ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
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Πανεπιστήμιο Θεσσαλίας

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ (ΠΜΣ)
«ΜΕΘΟΔΟΛΟΓΙΑ ΒΙΟΪΑΤΡΙΚΗΣ ΕΡΕΥΝΑΣ ΒΙΟΣΤΑΤΙΣΤΙΚΗ & ΚΛΙΝΙΚΗ ΒΙΟΠΛΗΡΟΦΟΡΙΚΗ»
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Διπλωματική Εργασία/ Senior Thesis
Τσόκολας Π. Γεώργιος, ΑΜ Μ060615041

«Randomized 2-Way Crossover Open Label Study Of a Single Dose Atorvastatin Commercial tablet compared to an Atorvastatin Suspension Formulation in Healthy Subjects To Estimate The Relative Bioavailability»
«Τυχαιοποιημένη, διασταυρούμενης μετάβασης, ανοιχτή μελέτη μιας Ατορβαστατίνης σε χάπι, συγκριτικά με ένα εναιώρημα Ατορβαστατίνης, σε υγιείς εθελοντές, με σκοπό την εκτίμηση της σχετικής βιο-διαθεσιμότητας των 2 φαρμακοτεχνικών μορφών»

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1) ABSTRACT/ ΠΕΡΙΛΗΨΗ

Σκοπός της μελέτης είναι η εκτίμηση της σχετική βιοδιαθεσιμότητας δύο διαφορετικών φαρμακοτεχνικών μορφών, της κοινής ταμπλέτας Lipitor (atorvastain) συγκριτικά με ένα πρότυπο εναιώρημα ατορβαστατίνης, ώστε να εκτιμηθεί/αξιολογηθεί η απόφαση ανάπτυξης της νέας φαρμακοτεχνικής μορφής.

Οι λόγοι ανάπτυξης νέας φαρμακοτεχνικής μορφής μπορεί να είναι 1)λόγοι ευληπτότητας , 2)λήψης ακριβέστερης δόσης 3) λήψης από συγκεκριμένη ομάδα ασθενών (πχ παιδιά, ηλικιωμένοι με δυσκολία κατάποσης) ή/και λόγοι 4)marketing

Η περίοδος recruitment διαρκεί 1 ημέρα. Οι 70 υγιείς εθελοντές εφόσον εξετάζονται και πληρούν τα κριτήρια εισόδου στην μελέτη τυχαιοποιούνται σε 2 ομάδες των 35 ατόμων έκαστη και τους χορηγούμε εφάπαξ 80mg ατορβαστατίνης (σε χάπι ή εναιώρημα και αντίστροφα , βάσει του πρωτοκόλλου-σχήμα παρακάτω της 2-way-cross over study).

Δείγματα αίματος (4ml) συλλέχθηκαν από μία κατάλληλη φλέβα στα ακόλουθα χρονικά σημεία t=0 (πριν την χορήγηση), 0.25(15min μετά την χορήγηση), 0.5(30min), 1h , 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 48h and 72h μετά την χορήγηση.

Τα δείγματα αίματος συλλέγονται και αποθηκεύονται στους -28°C

Τις πρώτες 24 ώρες της Α περιόδου οι εθελοντές παραμένουν όλη την μέρα στο κέντρο , λόγω των συχνών αιμοληψιών(δες παραπάνω χρόνους), ύστερα έρχονται στο κέντρο για αιμοληψία την 48η και 72η ώρα μετά την χορήγηση φαρμάκου.Την περίοδο Α ακολουθεί μια washout period(περίοδος έκπλυσης φαρμάκου) 7 ημερών (168 ώρες), όπου πρέπει να ακολουθήσουν πιστά το πρωτόκολλο. Μετά την περίοδο έκπλυσης της Α περιόδου , ακολουθεί κατά ίδιο τρόπο η περίοδος Β , όπου οι 2 ομάδες εθελοντών εναλλάσσονται ως προς την φαρμακοτεχνική μορφή λήψης(περίοδος Β) και γίνονται κατά τον ίδιο τρόπο αιμοληψίες. Ακολουθεί μια δεύτερη περίοδος έκπλυσης (7 ημερών) και μια τελευταία αιμοληψία (last Visit).

