours for the single dose phase, therefore subjects will remain at site for around 24 hours.
At the end of this visit, if no SAE occurs, subjects will be dismissed and will be requested to return after 1 week for the second study visit and multidose phase start.
In the wash-out period subjects will have to respect the same lifestyle regimen and no medication shall be taken, if not necessary.
Subjects will be given a diary and will be requested to report any possible adverse event experienced between V1 and V2, as well as any treatment taken for treating an AE, if applicable.

10.5.2 Ambulatory visit V2, Day 0 (multidose phase)
Subjects will return at site for entering the multidose phase and will be randomly divided into two groups of treatment:
- group A: 12 adult healthy subjects will be given OD 100mg of COQUN ORAL FORMULATION, to be taken after dinner
- group B: the other 12 adult healthy subjects will be given BID a dose of 100 mg of COQUN ORAL FORMULATION, to be taken after lunch and after dinner;
Plasma coenzyme Q10 will have to be measured over the next 4 weeks.
During V2 the following study procedures will be done:

- vital signs (blood pressure, heart rate, temperature and respiratory rate)
- blood sampling for pharmacokinetic determination
- safety laboratory analysis
- record of concomitant medication
- adverse events
- subject diary check

10.5.3 Ambulatory visits V3 (Day 7), V4 (Day 14), V5 (Day 28, EOS) (multidose phase)
During V3, V4 and V5 the following study procedures will be done:

- vital signs (blood pressure, heart rate, temperature and respiratory rate)
- blood sampling for pharmacokinetic determination
- safety laboratory analysis

- record of concomitant medication
- adverse events
- subject diary check

End of study (EOS) is foreseen on Day 28, at 4 weeks after entering the multidose phase.

10.6 Study procedures schedule

10.6.1 Subject information and inform consent

This procedure will be done at screening (V1) and will be **PRIOR** to any other study procedure.

10.6.2 Demographic data

Date of birth, age, gender and ethnicity will be recorded at screening visit.

10.6.3 Medical history

Relevant medical history and current medical conditions will be recorded at screening visits. Subjects will be asked about their smoking habits.

10.6.4 Psychical examination

A general examination of overall appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic assessment of the nervous system will be performed at study visit.
Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present at screening visit will be documented in the Medical History section of the CRF. Significant findings present after this visit which meet the definition of an AE must be recorded by subjects in their subject diary and then reported by the investigator in the CRF.

10.6.5 Vital signs

Systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature will be assessed at screening, hospitalization day and during ambulatory visits.

10.6.6 Body measurements

Subject's body height and weight will be measured at screening visit. During the ambulatory visits only the body weight will be measured.

10.6.7 12 lead ECG

A standard 12-lead ECG will be performed after the subject has rested for at least 5 minutes in the supine position at screening and at end of study.
The time of ECG and the overall interpretation (normal, clinically insignificant abnormality, clinically significant abnormalities) will be recorded. Copies of the tracings must company the corresponding CRF.

The subject number, the actual date and time of the tracing and the study code must appear on each page of the tracing. The tracings must be signed by the study investigator performing the interpretation.

10.6.8 Record of concomitant medication

At screening visit all medication taken by the subjects in the 2 months before screening visit will be recorded.

Any concomitant medication taken by the subjects will be documented during the hospitalization on Day-7 and at each of the ambulatory visits on Day 0, 7, 14 and Day 28 (EOS).

10.6.9 Laboratory assessments

Screening and early morning assessments will be performed at V1 (screening) and each of the ambulatory visits on Day 0, 7, 14 and Day 28 (EOS).

Subjects will be required to be fasted for at least 8 hours before blood sampling.

Hematology

RBC count, WBC count (total, i.e, leucocyte count and differential, i.e., neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelet count, hemoglobin, hematocrit.

Blood sample handling

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. When not using a cannula, the location of venipuncture will be varied from one draw to the next to minimize subject discomfort. Blood samples will be taken in 3.5 ml Vacutainers® (serum chemistry), 3 ml EDTA Vacutainers (hematology) and 3 ml Vacutainers (glucose).

A copy of laboratory parameters normal ranges will be filed in the TMF and in the ISF.

The investigator will evaluate the clinical significance of each laboratory value outside of the reference range. Values which are considered clinically significant and/or IP-related will be noted in the CRF. The investigator may choose to repeat any abnormal result ONCE in order to rule out laboratory error. “NCS” will be entered on the patient chart and on the laboratory CRF page for all laboratory values which are outside the reference range but are judged “not clinically significant” The physician making the assessments shall be specified on the patient chart.

10.6.10 IP administration

IP will be administered at site by the subject on Day -7 by intake of 1 IP capsule of 100mg, under investigator’s supervision.

Subjects should be fasted for at least 10 h prior to and 2 h after administration. Water will not be permitted 1 hour before dosing dose and 1 hour post dosing.

Per protocol IP dose is 100mg.

10.6.11 Pharmacokinetic assessments

Pharmacokinetic parameters will be assessed in serum. For pharmacokinetics analyses blood samples will be collected for the analysis of plasma coenzyme Q10 before dosing and over the

next 12 hours: at 1, 2, 4, 8 and 12 hours after intake on the single dose period (day -7) and at each following ambulatory visit.

