PROTOCOL OF A NON-INTERVENTIONAL CLINICAL STUDY

Protocol title:	**An observational, open-label, multi-center prospective study for assessing the patients' adherence to TRAVATAN® in routine daily clinical practice.**
Study code:	**TRAVO**
Protocol no:	CRO-Sponsor-Travo
Date:	28 Aug 2015
Version:	1
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Contract Research Organization (CRO):	CRO
Sponsor:	SPONSOR

STATEMENT OF COMPLIANCE

This document is a clinical research protocol. The study will be conducted in compliance with the protocol and in accordance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), with the ethical principles laid down in

the Declaration of Helsinki and with the Greek National Organization of Medicines (EOF) regulations.

All personnel involved in the conduct of this study have completed human subjects' protection training.

Study Protocol Synopsis

Title:	An observational, open-label, multi-center prospective study for assessing the patients' adherence to TRAVATAN® in routine daily clinical practice.
Phase:	Phase IV
Number of study sites:	40
Primary Objective:	To investigate patients' adherence to TRAVATAN® (Travoprost 40μg/ml Eye Drops) in adult patients with ocular hypertension or ocular hypertension or open angle glaucoma, when administered according to standard clinical practice.
Secondary Objective:	To identify potential factors that may be associated with TRAVATAN® non-adherence in daily clinical practice.
Study Design:	Multicenter, prospective, non-interventional, one arm, open label cohort study of patients with ocular hypertension or open angle glaucoma receiving TRAVATAN®. The total duration of the study is 36 weeks (12 weeks recruitment period and 24 weeks follow-up period).
Target population:	Male and female patients with ocular hypertension or open angle glaucoma, aged ≥18 years, receiving Travoprost 40μg/ml Eye Drops.
Inclusion criteria:	• Adult patient (≥18 years old) with ocular hypertension or open angle glaucoma • Patient receiving TRAVATAN®. • Patients willing and able to provide written informed consent

	personally or by legal proxy. • Patients willing to comply with all study procedures and to be available for the duration of the study.
Exclusion criteria:	• Patient with uncontrolled IOP≥21 mmHg. • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test • Patients in treatment for ocular diseases (including OH or OAG) with more than one therapy. • Patient with hypersensitivity to the active substance or to any of the excipients of this medicinal product. • Current enrollment in other clinical trial.
Data collection plan	At baseline, at 8 weeks and end of follow-up period (24 weeks).
Primary endpoint:	Proportion of patients reporting high adherence to TRAVATAN® at 24 weeks defined as a Morisky Medication Adherence Scale (MMAS-4) score equal to 0.
Secondary endpoints:	• Proportion of patients with a Medication Persistence Ratio (MPR), defined as the number of days without receiving medication after study enrolment divided by the number of days participating in the study, less than 0.20. • Proportion of patients encountering difficulties with medication supply due to coexisting medical conditions. • Proportion of patients encountering difficulties with medication supply due to lack of insurance coverage. • Proportion of patients encountering difficulties with medication

	supply due to inability to access or difficulty accessing pharmacy. • Proportion of patients with TRAVATAN® discontinuation during the follow-up period.
Sample size:	The sample size calculation was conducted with the precision-based sample size calculation. In order to calculate a 95% confidence interval for the proportion of patients reporting high adherence to TRAVATAN® at 24 weeks, which is expected to be 80% with a margin error (Δ) (Okeke et al, 2009) no more than 2%, the required sample size is at least 1537 patients. A total sample size of at least 1843 patients (20% additional) will allow compensation for incomplete datasets.
Statistical methods:	Demographic and clinical/prognostic data of the patients at baseline will be described with numerical and graphical summary statistics. The statistical significance of the proportion of patients reporting high adherence to TRAVATAN® will be assessed using a binomial test and the respective 95% confidence interval (CI). For the secondary endpoints, categorical data will be analyzed using a binomial test with the respective 95% CI, and continuous data will be analyzed using the paired t-test or the Wilcoxon signed rank test, depending on the nature of the data. The association between categorical variables will be tested using a chi-squared test and/or logistic regression. A result will be considered significant when $P \leq 0.05$. The statistical analysis will be performed using SPSS v.21

STUDY CONTACT DETAILS

Principal Investigator:

CRO:

Sponsor:

PROTOCOL SPONSOR APPROVAL

An observational, open-label, multi-center prospective study for assessing the patients' adherence to TRAVATAN® in routine daily clinical practice Study code: TRAVO

Signature: .....