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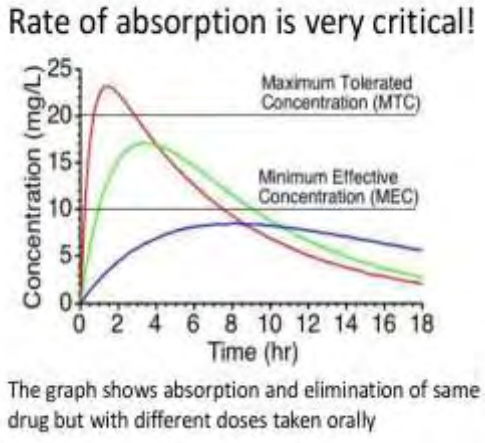
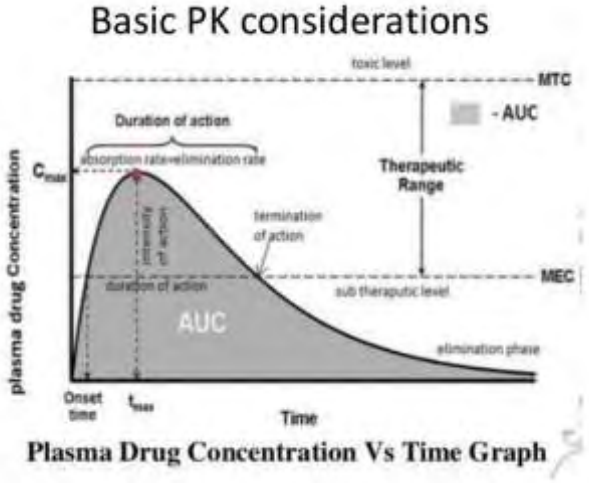
Βάσει της συλλογής των αποτελεσμάτων , της συγκέντρωσης ατορβαστατίνης και του χρόνου t , κατασκευάζουμε τα ανάλογα γραφήματα C/t, όπου και εξάγουμε πρωταρχικά συμπεράσματα για 1)την βιοδιαθεσιμότητα των δύο φαρμακοτεχνικών μορφών (εμβαδά κάτω από τις καμπύλες) 2) το Cmax (την μέγιστη θεραπευτική συγκέντρωση) και δευτερεύοντα συμπεράσματα όπως 3)ο χρόνος ημιζωής t1/2 και 4) ο Tmax (χρόνος που απαιτείται για να επέλθει μέγιστη συγκέντρωση στο αίμα) και τέλος 5) το θεραπευτικό εύρος.

Συμπερασματικά:Σκοπός της μελέτης είναι να αποδείξει ότι το προϊόν ελέγχου είναι ίδιο με το προϊόν αναφοράς . Συγκεκριμένα, οι λόγοι των παραμέτρων AUC και Cmax, του ουσιωδώς όμοιου φαρμάκου και του πρωτότυπου, που επεξεργάζονται από το ANOVA test , πρέπει να κυμαίνονται εντός της περιοχής 80 - 125% που καθορίζει το όριο εμπιστοσύνης (CL 90%). Το Tmax να υπάκουει στο Wilcoxon signed rank test



The graph shows absorption and elimination of same drug but with different doses taken orally



Plasma Drug Concentration Vs Time Graph

The purpose of this study is to estimate the relative bioavailability of the commercial tablet Lipitor (atorvastatin) with one prototype preparation suspension formulation, so as to assess internal decision making on formulation development. Reasons for the development of this new formulations should be taken into consideration:1)availability reasons 2)reception of the precise dose 3)reception by a particular group of people (eg.children, elderly adults with signs of dysphagia) 4)marketing.

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The recruitment period lasts one day. After the 70 healthy objects have been examined and are found eligible for the study, they are randomized into 2 groups of 35 people in each sequence. 80 mg of atorvastatin is administered (either in the form of a tablet or suspension and vice versa, according to the protocol – 2 crossover design study as detailed below).