4 ml of blood will be collected in blood collection tubes. Each blood sample will be allowed to clot for 20-25 minutes at room temperature. Then they will be centrifuged for 15 minutes at 1300g at 4°C. Afterwards the plasma will be separated into the secondary sample tubes as follows: 0.5 ml plasma into two cryotubes, one to be send to the pharmacokinetic laboratory and one back-up. The plasma cryotubes will be appropriately labeled (study code, treatment period, subject number, sampling time) and stored at -20°C to -80°C at the study center until shipment to the specified laboratory. The backup cryotubes will be kept at the study center at least until the confirmation from the pharmacokinetic laboratory that the samples arrived in good conditions.

10.6.12 Pharmacodynamics assessments

Pharmacodynamic parameters will be assessed in blood.
For pharmacodynamics blood samples will be collected for the analysis of reticulocytes, hematocrit (HCT), hemoglobin (Hb) and red blood cells during hospitalization on Day -7 and at each following ambulatory visit.

Blood will be drawn within ± 2 minutes for dose sampling and within ±30 minutes for post dose sampling.

For the analysis of reticulocytes, red blood cells, haematocrit and haemoglobin, blood samples (3 ml) will be collected in 3 ml EDTA Vacutainers. Samples will remain at room temperature and will be transferred, for assay, at room temperature as well to laboratory.

The sampling tubes will be appropriately labeled (study code, treatment period, subject number, sampling time) and stored at room temperature at the study center until shipment to the specified laboratory.

10.6.13 Hospitalization

The subjects will be hospitalized for at least 12 hours for the single dose phase, therefore subjects will remain at site for around 24 hours.
Subjects will be offered a dinner for the evening before entering the single dose phase.

10.6.14 Ambulatory visits

Subjects must return to the study center for blood sampling for pharmacokinetic and pharmacodynamic assessments at each planned ambulatory visit of the multidose phase: V2 (day 0), V3 (day 7), V4 (day 14) and V5 (day 28).

10.6.15 Meals schedule

During hospitalization (V1, day -7) a dinner will be served at around 8 o`clock in the evening. If subject will remain until next day hospitalized, on next day 1 a breakfast will be served before leaving.
Water will not be permitted 1 hour before IP intake.

10.6.16 Subject restrictions during the study

During informed consent review at screening and at each study visit, subjects will be informed and reminded of the following restrictions:

- No strenuous physical exercise (e.g., weight training, aerobics, football), sunbathing or sauna bathing for 7 days before dosing until after the end-of-study evaluation.
- No alcohol for 72 hours before dosing until after the end-of-study evaluation.
- No consumption of foods or beverages that contain grapefruit 7 days before dosinguntil after the end-of-study evaluation.
- Intake of xanthine (e.g., caffeine) containing food or beverages must be discontinued 24 hours before dosing. Consumption of such foods and beverages (i.e., coffee, tea, soda, chocolate) or poppy seeds is not permitted at any time while the subjects are hospitalized. If a violation occurs during the domicile period, it must be noted in the source documents and CRF.
- No other food will be consumed at any time during hospitalization.
- No concomitant medication throughout the course of the study until after the end-of study evaluation
- Water will not be permitted 1 hour before visit at site.
- Before blood sampling at screening and at each ambulatory visit, the subjects will be required to fast overnight for at least 8 hours before.

10.6.17 Immediate tolerance after IP intake

Possible immediate reactions like rash, nausea, upper abdominal pain, dizziness, sensitivity to light, irritability, headache, heartburn and fatigue after the IP intake will be closely monitored if will appear; such reactions will be closely monitored and observed changes should be measured and recorded as AEs.

10.7 Premature Termination of the Study

The subject may withdraw from the study any time without giving reasons and without any disadvantageous consequences for his subsequent medical care. Furthermore, the subject should be withdrawn from the study if the investigator has the impression that it would be to the subject's detriment to continue the study.
In case of premature termination from the study the investigator should perform the following:

- physical examination
- vital signs (blood pressure, heart rate temperature and respiratory rate)
- body measurements (weight)

- 12 lead ECG
- blood laboratory analysis (Hematology,) to be performed at investigator discretion whenever indicated by the subject health status
- record of concomitant medication
- adverse events

Note: If the subject did not receive any IP (i.e., premature termination between the ICF signature and the single dose phase) no further examination are necessary to be performed and subject will be declared screening failure.

10.8 Discussion of Study Design

This is an interventional, single-center, single- and multi-dose bioavailability study of COQUN ORAL FORMULATION in Healthy Adults with 2 treatments periods: a 100mg single dose phase of 1 day, and a multi dose 1 month period, with a 1 week washout between the two phases. Study population: 24 healthy adult volunteers.

The results demonstrated by numerous recent scientific studies regarding the antioxidative properties of CoQ10 provided a promising therapeutic potential for ameliorating oxidative stress-mediated mitochondrial dysfunction in ischemic retinal injury, as well as on preventing RGC apoptosis and loss in glaucoma-related models.
Considering that many factors can affect the Q10 blood level of people who are not taking a Q10 supplement: age, diet, disease, medications (for example, statin medications), it is expected that supplementing regularly with Q10 will raise the Q10 blood level, but much depends on the way in which the Q10 product has been prepared and much depends on the dosage. It was demonstrated that taking 30 milligrams or 50 milligrams of Q10 daily will not raise the Q10 level as much as taking 100 mg of Q10 daily will do, while taking 100 milligrams of Q10 twice daily will yield even greater gains in Q10 blood levels.

