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Master of Science thesis

"A protocol for an observational study for Telmisartan in people with moderate Hypertension"

“Πρωτόκολλο μελέτης παρατήρησης για χορήγηση Τελμισαρτάνης σε άτομα με μετρίου βαθμού Υπέρταση’’

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Φάση: Μελέτη παρατήρησης

Ερευνητικό Προϊόν: Τελμισαρτάνη

Ένδειξη: Μετρίου Βαθμού Υπέρταση

Κύριο τελικό σημείο αποτελεσματικότητας: Το κύριο τελικό σημείο αποτελεσματικότητας της μελέτης θα είναι η αλλαγή της συστολικής και της διαστολικής αρτηριακής πίεσης από την αρχή μέχρι και την 24^{η} εβδομάδα.

Δευτερεύοντα τελικά σημεία αποτελεσματικότητας: Τα δευτερεύοντα τελικά σημεία αποτελεσματικότητας θα είναι η αλλαγή των μέσων εργαστηριακών παραμέτρων(ολική χοληστερόλη, LDL,HDL,τριγλυκερίδια, γλυκόζη αίματος).

Κύριος στόχος ασφάλειας: Αξιολόγηση της εμφάνισης ανεπιθύμητων ενεργειών (Advesre events and serious adverse events) λόγω λήψης της τελμισαρτάνης.

Σχέδιο μελέτης και διάρκεια: Αυτή είναι μια μη παρεμβατική μελέτη παρατήρησης για την αξιολόγηση της αποτελεσματικότητας και της ασφάλειας της τελμισαρτάνης σε άτομα με μετρίου βαθμού αρτηριακή υπέρταση . Ο αριθμός των ατόμων καθώς και η διάρκεια της μελέτης εκτιμηθήκαν με βάση παλαιότερες δημοσιευμένες μελέτες. Η αναμενόμενη διάρκεια της μελέτης, από το πρώτο άτομο στην πρώτη επίσκεψη μέχρι την τελευταία επίσκεψη για το τελευταίο άτομο είναι περίπου 24 εβδομάδες. Οι ασθενείς θα επισκεφθούν την κλινική ένα μήνα μετά την πρώτη τους επίσκεψη και μετά κάθε 20 μέρες μέχρι το τέλος της περιόδου της μελέτης. Κατά τη διάρκεια της μελέτης θα αναφερθούν τα συμπτώματα τους ασθενούς καθώς και η ποιότητα ζωής που σχετίζεται με την υπέρταση. Τα δεδομένα για ανεπιθύμητες ενέργειες συλλέχθηκαν από την στιγμή της χορήγησης της πρώτης δόσης θεραπείας μέχρι τη διακοπή της θεραπείας.

Μελέτη πληθυσμού

Κριτήρια ένταξης

1. Άντρες και γυναίκες >18 χρονών
2. Ένδειξη αρτηριακής πίεσης :συστολική αρτηριακή πίεση>140mmHg αλλά <180mmHg
   Και /ή διαστολική αρτηριακή πίεση>90mmHg αλλά <110mmHg

Κριτήρια αποκλεισμού

1. Ασθενείς που συμμετέχουν σε άλλο πρωτόκολλο
2. Ασθενείς που έχουν αλλεργία στην τελμισαρτάνη
3. Οποιαδήποτε κατάσταση θέτει σε κίνδυνο την ικανότητα του ασθενούς να ολοκληρώσει τη μελέτη
4. Ασθενείς με καρδιακή ανεπάρκεια
5. Ασθενείς με ανεξέλεγκτο διαβήτη(γλυκοζιλιωμένη αιμοσφαιρίνη A_1C >10%)

Στατιστική μέθοδος: Η στατιστική δοκιμή που θα χρησιμοποιηθεί είναι t-test για ζευγαρωτές παρατηρήσεις με στάθμη σημαντικότητας p=0.05 μέσω του στατιστικού πακέτου SPSS.Θα παρατηρήσουμε αν υπάρχει στατιστικως σημαντική διαφορά στη μέση αρτηριακή πίεση από τη αρχή της περιόδου μέχρι και την $24^η$ εβδομάδα. Επίσης με τη Περιγραφική Στατιστική θα παρατηρήσουμε, αν υπάρχει αλλαγή στους εργαστηριακούς παράγοντες (ολική χοληστερόλη, LDL,HDL,τριγλυκερίδια, γλυκόζη αίματος) από την αρχή της περιόδου μέχρι και την $24^η$ εβδομάδα και θα καταγράψουμε το ποσοστό ασθενών (και τον απόλυτο αριθμό τους) που θα αναπτύξουν ανεπιθύμητες ενέργειες (Adverse Events ,Serious Adverse Events) οι οποίες θα οδηγήσουν σε διακοπή μελέτης/φαρμάκου.