Blood samples (4 ml) were collected from a suitable forearm vein by an indwelling catheter or by immediate venipuncture at the following time points: 0 (before administration),0.25(15min),0.5(30min),1(1hr), 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h, 48h and 72h after the administration.The blood samples are collected and stored in -28°C.

In the first 24hours of Period A the subjects remain all day in the study centre because of the frequent blood samplings (the period points are mentioned above).They come to the study centre for blood samplings 48 or 72 hours after the administration of the medicine.Period A is followed by a 7-day washout period (168 hours) according to the protocol. In Period B the same procedure is followed in which the 2 groups of subjects cross-over from one drug formulation to another during the course of the study. The blood samples are performed as well. A second washout period follows (7 days) and the last blood sampling.(Last visit)

According to the collection of the samples ,the atorvastatin concentration and the time t ,we put together the equivalent graph C/t where we can deduce the primary conclusions for 1)the bioavailability of the two formations (the area under the curves) 2)the Cmax (maximum concentration) and secondary conclusions such as 3)the half-life t1/2 and 4)Tmax (the time needed for the maximum blood concentration and finally5)the therapeutic range.

In conclusion,the purpose of this study is to prove that the new formulation is the same with the reference drug. More specifically,the reasons of the fractional of the AUC and Cmax, between reference drug (80mg tablet Atorvastatin and 80mg of the new formulation (suspension atorvastatin) which are processed by the ANOVA test must be in the 80 - 125% range which determines the CL 90%.The Tmax must comply with the Wilcoxon signed rank test

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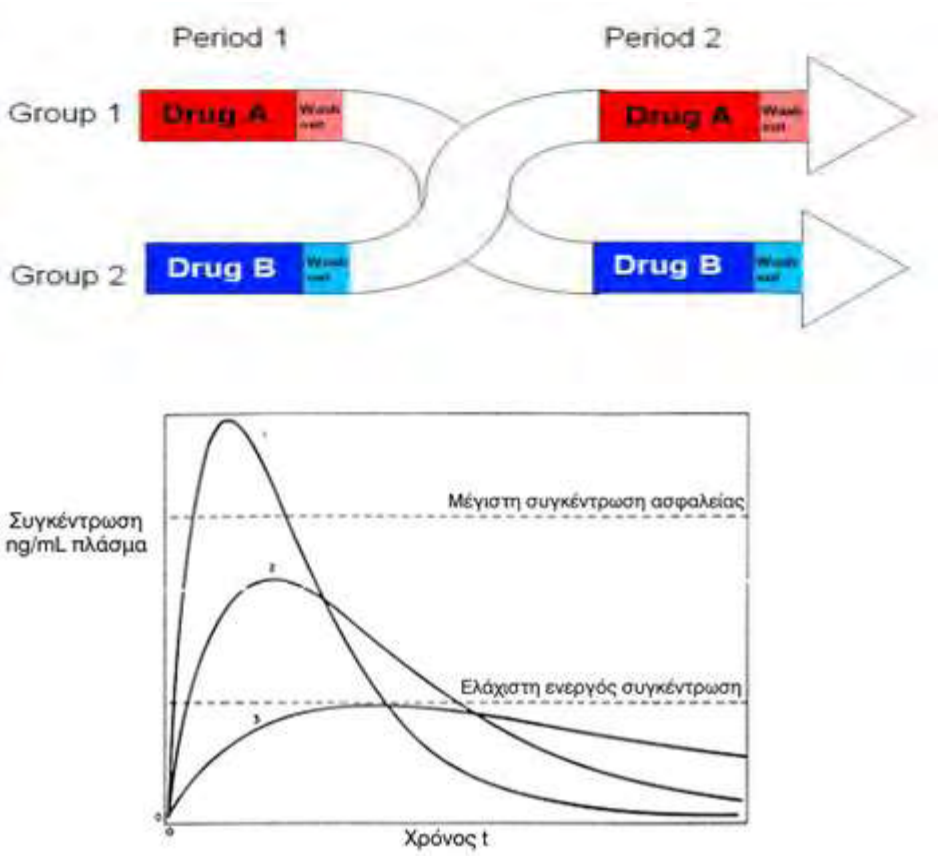
2-way cross over design