SPONSOR
Date: .....
(DD-mmm-YYYY)

PROTOCOL AUTHORS APPROVAL

Signature: .....

Paraskevi Xanthopoulou, MD
Consultant in Ophthalmology Department,401 General Military Hospital of Athens

Date: .....
(DD-mmm-YYYY)

INVESTIGATOR'S AGREEMENT

I have read the foregoing protocol, entitled "An observational, open-label, multi-center prospective study for assessing the patients' adherence to TRAVATAN® in routine daily clinical practice" and agree to conduct the study as detailed herein and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator's Name Signature Date

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Investigational Site

LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviation	Full term
AE	Adverse Event
ADR	Adverse Drug Reaction
CRF	Case Report Form
CRO	Contract Research Organization
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
VA	Visual Acuity
VF	Visual Fields
PEX	Pseudoexfoliation
PGs	Prostaglandins
logMAR	Logarithm of the Minimum Angle of Resolution
IOP	Intraocular pressure
BAC	Benzalkonium chloride
OH	Ocular Hypertension
OAG	Open Angle Glaucoma

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Background

1.1 Introduction

Data from population-based surveys (PBS) indicate that glaucoma is the leading cause of irreversible blindness; however, when detected and treated early, blindness is usually preventable (Quigly. 1996. Br J Ophthalmol). Accounting for 8% of blindness among the 39 million people who are blind world-wide in 2006 (Pascolini et Mariotti. 2012 Br J Ophthalmol), the number of individuals estimated to be bilaterally blind due to glaucoma was projected to increase from 8.4 million in 2010 to 11.1 million by 2020 (Quigley et Broman. 2006 Br J Ophthalmol). Open angle glaucoma (OAG) is a multifactorial characteristic optic neuropathy characterized by progressive retinal ganglion cell death and corresponding characteristic visual field loss (Siesky et Harris. 2012 Adv Ther) traditionally classified, concerning the cause, as primary and secondary.

Primary open angle glaucoma (POAG) is characterized by the absence of any anatomic identifiable underlying predisposing cause of events that led to aqueous outflow obstruction and raised IOP, whereas increased resistance in outflow system associated with other ocular or systemic disorders such as exfoliated material, pigment dispersion, inflammation or tumor cells and IOP increase, is classified as secondary open angle glaucoma (American Academy of Ophthalmology, The eye M.D. Association,2012,Glaucoma, Section 10, 250p).

Another variant of primary open angle is low-tension or normal-tension glaucoma, which is characterized by patients without elevated intraocular pressure, who may develop optic nerve head degeneration that results in a loss of peripheral vision. Additionally, it is estimated that a large population has elevated intraocular pressure without glaucomatous damage on standard clinical examination (Leibowitz et al. 1980 Surv Ophthalmol). Nevertheless, given that a substantial percentage of the optic nerve fibers are lost before glaucomatous visual field defects can be recognized, there is a need for early detection and treatment (Kerrigan-

Baumrind et al. 2000 Invest Ophthalmol Vis Sci.). Individuals who have elevated intraocular pressure without detectable optic nerve damage are at increased risk for developing POAG and are sometimes referred to as "ocular hypertensives" or "glaucoma suspects" (Quigley et al. 1994 Arch Ophthalmol). Although the etiology of glaucoma is multi-factorial, intraocular pressure (IOP) is the only modifiable factor in glaucoma management that has been proven to alter the natural course of the disease (Friedman et al. 2004. Am. J. Ophthalmol.). Open angle glaucoma is the most prevalent form in Caucasian and African population (Gordon et al. 2002 Arch Ophthalmol). The Ocular Hypertension Treatment study confirmed that age, cup-disc ratio, corneal thickness and baseline intraocular pressure are predictive factors for the development of POAG in individuals (Sommer et al. 1991 Arch Ophthalmol), whereas low diastolic perfusion pressure seems to be another factor leading to POAG (Tielsch at al. 1995. Arch Ophthalmol). Certain conditions, including refractive errors, diabetes mellitus, cardiovascular disease and retinal vein occlusion, have been associated with glaucoma (Wong et Klein. 2003 Ophthalmology).