SYNOPSIS

Title study: "A protocol for an observational study for Telmisartan in people with moderate Hypertension"

Phase: Observational study

Investigational Product: Telmisartan

Indication: Moderate Hypertension

Primary Efficacy Endpoint: The primary efficacy endpoint of the study will be the change in systolic and diastolic blood pressure from baseline to 24th week.

Secondary Efficacy Endpoint: The secondary efficacy endpoint of the study will be the change mean laboratory parameters (total cholesterol, LDL, HDL, triglycerides, blood glucose).

Primary Safety Objection: To determine the development of Adverse Events and Serious Adverse Events because of receiving Telmisartan.

Study Design and Duration: This is a non-interventional observational study to evaluate the efficacy and safety of Telmisartan in people with moderate Hypertension. The study will be event driven thus the number of subjects required and length of treatment are best estimates based on event rates in similar studies. The expected duration of the study, from first subject, first visit through the last follow up phone contact for the last subject is approximately 24 weeks.

Patients will visit the clinic 1 month after the first visit and then every 20 days until the end of study period. During the study, the patients' symptoms and the quality of life will be reported which associated with Hypertension.

Data on AEs (Adverse Events) were collected from the time of administration of the first study treatment dose until discontinuation.

Study Population

Inclusion Criteria

1. men and women >18 years old
2. indication of blood pressure :systolic blood pressure >140mmHg but <180mmHg
   And/or diastolic blood pressure >90mmHg but <110mmHg

Exclusion Criteria

1. Participating in another protocol
2. Allergy to Telmisartan
3. Any condition jeopardizing patient's ability to complete the study
4. Cardiac failure
5. Uncontrolled diabetes (hemoglobin A1c >10%)

Statistical methods: The statistical test which is going to be used is t-test for dependent data (paired samples t-test) with P-value=0.05 (level of significance) in SPSS. We are going to observe if there is statistically significant difference between mean Blood Pressure in 24th week vs mean Blood Pressure in baseline.

With Descriptive Statistics using SPSS,

- We will examine if there is statistical significant difference in laboratory parameters (total cholesterol, LDL, HDL, triglycerides, blood glucose) from baseline to 24th week.
- We are going to observe the percentage of the patients (and the cardinal number) that will develop AE, SAE and Adverse Events leading to study/drug discontinuation using SPSS.

CHAPTER 1: INTRODUCTION

1.1 Backround -Hypertension

Arterial hypertension is a chronic condition in which pressure in the arteries is increased. This increase in pressure makes the heart work more intensely than normal to circulate blood through the blood vessels. Blood pressure measurement includes two measurements, systolic and diastolic, depending on whether the cardiac muscle contracts (contraction) or relaxes between the pulses (dilation). Normal blood pressure at rest is within the range of 100 to 140 mmHg (systolic pressure) and 60 to 90 mmHg (diastolic pressure). Blood pressure levels> = 140/90 mmHg are referred to as arterial hypertension.

The World Health Organization (WHO) has ranked the blood pressure limits as follows:

Pressure in mmHg

Category	**Systolic**	**Diastolic**
Ideal	<120	<80
Normal	<130	<85
High Physiological Limits	130-139	85-89
Hypertension		
Level 1	140-159	90-99
Level 2	160-179	100-109
Level 3	> = 180	> = 110

Hypertension is the persistent increase in blood pressure above specific levels, affects many people and requires proper diagnosis and treatment, since it damages the body in many ways.

Hypertension is divided into 2 categories, primary (essential) hypertension and secondary hypertension. Approximately 90-95% of adults with high blood pressure have "primary hypertension" without apparent underlying medical cause. Other conditions affecting the kidneys, the arterial vasculature, the heart

or the endocrine glands cause the remaining 5-10% of the cases (secondary hypertension).

Hypertension is an important risk factor for the onset of stroke, myocardial infarction, heart failure, aneurysms (e.g., aortic aneurysm), peripheral arterial disease and chronic kidney disease. It should be noted that even moderate increase in blood pressure is associated with reduced life expectancy. However, it is often necessary to receive medication in people whose lifestyle changes are ineffective or inadequate.

1.2 Information about the drug

Telmisartan is an angiotensin II receptor antagonist, i.e. It inhibits the action of a hormone in the body called angiotensin II. Angiotensin II is a potent vasoconstrictor (a substance that causes contraction of blood vessels). By blocking the receptors to which angiotensin II normally binds, telmisartan suppresses the action of the hormone, thereby contributing to the expansion of the blood vessels. This reduces blood pressure and reduces the risks associated with high blood pressure, such as heart attack or stroke. At the same time, it allows the heart to swallow blood more easily, which can help reduce the risk of developing cardiovascular disease in the future.