Reporting Groups

	Description
Test Drug First (Atorvastatin EP Suspension)	80-milligram (mg) Extemporaneous preparation (EP) suspension atorvastatin prototype formulation as a single dose in the first intervention period and commercial (reference) 80 mg atorvastatin tablet (Lipitor®) as a single dose in the second intervention period. Period 2 began after 7 days (wash out period) of period 1.
Reference Drug First (Atorvastatin Tablet)	80-mg Commercial atorvastatin tablet (Lipitor®) as a single dose in the first intervention period and 80-mg EP suspension atorvastatin prototype formulation as a single dose in the second intervention period. Period 2 began after 7 days (wash out period) of period 1.

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- ✓ Ο λόγος χορήγησης 80mg ατορβαστατίνης είναι ότι γνωρίζουμε διεξοδικά από παλαιότερες μελέτες ότι αυτή είναι η μέγιστη ημερήσια επιτρεπόμενη δόση καθώς και ότι σε αυτή τη C της ουσίας αυτής παρατηρείται η μεγαλύτερη ευαισθησία .
- ✓ Τέλος να αναφερθεί ότι πλέον με τις νέες μεθόδους μπορούμε να μετρήσουμε την (πρόδρομη) δραστική ουσία (ατορβαστατίνη), εξάγοντας ασφαλέστερα αποτελέσματα και υποστηρικτικά τον μεταβολίτη της (υδροξυ-ατορβαστατίνη) που μετράγαμε σε παλαιότερες μελέτες.

Number of study sites:	1
Primary Objective:	• Area under the curve from predose(time zero) to 72 hours post-dose(AUC72) • Maximum Observed Plasma Concentration (Cmax) • Area Under the Curve From Predose (Time Zero) to Extrapolated Infinite Time (AUC Infinity)
Secondary Objective:	• Plasma Elimination Half-life (t1/2) • Time to Reach Maximum Plasma Concentration (Tmax • Area Under the Curve From Predose (Time Zero) to Last Quantifiable Concentration (AUClast) • Therapeutical Range
Study Design:	One center in Larisa, interventional , randomized , open label, Crossover assignment study of 70 healthy volunteers. The total duration of the study is 21 days (504 hours)
Target population:	Male and female healthy volunteers , ages 18 years to 60 (Adult),
Inclusion criteria:	• Healthy male and/or female subjects • Age: from 18 years to 60 . • Body Mass Index (BMI) of approximately 18 to 30 kg/m2. • Patient signed an informed consent document.

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Exclusion criteria:	• Any condition possibly affecting drug absorption • A positive urine drug screening • Pregnant or lactating woman. • Patient with active liver disease or unexplained persistent elevations of serum transaminases upper limit of normal • Patient with hypersensitivity to the active substance or to any of the excipients of this medicinal product.
Primary endpoint:	Primary endpoints are the comparison of AUC72 , Cmax and AUCInf , of atorvastatin between the commercial tablet (reference) and the new formulation (test)
Secondary endpoints:	Secondary endpoints are other parameters (Tmax, t1/2 and AUClast,) and safety assessments based on adverse events
Sample size:	two sequences of 35 healthy subjects per sequence (70 subjects total). Each sequence received either test treatment followed by reference treatment, or reference treatment followed by test treatment. The order of administration was randomized to either of 2 sequences.
Statistical methods:	• The fractional of the AUC and Cmax, between reference drug (80mg tablet Atorvastatin and 80mg of the new formulation (suspension atorvastatin) which are processed by the ANOVA test must be in the 80 - 125% range which determines the CL 90%.The Tmax must comply with the Wilcoxon signed rank test • Pharacokinetic deals with the effect of the drug on the body so all the statistical parameters extracted are called pharmacokinetic statistical parameters such as Cmax, Tmax, UC, AUC∞, AMUC, AMUC∞, MRT, t½, Volume of Distribution,