Regarding low – tension glaucoma, it is a condition, which is characteristically bilateral and progressive, often despite lowering IOP. The Collaborative Normal-Tension Glaucoma Study (CNTGS) found that lowering IOP reduced the rate of visual field progression, confirming that IOP has a clear role in this disease (Coll Normal-Tension Glau Study Group. 1998 Am J Ophthalmol).

Secondary open-angle glaucomas mostly encountered are pseudoexfoliation (PEX) and pigmentary. In PEX, an age-related, complex, generalized disorder of the extracellular matrix, the progressive accumulation of intraocular abnormal fibrillar materials in the anterior segment is considered the primary cause of chronic IOP elevation (Schlotzer-Schrehardt et Naumann,. 2006, Am J Ophthalmol). Pigmentary OAG typically develops in young myopic patients with pigment dispersion syndrome, which is characterized by melanin pigment liberation from the iris pigment epithelium (Sugar. 1966 Am J Ophthalmol).

Despite significant surgical and laser parasurgical progress, lowering IOP with topical drugs remains the initial and probably main treatment for most patients, including those with normal-tension glaucoma or ocular hypertension (Russo et al. 2008 Clin Ophthalmol). The eye drops work by enhancing the drainage of fluid from the eye or by reducing the production of aqueous fluid in the eye. These medications will usually have to be administered for the rest of the patient's life, and regular use according to a physician's instructions is absolutely necessary to control the disease. If eye drops and/or oral medications are not effective in controlling the intraocular pressure, there are several laser or surgical procedures that might be employed, which have shown to halt or significant slow the progression of the disease (Gedde et al. 2007 Am J Ophthalmol).

While safe and effective treatments for glaucoma exist, their effectiveness is compromised by poor compliance. Patients who have problems with their topical glaucoma medication are acknowledged to be at higher risk for poor compliance, frequent medication switching, and surgery. Patient satisfaction with therapy and its associated benefits have until recently taken second place to efficacy. Lemij et al conducted a transverse cross-sectional epidemiological survey among glaucoma patients receiving therapy with prostaglandin analogs. The primary objective was to determine and characterize patient satisfaction with glaucoma therapy, and the secondary objective was to identify factors that may contribute to poor patient satisfaction. Ophthalmologists in the Netherlands included 199 patients and 164 were analyzed (Lemmij et al, 2015, Clin Ophthalm). Patients were predominantly elderly with early, primary, open angle glaucoma. Eighty-nine percent of them stated they were satisfied or very satisfied with their treatment. However, signs of ocular surface disorder on ophthalmological examination were evident in 44% of patients, corneal fluorescein staining was positive in 28% of patients, and 38% of patients were using tear substitutes. The prevalence of blepharitis/meibomian gland dysfunction and dry eye was more than twice as high after the commencement of therapy compared with before therapy. Univariate analysis revealed that patient dissatisfaction with their glaucoma therapy was statistically significantly

(P<0.001) associated with the presence of ocular surface disease, hyperemia, ocular signs, symptoms upon and between instillation, and the use of tear substitutes. Apparently, patients in the present study are satisfied with their treatment; 89% expressed satisfaction compared with only 11% who professed dissatisfaction. The results suggest that even if local adverse events and ocular surface disease, in particular, contribute to glaucoma patient dissatisfaction, only a minority of patients expressed such dissatisfaction. At the time of the study, most (94%) of the patients included were receiving preserved preparations. Further studies should evaluate the influence of preservative on patient satisfaction.

Recent reports indicate that more than 90% of patients with glaucoma fail to refill their ocular medications continuously during the first year of therapy and that less than 60% continue to refill eye drop prescriptions at 1 year(Friedman et al, 2007, Inv Ophth Vis Sci; Nordstrom et al, 2005, Am J Ophth). It has been suggested that medication adherence may be improved substantially by choosing a drug that needs to be taken less often (Norell, 1981, Am J Ophthalmol).