1.3 Non-interventional observational studies

In non-interventional observational studies which examine the safety of telmisartan as used in general medicine to treat hypertension, the results were impressive. More specifically, 19,870 patients (52.3% men, mean age 59.1 years), of whom 47.6, 18.3, 13.2 and 2.1%, respectively, had concomitant hypercholesterolemia, diabetes mellitus, congestive heart failure and renal insufficiency. The adverse reactions reported in the study were only in 1.9% of patients. Tolerability was rated as very good, good, moderate or poor, respectively, in 74.7, 22.1, 0.7 and 0.5% of patients. Tolerability was similar across all subgroups of patients. Telmisartan did not increase creatinine or potassium in any subgroup, including 400 patients with impaired renal function (basal creatinine 1.73 mg / dL). Telmisartan had no adverse effects on glucose, triglyceride or cholesterol levels. Overall, telmisartan reduced the mean ± standard deviation (SD) of systolic blood pressure from 171.3 ± 16.4 mm Hg to

141.3 ± 12.0 mm Hg and diastolic blood pressure from 99.0 ± 9, 4 mm Hg at 83.4 ± 6.9 mm Hg. The reductions were similar between sexes, age groups and patients and did not depend on previous or concomitant treatment with other antihypertensive drugs. The results of this study showed that this drug is acceptable safe when used according to current prescribing guidelines.

In another older, multicenter, multinational study evaluating the efficacy and safety of Telmisartan, the drug was administered alone or as adjunctive therapy to 2121 adults with mild to moderate essential hypertension. Patients received Telmisartan 40-80 mg daily for 12 weeks and were able to participate in the study for up to 96 weeks or until the supply of telmisartan was commercially available. The mean change in mean diastolic blood pressure (DBP) after 12 weeks of treatment was -11.8 mmHg while the mean change in mean systolic blood pressure (SBP) was -20.2 mmHg. Both changes were statistically significant. The mean DBP and SBP reductions were evident from week 4 and were maintained throughout the treatment period. Telmisartan was well tolerated. The most common adverse events were headache (6%) and dizziness (3%), while 10% of the adverse events were considered to be drug-related. In conclusion, Telmisartan is an effective and well tolerated drug when used as monotherapy or adjunctive therapy in this broad patient population.

CHAPTER 2: STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy and safety of 24 weeks treatment of Hypertension with Telmisartan

Efficacy assessments will include Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

Safety assessments will include adverse events (AE) and Serious Adverse Events (SAE)

CHAPTER 3: ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP) as defined by the International Conference of Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive. Furthermore, the study will be conducted in compliance with the protocol. The protocol, the amendments of protocol and the subject informed consent will receive IRB/IEC approval opinion prior to initiation of the study.

3.2 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues of the study in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or in those situations where consent cannot be given by subjects, their legally acceptable representatives.

Subjects unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the study at any time should be considered by the investigator.

Subjects may withdraw consent from participation in the study at any time. In the event a subject withdraws consent to receive study drug, the site pay (with the subject's agreement) continue to contact the subject, general practitioner and any other physician or medical care provider for the collection of outcome and survival follow up data.

3.3 Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. The Investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designed by the Sponsor. Sponsor personnel whose responsibilities require access to personal data should agree to keep the identity of study subjects confidential.

CHAPTER 4: INVESTIGATION PLAN

4.1 Study Design and duration

This is a non-interventional observational study to evaluate the efficacy and safety of Telmisartan in people with Hypertension. The study will be event driven thus the number of subjects required and length of treatment are best estimates based on event rates in similar studies. The expected duration of the study, from first subject, first visit through the last follow up phone contact for the last subject is approximately 24 weeks.

- Screening period will start from 1st October 2017 and will last for 12 weeks, ending 24th of December 2017.
- Enrollment in the study will start after the screening period from the 26th until the 31st of December 2017.
- Treatment period will start on the 1st of January 2018 and will last for 24 weeks (i.e. until 11th of June 2018).

Also, in the 1st visit, the following baseline characteristics of the patients will be collected:

General Characteristics:

- Male (%)
- Female (%)
- Age (mean, SD)
- Blood pressure (mean, SD)
- Current smoker (%)
- Ex-smoker (%)

Clinical history:

- Prior cardiovascular disease (%)
- Stroke (%)
- Peripheral vascular disease (%)
- Coronary revascularization (%)

Patients will visit the clinic 1 month after the first visit and then every 20 days until the end of study period. During the study, the patients' symptoms and the quality of life will be reported which associated with Hypertension. Also, the laboratory tests such as general blood test, urine measurement of serum,

potassium and sodium creatinine levels will be performed to avoid possible renal damage.