From the literature it is known that a well-absorbed Q10 supplement should over time raise the blood level to about 2.5 micrograms per milliliter if the individual is taking a 100-milligram dosage once a day, while if taken the same Q10 supplement in a dosage of 100 milligrams twice a day, its blood level should, over time, raise the steady-state Q10 blood level to somewhere in the area of 3.5 micrograms per milliliter. But, the attainable levels will vary from individual to individual, beside depending on the product itself as formulation.

COQUN ORAL FORMULATION, a food supplement based on Coenzyme Q10 MINIACTIVES®, innovative technology based on the modified release of active at certain time intervals (which is not affected by physiological variables such as pH, gastro-intestinal motility, presence of food and others) thanks to the presence of a permeable and insoluble multi-membrane polymer system, so thanks to its modified and controlled release technology, was conceived

in order to allow the Coenzyme Q10 transport, without undergoing alterations and favoring its maximum absorption.

The dosing schedule in this study was planned to evaluate the best dosage for COQUN ORAL FORMULATION in order to reach a level of plasma concentration which might assure its antioxidant effect if taken on a regular basis.
Further studies are planned in case the results of this bioavailability study show positive results, in order to support the intended use for COQUN ORAL FORMULATION to be food support added to hypotonic pharmacological therapy in glaucoma patients, where the high oxidative stress linked to the pathology is well known.

11 ADVERSE EVENTS

11.1 Definition

11.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical study subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (see list below), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.
AEs can be:

- Drug reactions,
- Accidents,
- Illnesses with onset during the study,
- Exacerbation's (increase in severity or frequency of existing symptoms or appearance of a new symptom) of pre-existing illnesses,
- New illness or change in existing illness requiring new drug therapy or an increase in the dosage of an existing drug therapy,
- Any clinically significant changes from baseline detected concerning the physical examination, vital signs, ECG, or laboratory values.

The definition covers the entire study period, independent of whether IP was administered or not.
The most frequent symptoms and signs observed after CoQ10 intake might be mild insomnia, elevated levels of liver enzymes, rash, nausea, upper abdominal pain, dizziness, sensitivity to light, irritability, headache, heartburn, and fatigue
The investigator is responsible for ensuring appropriate clinical management of all (S)AEs until they are resolved or stabilize at a level acceptable to the investigator and the sponsor.
Note: any newly occurring disease or condition and/or a deterioration of a current disease or condition must be documented as adverse events in the source document and then transferred in the section AE of the CRF.

The following applies to changes in laboratory values:
Laboratory alert limits are defined by an upper and a lower limit of the individual parameter. All values beyond these limits are considered possibly clinically significant. The investigator has to ensure that each parameter out of the normal range is checked for clinical significance. For any deviation beyond the alert limits detected at any visit after screening visit, the investigator has to document the change as an AE in the source document and CRF. No AE has to be recorded if the parameter already deviated from the alert limit at screening visit.

The following cases define conditions where values beyond alert limits should not be reported as an AE:

- Abnormal parameters that are obviously biological implausible (e.g. values, which are incompatible with life).
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (e.g. hemolysis) and marked as such by the laboratory on the laboratory report,

It is at the discretion of the investigator to document any change or trend over time in laboratory tests or vital signs as an AE if he considers the change to be clinically significant, even if the absolute value is within the alert limits or reference range. In case of clinically significant changes in laboratory values it is preferable to document the condition or disease suspected for the aberration.
Surgery and other invasive procedures that are planned prior to the start of the study do not have to be documented as AE. Planned procedures have to be recorded by the investigator in the source data at screening visit. In this context, it should be noted that surgery is usually not an AE but rather a measure to treat an AE. Therefore, a precise description of the medical event should be given.
The subject has to be instructed to inform the investigator immediately about all AEs and complete the subject diary in the periods during the study visits. During the treatment period visits, the AEs have to be documented in the CRF together with their intensity (mild, moderate or severe, refer to Section 11.1.3).
Any AE, which is in accordance with the above definition, has to be documented by the investigator, regardless of any consideration on causality.

11.1.2 Serious Adverse Events

Any untoward medical occurrence or response to a medicinal product that at any dose:

- Results in death,
- Is life threatening,
- Results in in-subject hospitalization or prolongation of existing hospitalization,
- Results in a persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect or,

- Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed.

A life-threatening AE is any adverse drug experience that places the subject at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization is defined as any in-subject treatment covering more than one calendar day. Hospitalization does not include the following:

- Emergency Room/Accident and Emergency/Casualty Department visits,
- Out-patient/same-day/ambulatory procedures,
- Observation/short-stay units,
- Rehabilitation facilities,
- Hospice facilities,
- Respite care (e.g. caregiver relief),
- Skilled nursing facilities,
- Nursing homes,
- Custodial care facilities,
- Clinical research/Phase I units,
- Hospitalization in the absence of a precipitating, treatment emergent, clinical AE may meet criteria for “seriousness” but may not be considered a SAE:
    - Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work up of persistent pre-treatment lab abnormality),
    - Social admission (e.g., subject has no place to sleep),
    - Administrative admission (e.g., for annual physical examination),
    - Protocol specified admission during a clinical study (e.g., for a procedure required by the study protocol),
    - Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery).