1.2 Name and description of study product

TRAVATAN® 40μg/ml eye drops have been registered for therapeutic use since 2001 (Whitson. 2002 Expert Opin Pharmacother). The current preparation of TRAVATAN® 40μg/ml contains 40 mcg of travoprost, a prostaglandin F2a analogue, in 1 ml solution. The preparation of TRAVATAN® 40μg/ml also contains 10 micrograms of polyquaternium-1 (POLYQUAD), 7.5 mg of propylene glycol, and 2 mg of polyoxyethylene hydrogenated castor oil 40 (HCO-40) in 1 ml solution. Further excipients are mannitol, sodium chloride, sodium hydroxide and/or hydrochloric acid disodium, boric acid, and purified water (SPC Travatan, 2013).Travoprost is a member of the prostaglandin analogue class of intraocular pressure-lowering drugs that also include other substances such as latanoprost or bimatoprost. Like other prostaglandin analogues, travoprost lowers intraocular pressure by enhancing the

egress of aqueous humor through both the uveoscleral and trabecular outflow pathway (Lim et al. 2008 Ophtalmology). Travoprost acts by binding to a specific receptor for prostaglandin (FP receptors/highly concentrated in the longitudinal ciliary muscle, iris, sphincter muscle and retina), and increases the flow of aqueous humor out of the eye, thereby reducing the pressure within the eye and the risk of nerve damage and blindness. In detail, travoprost is an isopropylester pro-drug that is hydrolyzed by corneal esterases into its biologically active free-acid form which is a highly selective, potent antagonist for the FP prostanoid receptor. Once travoprost acid binds to prostaglandin FP receptors, a numerous physiologic responses within ciliary muscle cells result in the remodeling of the extracellular matrix by creating spaces between the ciliary muscle fiber bundles. Thus, travoprost acid increases outflow primarily by the uveoscleral pathway. Reduction of IOP starts approximately two hours after administration and the maximum effect is reached after 12 hours. Travoprost has been compared to b-blockers such as timolol, other prostaglandin analogues such as latanoprost and bimatoprost. Summarizing the data comparing travoprost with other drugs, similar IOP reductions were seen with travoprost, bimatoprost or latanoprost (Denis et al. 2007 Clin Ophthalmol) whereas travoprost monotherapy lowers IOP by 6.5-9 mmHg and it is statistically superior or equal to timolol 0.5% dosed twice daily (Parrish et al. 2003 Am J Ophthalmol).

The need for sterilization in multi-dose eye drops requires the inclusion of an antimicrobial less toxic preservative in these solutions, such as polyquad (polyquaternium), which is a family of polycationic polymers. At least 37 different polymers exist, under the polyquaternium designation, but polyquaternium -1 is commonly used as multipurpose solution for contact lens care and has shown a good tolerability and safety profile compared to other multipurpose solutions (Lipener. 2009. Adv Ther). Polyquad is a cationic polymer of many quaternary ammonium structures with a 27-fold higher molecular weight than BAC, which lacks an hydrophobic region and as a result has no surfactant properties. Due to these

two chemical properties, Polyquad is unable to penetrate mammalian cells and cause cytotoxic effects (Tripathi et al. 1992 Eye Toxic Res).Except for concentrations of 0.5% or above, polyquad did not cause significant changes on the ocular surface compared with saline, whereas BAC induced apparent toxic effects at 0.1% and 0.5% concentrations, with a dramatically and extremely rapid destruction of ocular cells (Labbé et al. 2006 J Ocul Pharmacol Ther).Although Polyquad is considered relatively safe, it has been noted that this preservative dose have potent toxicity on the barrier function and cell viability after long-term exposure (Nakagawa et al. 2012 Invest Ophthalmol Vis Sci).

Study objectives

1.3 Primary objective

The primary objective of the current study is to investigate patients' adherence to TRAVATAN® (Travoprost) in adult patients with ocular hypertension or open angle glaucoma, when administered according to standard clinical practice.

1.4 Secondary objective

The secondary objective comprises the following: To identify potential factors that may be associated with TRAVATAN® non-adherence in daily clinical practice.

1.5 Study design

Multicenter, open – label, one – arm, prospective, non-interventional cohort study of patients with ocular hypertension or open angle glaucoma receiving TRAVATAN®. The total duration of the study is 36 weeks (12 weeks recruitment period and 24 weeks follow-up period). The recruitment period may be extended until the total number of patients is reached.