Data on AEs (Adverse Events) were collected from the time of administration of the first study treatment dose until discontinuation.

4.1.1 Independent Advisory Committee

An Independent Advisory Committee will provide ongoing scientific and operational oversight to the study. The Committee will evaluate the ongoing study outcomes twice a year.

4.2 Study Population

4.2.1 Inclusion Criteria

1. men and women >18 years old
2. indication of blood pressure :systolic blood pressure >140mmHg but <180mmHg
   And/or diastolic blood pressure >90mmHg but <110mmHg

4.2.2 Exclusion Criteria

1. Participating in another protocol
2. Allergy to Telmisartan
3. Any condition jeopardizing patient's ability to complete the study
4. Cardiac failure
5. Uncontrolled diabetes (hemoglobin A1c >10%)

4.2.3 Discontinuation of Subjects from treatment

Subjects should discontinue study treatment for any of the following reasons:

a) Withdrawal of informed consent (subject's decision to withdraw for any reason)
b) Any clinical AE or intercurrent illness which in opinion of the Investigator indicates that continued participation in the study is not in the best interest of the subject.

CHAPTER 5: STUDY ENDPOINTS & STATISTICAL ANALYSIS

5.1 Efficacy Assessments

5.1.1 Primary efficacy endpoint

The primary efficacy endpoint of the study will be the change in systolic BP and diastolic BP from baseline to 24th week.

5.1.2 Secondary efficacy endpoints

The secondary efficacy endpoint of the study will be the change mean laboratory parameters (total cholesterol, LDL, HDL, triglycerides, blood glucose).

5.2 Safety Assessments

Safety assessments will include drug-related Adverse Events (AE) and Serious Adverse Events (SAE).

5.3 Statistical Analysis

5.3.1 Efficacy Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint of the study will be the change in systolic BP and diastolic BP from baseline to 24th week. The statistical test which is going to be used is t-test for dependent data (paired samples t-test) with P-value=0.05 (level of significance) in SPSS. We are going to observe if there is statistically significant difference between mean Blood Pressure in 24th week vs mean Blood Pressure in baseline.

Secondary Efficacy Endpoint

With Descriptive Statistics using SPSS, we will examine if there is statistically significant difference in laboratory parameters (total cholesterol, LDL, HDL, triglycerides, blood glucose) from baseline to 24th week.

5.3.2 Safety Analysis

In this study we are going to record the occurrence of drug-related Adverse Events, serious Adverse Events, or Adverse Events leading to study/drug discontinuation with Descriptive Statistics using SPSS . We are going to observe the percentage of the patients (and the cardinal number) that will develop AE, SAE and Adverse Events leading to study/drug discontinuation using SPSS.

CHAPTER 6: ADVERSE EVENTS

6.1 Definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administrated a pharmaceutical product and which does not necessarily have a casual relationship with this treatment.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

6.2 Severity of Adverse Event

- Mild (grade 1)- awareness of event but easily tolerated
- Moderate (grade 2)- discomfort enough to cause some interference with usual activity
- Severe (grade 3)- inability to carry out usual activity
- Very severe (grade 4)- life-threatening or disabling AE

6.3 Adverse Event Documentation-Reporting

Subjects must be carefully monitored for AE. All AE occurring after the subject has signed the informed consent form must be fully recorded in the subject's CRF. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

SAE must immediately (within 24 hours of the investigator's awareness) be reported and must be followed up until resolution or stabilization. If required and according to local law and regulations, SAE must be reported to the Ethics Committee and Regulatory Authorities.

6.4 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

CHAPTER 7: ADMINISTRATIVE SECTION

7.1 Compliance with the protocol

The study shall be conducted as described in this approved protocol. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to study subjects. Any significant deviation must be documented in the CRF.

7.2 Records Retention

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files) and source documents for the maximum period required by applicable regulations and guidelines or institution procedures, or for the period specified by the sponsor, whichever is longer. If the Investigator withdraws from the study (e.g. relocation, retirement) the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator).

7.3 Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper SAE, must be promptly reviewed, signed and dated by a qualified physician who is an investigator or subinvestigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
BP	Blood Pressure
CRF	Case Report Form
DBP	Diastolic Blood Pressure
GCP	Good Clinical Practice
HDL	High Density Lipoprotein
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low Density Lipoprotein
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SPSS	Statistical Package for Social Science
WHO	World Healthy Organization

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