Prolongation of an existing hospitalization is defined as any extension of an in-patient hospitalization beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician.
Prolongation in the absence of a precipitating, treatment emergent, clinical adverse event (i.e. not associated with the development of a new adverse event or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor. Pre-planned treatments or surgical procedures will be recorded on the appropriate page of the CRF as soon as the investigator is informed.

Disability is a substantial disruption of a person's ability to conduct normal life.

11.1.3 Intensity

In the course of the study, the investigator will determine whether any adverse events have occurred and will grade their intensity as follows:

Mild: Symptoms do not alter subject's normal functioning.

Moderate: Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject.

Severe: Symptoms hazardous to well-being, significant impairment of function or incapacitation.

11.1.4 Causal Relationship to Investigational Product

The investigator can assign the cause of an AE to the intake of the IP, or to another reason. The decision must be explained for each event. The investigator's final judgment on the causal relationship between the IP and the AE is based on the following scale:

Related: Reports of a reasonable temporal relation between the AE and the intake of the IP. There is no other explanation for the AE and subsidence or disappearance of the AE on withdrawal of the IP (dechallenge) and recurrence of the symptoms on restart at previous dose.

Probable: Reports including good reasons and sufficient information to assume a causal relationship in the sense that it is plausible, conceivable, or likely.

Possible: Reports containing sufficient information to indicate the possibility of a causal relationship in the sense of it not being impossible and not unlikely, although the connection may be uncertain or doubtful (e.g. due to missing data, insufficient evidence).

Not related: Reports of a clinical event, including laboratory test abnormality, with a temporal relationship to IP administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations i.e., no reasonable suspected causal relationship to IP administration.

Not assessable: Reports suggesting an AE that cannot be judged because information is insufficient or contradictory, and that cannot be supplemented or verified.

11.1.5 Management and Follow-up of Adverse Events

The investigator is responsible for ensuring appropriate clinical management of all (S)AEs until they are resolved or stabilize at a level acceptable to the investigator and the sponsor. Appropriate clinical management of (S)AEs is at the discretion of the investigator.

11.1.6 Documentation and Reporting

11.1.6.1 Adverse Events

All AEs have to be reported over the entire study period, i.e. the period from first (written Informed Consent) to last protocol-specific procedure.
All observed or reported AEs regardless of treatment group or suspected causal relationship to the IP will be recorded on the AE page(s) of the CRF. The investigator must assess all AEs for seriousness, severity, and relationship to the IP.
The investigator will follow all AEs, regardless of seriousness or severity, until the event or its sequel resolve or stabilize at a level acceptable to the investigator and the sponsor.

11.1.6.2 Serious Adverse Events

Reporting to CRO/sponsor

Any SAE or death must be reported immediately independent of the circumstances or suspected cause if it occurs or comes to the attention of the investigator at any time during the study within 30 days after the last administration of the IP. Completion of the study must be promptly reported if a causal relationship to IP is suspected.
The investigator is responsible for ensuring that any SAE, regardless of relationship to IP, is reported within 24 hours from its knowledge. SAEs must be documented on the SAE report forms provided by sponsor, in addition to the AE pages of the CRF.
The minimum information required from the investigator when reporting an SAE is as follows:

- Investigator's identification (name and center number),
- Protocol identification number,
- Subject identification number (randomization number),
- SAE description including criteria for seriousness and the immediate outcome.

All SAEs reports must be faxed directly to:

VISUfarma SpA
NAME: Anna Rita Bigioni
Role: Qualified Person for Pharmacovigilance
Phone: +39 06 3630 6842
Fax: +390636299730
e-Mail: a.bigioni@visufarma.com

A follow-up report must be done as soon as new information is available. Every SAE will be followed up until the outcome of the event is categorized as fatal, resolved completely, or resolved with sequel.
In the case of a subject's death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor.

Reporting to Independent Ethics Committee/health authorities

The investigator is obliged to report AEs to the Ethics Committee and authorities according to local legal requirements.

In accordance with applicable regulatory requirements, the investigator is obliged to notify the IEC/IRB as well as to the regulatory authorities of any suspected unexpected serious adverse reactions, including those notified to him by the sponsor, within expedited reported timelines. The investigator must obtain written acknowledgement of receipt of the SUSAR report from the Ethics Committee/regulatory authorities and forward a copy of this acknowledgement to the sponsor.

12 BIOSTATISTICAL METHODS

12.1 General

Due to the explorative aim of the study, descriptive statistics and confidence intervals at 90% level will be provided.
In particular, continuous variables will be presented as arithmetic mean values ± standard deviation (SD) and median values with interquartile range; geometric means will be provided as well; for categorical variables absolute and percentage frequencies will be provided.
All data collected during the study visits and up to V5 (EOS) will be presented for the two groups.
Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be explained in the Statistical Analysis Plan (SAP), which will give a detailed technical description of all statistical analyses. All deviations and/or alterations will be summarized in the Clinical Study Report (CTR).