2. Study population

2.1 Target population

The target population of the current clinical study is male and female patients with ocular hypertension or open angle glaucoma, aged ≥18 years, receiving Travoprost, according to standard clinical practice.

2.2 Inclusion criteria

To be eligible to participate in this study, a patient must meet all the following eligibility criteria at baseline:

•Adult patient (≥18 years old) with ocular hypertension or open angle glaucoma

•Patient receiving TRAVATAN®.

•Patients willing and able to provide written informed consent personally or by legal proxy.

•Patients willing to comply with all study procedures and to be available for the duration of the study

2.3 Exclusion criteria

A patient will be excluded from the study if any of the following exclusion criteria apply:

•Current enrolment in other clinical trial.

•Patient with uncontrolled IOP≥21 mmHg.

•Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test

•Patients in treatment for ocular diseases (including OH or OAG) with more than one therapy.

•Patient with hypersensitivity to the active substance or to any of the excipients of this medicinal product.

3. Study endpoints

3.1 Primary endpoints

The primary endpoints of the study is the Proportion of patients reporting high adherence to TRAVATAN® at 24 weeks defined as a Morisky Medication Adherence Scale (MMAS-4) score equal to 0.

3.2 Secondary endpoints

The secondary endpoints of the study comprise the following:

- Proportion of patients with a Medication Persistence Ratio (MPR), defined as the number of days without receiving medication after study enrolment divided by the number of days participating in the study less than 0.20.
- Proportion of patients encountering difficulties with medication supply due to coexisting medical conditions.
- Proportion of patients encountering difficulties with medication supply due to lack of insurance coverage.
- Proportion of patients encountering difficulties with medication supply due to inability to access or difficulty accessing pharmacy.
- Proportion of patients with TRAVATAN® discontinuation during the follow-up period.

4. Total study duration

Total study duration is three (3) months recruitment period and 6 months follow-up period for each patient.

5. Data collection plan and study variables

Data pertinent to the present study will be collected on three visits and recorded on the Case Report Form (CRF). A schedule of patients' visits and assessments are presented in attached Table.

5.1 Baseline visit (week 0)

The Baseline visit will include the screening phase during which inclusion and exclusion criteria are checked, the patient is informed about the study, and informed consent form is signed. Should the patient is eligible for participation in the study and upon signature of the informed consent form; the following data will be recorded: demographic data, medical history (type of glaucoma, date of diagnosis, previous and current treatment for glaucoma and duration of administration), IOP measurement, comorbidities and concomitant medications.

5.2 Visit at week 8

During the visit at week 8, the following will take place: administration of the MMAS-4 questionnaire, calculation of the Medication Persistence Ratio and the following data will be recorded: description of potential factors associated with non-adherence, treatment discontinuations and adverse events.

5.3 Final visit (week 24)

During the final visit, the following will take place: administration of the MMAS-4 questionnaire, calculation of the Medication Persistence Ratio and the following data will be recorded: description of potential factors associated with non-adherence, treatment discontinuations and adverse events.

5.4 MMAS-4

The Morisky Medication Adherence Scale (MMAS) is a generic self-reported, medication-taking behavior scale, validated for hypertension but used for a wide variety of medical conditions. The original version of the scale (MMAS-4) consists of four items with a scoring scheme of "Yes" = 0 and "No" = 1. The items are summed to give a range of scores from low adherence (3-4) to high adherence (0) (Morisky et al, 1986, Med Care).

5.5 MPR

The Medication Persistence Ratio (MPR) was defined as the number of days without receiving medication after study enrolment divided by the number of days participating in the study. High adherence was defined as a value less than 0.20.

6. Treatment and concomitant medication

Since this is an observational, non-interventional study, the treatment schedule is defined according to investigator's criteria. Treatment with TRAVATAN® should be according to the indication for treatment as defined in the Summary of Product characteristics (SmPC) and according to standard clinical practice. During this non interventional study, any changes and/or additions to the concomitant medications are allowed according to investigator's criteria. All concomitant medications will be recorded on the CRF.