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2)INTRODUCTION

Dyslipidemia, defined as elevated total or LDL cholesterol levels, or low levels of HDL cholesterol, contribute to the development of atherosclerosis and it is an important risk factor for CHD and stroke (cerebrovascular disease). Dyslipidemia has been traditionally classified by patterns of elevation in lipids and lipoproteins (Fredrickson phenotype). Primary (genetic) factors and secondary (lifestyle and other) factors contribute to dyslipidemia in various degrees. As with other statins, atorvastatin is a competitive inhibitor of HMG-CoA reductase. Unlike most others, however, it is a completely synthetic compound. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases de novo cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol.

Recent studies have shown that in patients suffering from acute coronary syndrome, high-dose statin treatment may play a plaque-stabilizing role. At high doses, statins have anti-inflammatory effects, incite reduction of the necrotic plaque core, and improve endothelial function, leading to plaque stabilization and, sometimes, plaque regression. However, there is an increased risk of statin-associated adverse effects with such high-dose statin treatment.[1] There is a similar thought process and risks associated with using high-dose statins to prevent recurrence of thrombotic stroke.[2]

Treating dyslipidemia focuses attention primarily on plasma total cholesterol (TC) and LDL-cholesterol (LDL-C) levels.3 Data disclose that a 10% reduction in plasma TC is followed by about a 25% reduction in coronary heart disease incidence (CHD), while a reduction of LDL-C by 40 mg/dl is accompanied by a 20% reduction in CHD events after 5 years.4 Statins (HMG-CoA reductase inhibitors), are proven in multiple randomized, controlled, clinical trials to lower cardiac morbidity and mortality. Statins successfully lower LDL cholesterol and total cholesterol in most patients, with substantial reductions in the risk of major coronary events, such as myocardial infarction, and stroke. 5-7 Atorvastatin is one of the most studied drugs with regards to clinical data, having been shown to reduce acute coronary heart disease events, coronary revascularization, and rate of stroke.8.9 In addition, its efficacy has been confirmed in a variety of populations. Atorvastatin a HMG-CoA reductase inhibitor , is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolemia including familial hypercholesterolemia (heterozygous variant) or combined (mixed) hyperlipidemia (corresponding to

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Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate. Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.10

3)Name and description of study product

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the receptor with high affinity to LDL (LDL receptor). Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering agents. Atorvastatin has been shown to reduce concentrations of total-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%), and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose-response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, non-familial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with non-insulin-dependent diabetes mellitus.Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce the risk for cardiovascular events and cardiovascular mortality.

4)Study objectives

4.A) Primary objective

- Area under the curve from predose(time zero) to hours post-dose(AUC72)
- Maximum Observed Plasma Concentration (Cmax)
- Area Under the Curve From Predose (Time Zero) to Extrapolated Infinite Time (AUC Infinity)
- Primary endpoints are the comparison of Cmax, and AUC72 of atorvastatin between the commercial tablet (reference/Lipitor) and the new atorvastatin product.

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4.B) Secondary objective

- Time to Reach Maximum Plasma Concentration (Tmax)
- Plasma Elimination Half-life (t1/2)
- Area Under the Curve From Predose (Time Zero) to Last Quantifiable Concentration (AUClast)

4.C) Study design

- One center in Larisa General Hospital . An Open Label, interventional, Single Dose, Randomized 2-Way Crossover Study with 70 healthy volunteers, To Estimate the Relative Bioavailability Of Atorvastatin Commercial Tablet, and An extemporaneous preparation (EP) Suspension Formulation, In Healthy Subjects.
- The total duration of the study is 21 days (1 day recruitment, 72 hours duration period A , 7 days washout of period A, 72hours duration period B, 7 days wash out period B)

- This study contained two sequences of 35 subjects per sequence. Each sequence received either test treatment followed by reference treatment, or reference treatment followed by test treatment. The order of administration was randomized to either of 2 sequences.