12.2 Objective

To evaluate the best dosage for COQUN ORAL FORMULATION in order to reach a level of plasma concentration which might assure its antioxidant effect if taken on a regular basis.

12.3 Determination of Sample Size

The simple size for this study is not based on any power calculation.
24 subjects (12 for each arm) have been considered sufficient to obtain reliable results for the exploratory purposes of the study.

12.4 Analysis Sets

The following analysis sets will be considered in this study.

12.4.1 Safety Set

This set consists of all randomized subjects who sign informed consent and take at least one dose of study product.

12.4.2 Intention-to-treat Population

This set contains all randomized subjects.

12.4.3 Per Protocol Population

The per protocol population consists of all subjects who meet all inclusion/exclusion criteria and who do not have any major protocol deviation.

12.5 Subgroup Analysis

N.A

12.6 Statistical Hypothesis

The study aims are to explore, compare and describe the data for research purposes; no hypotheses are pre-specified.

12.7 Analysis of Primary Variable

The primary variables are the pharmacokinetic properties:
- Area under the curve (microg/ml x h): ≥5
- Cmax: ≥0,8
- Tmax: ≥3
- elimination half-life (t 1/2)

At each time point and for each group, descriptive statistics and 90% confidence intervals will be provided. See section **12.1** for details.

Analysis of primary endpoints will be performed on Intention-To-Treat population and Per Protocol population.

12.8 Analysis of Secondary Variables

The secondary variables are the ones regarding safety which will be monitored through vital signs, physical exams, ECGs, clinical laboratory tests and adverse events, as follows:
- Following a single oral dose of 100mg COQUN ORAL FORMULATION
- in 1 month period of daily oral intake of 100mg OD or BID COQUN ORAL FORMULATION

Symptoms and signs like mild insomnia, elevated levels of liver enzymes, rash, nausea, upper abdominal pain, dizziness, sensitivity to light, irritability, headache, heartburn, and fatigue will be closely monitored.

At each time point and for each group, descriptive statistics will be provided. See section **12.9** for details.

12.9 Analysis of Safety Variables

12.9.1 Adverse Events

Safety will be monitored through vital signs, physical exams, clinical laboratory tests (hematology) and adverse events including assessment of relationship to the IP.

Analysis of safety will be performed on the safety set.

The recorded adverse events will be coded according to MedDRA. The adverse events will be summarized by treatment, System Organ Class, preferred-term and intensity.
Nature, incidence and intensity, as well as the investigator's and the sponsor's causality assessment will be reported for each treatment-emergent adverse event. Descriptive summary statistics, e.g., with regard to the incidence of symptoms and the causality assessment, will be presented for the period between V1-V5. Furthermore, all non treatment-emergent adverse events during pre-treatment will be reported between the ICF signature and the first IP intake at V1.

12.9.2 Clinical Laboratory

Clinical laboratory data will be presented on an individual basis and will be marked according to the normal ranges provided by the selected central laboratory and corresponding sponsor guidelines, respectively. Descriptive summary statistics will be presented for each variable. In addition, the number of subjects with values outside the normal range and extended normal ranges will be presented.

12.10 Analysis of other Variables

N.A

12.11 Missing Values

No replacement of missing values will be performed.

13 SUBJECT SCREENING

Subjects screened for inclusion irrespective whether they are enrolled or not, have to be documented on the screening log provided by the sponsor and screening visit procedures shall be described in the source document, as well as the reasons for non-inclusion.
The screening/enrolment is finished as soon as the sponsor terminates the screening period of the study for having reached the planned subject number.

14 DATA QUALITY ASSURANCE AND STUDY DOCUMENTATION

All data concerning the study will be documented in the subject's medical records and transferred afterwards in the CRF designed especially for this study; for data clarifications, if necessary, query forms will be used and filed together with the CRF. The CRF will be checked for completeness and plausibility by the monitor together with the clinical investigator.

14.1 Monitoring

It is the responsibility of the investigator to assure that the study is conducted in accordance with the protocol and that valid data are entered into the CRF.

The investigator will permit a representative of the sponsor/CRO to monitor the study as frequently as necessary, to determine that data recording, IP handling, and adherence to the Study Protocol are satisfactory. The CRF and all related documents will be reviewed in detail in accordance with the SOPs of the CRO and Good Clinical Practice regulations.

To verify compliance with this Study Protocol, the sponsor will require that the investigator permits the monitor to review those portions of the subject's primary medical records which directly concern this study.

It is the investigator's obligation to ensure that documentation of all relevant data such as medical history/concomitant diseases, date of study enrollment, visit dates, results of examinations, administration of IP, and AEs (incl. clinical relevant abnormal laboratory results, if any) are correctly entered in the subjects' files as well as in the CRF.

The sponsor/the sponsor's delegates will affirm and uphold the principle of the subject's right to protection against the invasion of privacy. Throughout the study and for all analysis, all data will only be identified by the subject number.

14.2 Source Data Verification and Source Documents

As required by GCP, the sponsor/CRO must verify, by direct reference to the source documents, that the data required by the Study Protocol are accurately reported in the CRF.