7. Treatment discontinuation

A patient should be withdrawn from the study if:

- according to the investigator's criteria treatment with TRAVATAN® should be discontinued
- the patient withdraws her consent for participation in the study
- any of the exclusion criteria becomes applicable.

The reason of patient's withdrawal should be recorded on the CRF.

8. Safety assessments

8.1 Definition of an adverse event

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment. In this study, any AE occurring after the study patient has signed the informed consent form should be recorded and reported as an AE. An AE can, therefore, be any unfavourable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study will not be considered AEs. Accordingly, an AE can include any of the following:

- Intercurrent illnesses
- Physical injuries
- Events possibly related to concomitant medication
- Significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition recorded as pre-existing that is intermittently symptomatic [e.g., headache] and which occurs during the study should be recorded as an AE.)
- Drug interactions
- Events occurring during diagnostic procedures or during any washout phase of the study
- Laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event (SAE), or require medical treatment or further diagnostic workup, or are considered by the physician to be clinically significant.

8.2 Definition of an Adverse Drug Reaction

An adverse drug reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

8.3 Definition of a Serious Adverse Event

A SAE is an AE occurring at any dose that results in any of the following outcomes or actions:

•Death (other than disease progression in this study)

•A life threatening AE (i.e., the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death

•Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a preexisting condition that has not worsened during participation in the study will not be considered SAEs.

•Persistent or significant disability or incapacity (refers to a substantial disruption of one’s ability to conduct normal life functions)

•A congenital anomaly/birth defect

•An important medical event that may not result in death, be life threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or

convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.
An AE that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious AE.

8.4 Recording and Reporting Adverse Events

Serious and non-serious Adverse Events that occur during the study period which are recorded in the patient's medical records or source documentation must be transcribed onto the CRF, regardless of the severity of the event. The clinical course of each AE will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The onset and end dates, duration (in case of AE duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each AE must be recorded on the source documentation and transcribed onto the eCRF. The relationship of each AE to study drug treatment and study procedures, and the severity and seriousness of each AE, as judged by the physician, must be recorded as well.

To satisfy regulatory requirements, all serious adverse events regardless of judged relationship to treatment with TRAVATAN®, that occur during the study period, must be reported to the sponsor by the physician. The event must be reported within 24 hours of when the physician learns about it or, if the event occurs on a weekend or national holiday, on the next working day. Contact details of the sponsor are provided below:

"sponsor"

Completing the Adverse Events/Adverse Drug Reaction Form and reporting the event must not be delayed, even if not all the information is available. The physician does not need

to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the physician becomes aware of them.

8.5 Relationship of an Adverse Event to the Study Drug

The relationship of an AE to the study drug is characterized as follows:

No reasonable possibility (not related)

This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug. The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply:

•It does not follow a reasonable temporal sequence from the administration of the test drug.

•It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

•It does not follow a known pattern of response to the test drug.

It does not reappear or worsen when the drug is re-administered.

Reasonable possibility (related)

This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug. The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply:

•It follows a reasonable temporal sequence from administration of the drug.

•It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

•It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists.

It follows a known pattern of response to the test drug.

8.6 Pregnancy

All pregnancies that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the physician must provide the LSO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting an SAE. All patients who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and new-born complications, will be reported to the sponsor. Any complication of pregnancy will be reported as an AE or SAE, as appropriate. For pregnancies of partners of men participating in the study, the Sponsor's Pharmacovigilance (PhV) Department will determine the procedure to appropriately follow up after notification as described above. All partners who become pregnant and provide appropriate consent to Sponsor's PhV will be monitored to the completion or termination of the pregnancy.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report an SAE.
- For an elective abortion due to developmental anomalies, report as an SAE.

- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form.

9. Sample size

In order to calculate a 95% confidence interval for the proportion of patients reporting high adherence to TRAVATAN® at 24 weeks, which is expected to be 80% with a margin error (Δ) (Okeke et al, 2009) no more than 2%, the required sample size is at least 1537 patients. A total sample size of at least 1843 patients (20% additional) will allow compensation for incomplete datasets.

10. Statistical methods

Demographic and clinical/prognostic data of the patients at baseline will be described with numerical and graphical summary statistics. The statistical significance of the proportion of patients reporting high adherence to TRAVATAN® will be assessed using a binomial test and the respective 95% confidence interval (CI). For the secondary endpoints, categorical data will be analyzed using a binomial test with the respective 95% CI, and continuous data will be analyzed using the paired t-test or the Wilcoxon signed rank test, depending on the nature of the data. The association between categorical variables will be tested using a chi-squared test and/or logistic regression. A result will be considered significant when $P \leq 0.05$. The statistical analysis will be performed using SPSS v.21.

11. Insurance coverage

Since this is a non-interventional clinical study, an insurance coverage is not applicable.

12. Regulatory Authority approval

The protocol will be submitted for approval to the Scientific Committee of each participating clinical site. Approval by the Greek Regulatory Agency (Hellenic Organization for Medicines, EOF) is not required due to the nature of the study (phase IV).

13. Data collection – Quality control

Data will be entered at the study sites into a central database using an electronic CRF (eCRF) with a delegated CRO as an administrator.

The investigator should keep accurate files to record study conduction. Study documents will be kept by the investigator on site as confidential documents. All applicable data will be transferred to the patient's Case Report Form (CRF). The Case Report Form is essential for the study conduction and should be completed for all patients entering the study by the investigator. The Sponsor has the rights of the completed original CRFs and therefore data should not be released in any format without the prior written approval of the Sponsor. Monitoring visits by authorised personnel may take place at the site to ensure conduction of the study in accordance to the protocol and ICH GCP Guidelines. The study monitor will be given access by the investigator or sub-investigator to the patient files and any relevant documents to ensure source data verification and will be assisted in resolving any issues arisen during the monitoring visits.

The investigational site may also get quality control audits by the sponsor company or the Regulatory Authorities. The investigator will ensure access of any study related documents to the authorised personnel of the sponsor company or the Regulatory Authorities during the quality control audits. For the smooth conduction of the study, it is important that investigational staff will be available during the monitoring visits or the quality control audits.

14. Protocol Amendments and violations

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the scientific committees as applicable to local regulations.

Any significant deviation from the protocol will be considered a protocol violation. Protocol violations include non-adherence on the part of the patient, the physician, or the sponsor to protocol-specific inclusion/exclusion criteria. Protocol violations will be identified and recorded by investigational site personnel on the eCRF. If investigational site personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

15. Ethics

15.1 Informed Consent

This study is non-interventional, and by definition no additional procedures will be performed on the patient in addition to the normal clinical practice of the treating physician. Informed consent should be obtained from patients for their clinical data to be recorded anonymously. They will also be informed of their right to withdraw their consent at any time. The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The physician will keep the original consent forms, and copies will be given to the patients. Written information about the study in a language understood by the patient will be given to all patients.

15.2 Health Authorities and Independent Ethics Committees/Institutional Review Boards

This study will be conducted in full accordance with the all relevant European and national guidelines and regulations for conducting studies with human subjects. Specifically, the study will comply with the Helsinki Declaration and the guidelines for Good Epidemiological Practice (GEP), Good Pharmacoepidemiology Practices and Good Pharmacovigilance Practices (GVP).

15.3 Confidentiality Regarding Study Patients

The physician must assure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (e.g., identification number).

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the eCRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

16. Study Termination

The sponsor may terminate the study, or a site’s participation at any time. The end of study will be when the last subject complete the last scheduled visit.

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Table. Flow Chart of Study Assessments for patients

Assessments	**Baseline**	**Interim visit**	**End of observation visit**
	Day 0	8 weeks after patient enrollment (± 3 days)	24 weeks after patient enrollment (± 7 days)
Informed consent[1]	X		
Demographic data	X		
Medical history	X		
Concomitant medication	X	X	X
Study drug administration	X	X	X
MMAS-4 assessment	-	X	X
MPR assessment	-	X	X
Assessment of difficulties in medication supply due to coexisting medical conditions	X	X	X
Assessment of difficulties in medication supply due to lack of insurance coverage	X	X	X
Assessment of difficulties in medication supply due to inability to access or difficulty accessing pharmacy	X	X	X
Treatment discontinuation	-	X	X
Adverse Event Reporting	-	X	X

NOTES: [1]The signed and dated informed consent should be in file before recording any study-related data in the study case report form (CRF).