The source documents must, as a minimum, contain the following: a statement that the subject is included in a clinical study, the identity of the study, diagnosis and eligibility criteria, visit dates and description (with subject status), IP administration, and any SAEs.

Definitions for source data and source document are as follows:

Source data:

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Source documents:

These are original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by personnel authorized by the sponsor and by local and possibly foreign regulatory authorities. This information is included in the Informed Consent.

14.3 Case Report Form

In compliance with GCP, the medical records, medical notes, and other source documents, should be clearly marked and permit easy identification of participation by an individual in the specified clinical study.
The investigator is obliged to record all data with respect to protocol procedures in the Case Report Form (CRF) sections. The investigator may designate authority to complete CRFs to appropriately qualified staff. This has to be documented by authorizing and completing the signature log. CRFs will be provided by CRO.
All corrections/changes to the CRF are automatically documented and recorded through an audit trail.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention, the sponsor must be notified in writing so that adequate provision can be made with regard to the study documents.
The study documents will include:

- All documents directly related to the study e.g. Study Protocol and amendments, Case Report Forms and queries, signed Informed Consent, screening and enrollment log, approval of Ethics Committee, and all correspondence with the sponsor or with health authorities related to the study,
- All subject's clinical source documents e.g. subject hospital records, laboratory reports, ECG, consultant letters, etc.

14.4 Data Management

The statistical evaluation of the clinical study data is performed by CRO using the statistical software package SAS version 9.4.

The investigator will enter the data in the respective CRF sections.
After data are entered into the database, they will be checked according to a pre-specified Data Validation Plan. All numeric data, coded entries, tick boxes, and date fields will be checked automatically for plausibility, completeness, and validity. Verbatim entries (e.g. concomitant medication, AEs) will be provided in special data listings and cross-checked by appropriately trained staff at CRO. Questions, errors, and missing data found will be collected in Data Query Forms and sent to the investigator for clarification. Returned query forms will be checked for correctness, resolved queries will be entered to the study database and unresolved or new queries will be returned to the investigator. This process will be repeated until all queries are resolved. Finally, the responsible data manager will lock the database.
Verbatim entries (AEs, prior or concomitant diseases, and medication) will be coded by means of the following internationally accepted systems:

- Adverse events: MedDRA
- Concomitant medication: WHO Drug Reference List
- Concomitant diseases and diagnoses: MedDRA

For further details refer to the Data Management Plan filed in the TMF of this study.

14.5 Audits and Inspections

In order to guarantee that the performance of the study is in accordance with GCP and all relevant regulatory and formal stipulations, in-house, on-site, and CRO audits may be carried out.

The auditor will be independent from the staff involved in the proceedings of this clinical study.

By signing this Study Protocol, the investigator agrees to give the auditor access to all relevant documents for review and support the sponsor to solve possible audit findings concerning the study conduct at the respective site. The same applies in case of an inspection by local or international authorities.

After every on-site/CRO audit the investigator/CRO will receive an audit confirmation by the auditor. This document has to be filed together with the study documentation and has to be made available to the authorities in the case of an inspection. At the end of the study, a copy of the audit certificate(s) will be included in the final CTR.

14.6 Clinical Study Report

A final CTR will be prepared according to the ICH guideline on 'Structure and Content of Clinical Study Reports'. A CTR will be prepared regardless of whether the study is completed or prematurely terminated. A summary of the CTR will be provided to the investigator following finalization of the report.

14.7 Archiving

The investigators are responsible for the archiving of the data according to the international legal requirements (EU Directive 2001/83/EC, Commission Directive 2005/28/EC, ICH E6), or according to the local applicable regulatory requirements. The sponsor and the investigator shall retain the essential documents relating to a clinical study for at least five years after its completion.

In applicable cases, study documents should be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product by the sponsor. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator/institution should take measures to prevent accidental or premature destruction of these documents. The archiving arrangements will be addressed by the monitor when closing out the site and archiving location will be specified in the record retention form. The

sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

15 ETHICS AND LEGAL ASPECTS

The study will be conducted in compliance with the independent Ethics Committee/Institutional Review Board (IEC/IRB)'s recommendation, informed consent regulations, ICH GCP Guidelines and this Study Protocol. In addition, this study will adhere to all local regulatory requirements.
The study will be conducted in conformity with the principles of the Declaration of Helsinki and its amendments and/or the regulations of the country in which the study is performed. The study should follow the International Conference on Harmonization: Guideline for Good Clinical Practice.

15.1 Independent Ethics Committee and Institutional Review Board

This protocol and other documents (e.g. Investigator's Brochure, Subject's Information), will be submitted by the investigator to an Independent Ethics Committee/Institutional Review Board. Before starting the study, the investigator must have received the written approval on the Study Protocol and the Subject Information from the IEC/IRB. The IEC/IRB approval must identify the Study Protocol version as well as the documents reviewed.
During the study, the investigator must inform the IEC about any changes or deviations from the Study Protocol, all AEs that are both suspected and unexpected and any new information that may affect the safety of the subjects or the conduct of the study.

15.2 Protocol Modification

The Principal Investigator as well as the authorized qualified delegates of the sponsor have to consent to the study protocol by giving their personally dated signatures.

Any change to the protocol concerning the purpose of the study, the study design, or the subject's eligibility can only be made in the form of a written amendment to the Study Protocol. Such amendments have to be discussed and signed by the sponsor and the Principal Investigator prior to implementation.
Substantial amendments likely to affect the safety of the subjects or the conduct of the study e.g. such as the use of additional invasive examination methods, or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, require a new vote by the Ethics Committees/approval by the National Authorities and a further Informed Consent Form that is to be signed by all subjects enrolled in the study who are affected by the amendment.

15.3 Authorities

As required by local regulations, the sponsor acting through the CRO and Investigator, is obliged to ensure that all legal aspects are covered and to obtain approval of the appropriate regulatory authorities as necessary, prior to study initiation.
The Summary of Product Information (SPC), the Study Protocol, name and site of the investigator, the votes of the IEC(s) will be submitted to the National Authorities before the beginning of the study. Amendments to the Study Protocol will also be forwarded to the EC and the National Authorities. In accordance with the national drug law all approvals needed for conducting the study in this country will be obtained.
The relevant local and federal authorities have to be informed by the sponsor about the clinical study performance and may observe the study progress.

15.4 Informed Consent Form and Subject Information Sheet

Prior to being enrolled into the study, each subject's written Informed Consent must be obtained in response to a fully written and verbal explanation of the nature of the study.

Each subject and the investigator have to sign and date an Informed Consent Forms personally. The original signed one will be kept by the investigator in the ISF, while the subject must receive the copy of it.
The Subject Information Sheet will be prepared by CRO. It will explain the nature of the study, its objectives, type and methods, tests to be performed, and potential risks. Furthermore, it will detail the obligations of the participant and the fact that he/she is free to withdraw his/her consents at any time without providing any reason. Details of indemnity and insurance are also stated.
The investigator has to inform the subject that his consent to participation can be withdrawn at any time, without giving any reason, and that no disadvantages will result regarding further medical treatment. The refusal of a subject to participate in a study must never interfere with the investigator-subject relationship. The investigator shall ask for the reason of premature termination without violating the subject's rights. Furthermore, the subject must be informed about the insurance coverage provided by the sponsor and required by law, as well as his corresponding obligations
As required by GCP, the subject will give his/her authorization in writing that the subject's original medical records may be validated by the monitor(s), the auditor(s), and the regulatory authorities by direct access in accordance with the applicable laws and regulations. The Subject Information and Informed Consent Form will be available in the subject's local language, which will be handed out to the subject, and additionally in English for documentation purposes.
It is recommended that the investigator informs the subject's primary physician about the subject's participation in the study; if the subject has a primary physician and if the subject agrees to the primary physician being informed, a letter for the general practitioner shall be handed to the subject.

15.5 Subject Insurance

In accordance with the applicable national laws and GCP, the sponsor has effected a subject insurance. The investigator will receive a copy of the insurance certificate as well as of the corresponding insurance conditions prior to the start of the study. Following the clauses of the contract, persons insured are to be informed about the existence of the insurance contract and about their obligations. It is the subject's obligation to notify the insurance company and additionally the investigator about any health impairment. In case of death of the subject it is the obligation of his/her relatives to notify the insurance company.

15.6 Data Protection

All measures must be taken in order to insure the subject's anonymity. The subject should not be identified by name but by code (subject screening number) on CRFs and laboratory printouts. A subject identification log with name and code for each subject must be kept and updated by the investigator.
For data protection reasons, the investigator has to disclose the identity of the subjects involved in this study only in a pseudonymous form (e.g. subject names possibly printed on laboratory printouts must be obliterated by the investigator).

15.7 Discontinuation of the Study

The study can be terminated prematurely for the following reasons:

- New toxicological or pharmacological findings or serious adverse events invalidate the earlier positive risk-benefit-assessment,
- Adverse events occur in such severity and frequency that the proposed schedule can no longer be adhered to.

All, sponsor, Principal investigator and safety board should agree upon the decision. The reasons for such a decision should be documented in written form.

Termination of the study by the sponsor
The sponsor can decide at any time to discontinue the development of the IP. He may terminate the study for safety, ethical, or administrative reasons at any time. In such cases, all investigators have to be notified in writing, outlining the reasons for the termination.

Termination of a study center by the sponsor
In particular cases, the study may be terminated at a single investigational site at any time if it becomes apparent that subject enrollment or the quality of the data is unsatisfactory. Or if the sponsor has relevant reasons, e.g., suspicion of a deceit or conduct of the study, which is not in accordance with the guidelines for GCP or no recruitment of subjects 1 month after the site initiation.

It is at the discretion and responsibility of the investigator to decide in individual cases on the subject's withdrawal from the study due to medical reasons.
Furthermore, the subject can withdraw from the study at any time, without giving any reason.

16 AGREEMENTS

16.1 Study Initiation

The investigator or his/her delegated staff may not enroll any subjects prior to the completion of a study initiation visit, conducted by a representative of the CRO and before the approval of the responsible Ethics Committee has been received.
This visit will include an inventory of study supplies and a detailed review/explanation of the Study Protocol and the filling of CRF.

16.2 Confidentiality

All information and documents received by the investigator in the course of the study, regarding the test substance (e.g. expert information) are to be treated in complete confidentiality. The passing of such information to a third party is limited to those involved in the study only.

16.3 Investigator Signature

By his signature to the Study Protocol the investigator confirms that he assumes responsibility that the study is conducted according to the protocol, GCP, and he will ensure that national drug laws and the revised Declaration of Helsinki are observed in meaning and content in order to protect the participating persons.

16.4 Publication

Investigators have no right to publish or present any data or other information derived from the study in any media, journal, symposium, professional meeting, or other publication without the prior written consent of the sponsor which shall not be unreasonably withheld.

16.5 Fee

Financial agreements will be signed between the study site (institution), the Principal Investigator and sponsor or its representatives, outlining overall sponsor and investigator responsibilities to the study. The agreement should describe the costs for protocol required services and the remuneration needed to be paid (directly or indirectly).

17 REFERENCE LIST

1. Mortensen SA, Rosenfeldt F, Kumar A, et al. The Effect of Coenzyme Q10 on Morbidity and Mortality in Chronic Heart Failure: Results From Q-SYMBIO: A Randomized Double-Blind Trial. JCHF. 2014;():. doi:10.1016/j.jchf.2014.06.008.
2. Alehagen, U., Johansson, P., Björnstedt, M., Rosén, A., & Dahlström, U. (2013). Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: a 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. International Journal Of Cardiology, 167(5), 1860-1866. doi:10.1016/j.ijcard.2012.04.156.
3. Shults, C. W., Oakes, D., Kieburtz, K., Beal, M. F., Haas, R., Plumb, S., & … Lew, M. (2002). Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Archives of Neurology, 59(10), 1541-1550.
Huntington Study Group. (2001). A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. Neurology, 57(3), 397-404.
4. Zita, C., Overvad, K., Mortensen, S. A., Sindberg, C. D., Moesgaard, S., & Hunter, D. A. (2003). Serum coenzyme Q10 concentrations in healthy men supplemented with 30 mg or 100 mg coenzyme Q10 for two months in a randomised controlled study. Biofactors (Oxford, England), 18(1-4), 185-193.
5. Fedacko, J., Pella, D., Fedackova, P., Hänninen, O., Tuomainen, P., Jarcuska, P., & … Littarru, G. P. (2013). Coenzyme Q(10) and selenium in statin-associated myopathy treatment. Canadian Journal Of Physiology And Pharmacology, 91(2), 165-170. doi:10.1139/cjpp-2012-0118.
6. Eriksson, J. G., Forsén, T. J., Mortensen, S. A., & Rohde, M. (1999). The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus. Biofactors (Oxford, England), 9(2-4), 315-318.
7. Huntington Study Group. (2001). A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. Neurology, 57(3), 397-404.
8. D. Lee, K.-Y. Kim, M. S. Shim, S. Y. Kim, M. H. Ellisman, R. N. Weinreb, W.-K. Ju. Coenzyme Q10 ameliorates oxidative stress and prevents mitochondrial alteration in ischemic retinal injury. Published online: 12 December 2013, Springerlink.com
9. B. M. Davis, K. Tian, M. Pahlitzsch, J. Brenton, N. Ravindran, G. Butt, G. Malaguarnera, E. M. Normando, L. Guo, M. F. Cordeiro. Topical Coenzyme Q10 demonstrates mitochondrial-mediated neuroprotection in a rodent model of ocular hypertension. 1567-7249/ 2017, Elsevier B.V.
10. Guideline on similar biological medicinal products, EMEA/CHMP/437/04; available online
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf

18 SIGNATURES

18.1 Investigator's signature

I recognize that all information concerning the study VF-BAQ10/2018, final version dated March 03, 2018 supplied to me by the sponsor is not previously published and confidential information. This information includes the IP description, protocol, case report forms, assay methods, technical methodology, and scientific data.

I recognize that any changes in the protocol must be approved in writing by the Principal Investigator, the sponsor, the corresponding Competent Authorities and the Ethics Committee before implementation except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the study.

I herewith confirm that the Study Protocol, CRF and appendices contain all the information and rules necessary to conduct the study according to GCP and that the study will be carried out and documented in complete compliance with this Study Protocol. The legal regulations and described agreements will be observed and that the investigational products will be used only for the purpose of the clinical study.
By my signature of the Study Protocol, I, the Principal Investigator, certify to have experience in the conduct of clinical studies.
I confirm that I will conduct this study in compliance with the Declaration of Helsinki, the GCP guidelines, and on the basis of applicable national laws in each participating country.

By my signature below, I hereby certify that I have read, understood and agree to abide by all conditions, instructions, and restrictions contained in the protocol code VF-BAQ10/2018, final version dated March 03, 2018.

_____

Date, Investigator's Signature

18.2 Study Protocol Approval, Obligations, and Responsibilities

ON BEHALF OF THE SPONSOR

Name & Title: Anna Rita Bigioni, PhD

Role: Qualified Person for Pharmacovigilance and Regulatory Affairs Manager

_____

Signature, Date

ON BEHALF OF THE CRO:

Name & Title: Daniela Rotaru, M.D.

Role: Medical Director

_____

Signature, Date

19 APPENDICES

Not applicable