5) Study population

5.A) Target population

The target population of the current clinical study is male and female healthy volunteers , ages 18 years to 60 with Body Mass Index (BMI) of approximately 18 to 30 kg/m2.

5.B) Inclusion criteria

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

- Healthy male and/or female subjects
- Age: from 18 years to 60 .
- Body Mass Index (BMI) of approximately 18 to 30 kg/m2.
- Patient signed an informed consent document.

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5.C) Exclusion criteria

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

- Any condition possibly affecting drug absorption
- Out of normal range urine results
- Pregnant or lactating woman.
- Patient with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- Patient with hypersensitivity to the active substance or to any of the excipients of this medicinal product.
- No other Treatment and concomitant medication

6) Study endpoints

6.A)Primary endpoints

- Primary endpoints are the comparison of Cmax, AUCinf and AUC72 of atorvastatin

between the commercial tablet (reference/Lipitor) and the new atorvastatin formulation

- Area under the curve from predose(time zero) to 72 hours post-dose(AUC72)
- Area Under the Curve From Predose (Time Zero) to Extrapolated Infinite Time (AUC Infinity)
- Maximum Observed Plasma Concentration (Cmax)

6.B)Secondary endpoints

- Time to Reach Maximum Plasma Concentration (Tmax)
- Plasma Elimination Half-life (t1/2)
- Area Under the Curve From Predose (Time Zero) to Last Quantifiable Concentration (AUClast)

6.C)Total study duration

The total duration of the study is 21 days (1 day recruitment, 72 hours duration period A , 7 days washout of period A, 72hours duration period B, 7 days wash out period B)

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7) Data collection plan and study variables

In each blood sampling the concentration of atorvastatin and the time the sample is received will be compared so as to put together the graph C/t.

Baseline visit (hour 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,
- In the first 24hours of Period A the subjects remain all day in the study centre because of the frequent blood samplings (the period points are mentioned above).

Visit 1 (48^{h} after administration)

Blood sampling

Visit 2 (72h after administration)

Last blood sampling of period A

First Washout period (the 7 days after Period A)

The duration is 7 days.

Visit 3-(baseline 0') (Start period B)

In Period B the same procedure is followed in which the 2 groups of subjects rotate as for the reception of the formulation

Blood samples (4 ml) were collected from a suitable forearm vein by an indwelling catheter or by immediate venipuncture at the following time points: 15min after administration, 30min , 1hr, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h

Visit 4 (48h after Period B)

Blood sampling

Visit 5 (72h)

Blood sampling

Second Wash out period (7 days after period B)

The duration is 7 days.

Last Visit (Visit 6)

Last blood sampling of period B

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Treatment discontinuation

A patient should be withdrawn from the study if:

- the patient withdraws his/her consent for participation in the study
- any of the exclusion criteria becomes applicable.
- If any SAE occured

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

8)Safety assessments

8.A) 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. All events of possible drug induced liver injury with hyperbilirubinaemia (defined as aspartate aminotransferase or alanine aminotransferase ≥3 times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN or International Normalized Ratio >1.5) or Hy's Law events require immediate study treatment cessation and reporting as an SAE.

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(8.B) 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.C) 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 pre-existing 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.D) Pregnancy

The study will be terminated immediately in case of pregnancy

All pregnancies that occur during 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

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(9) Statistical methods

- The fractional of the AUC and Cmax, between reference drug (80mg tablet Atorvastatin and 80mg of the new formulation (suspension atorvastatin) which are processed by the ANOVA test must be in the 80 - 125% range which determines the CL 90%.The Tmax must comply with the Wilcoxon signed rank test
- Pharacokinetic deals with the effect of the drug on the body so all the statistical parameters extracted are called pharmacokinetic statistical parameters such as Cmax, Tmax, UC, AUC∞, AMUC, AMUC∞, MRT, t½, Volume of Distribution,

(10) Insurance coverage

Since it is a study of bioavailability and the object of the study is a new formulation the lealthy subjects are covered by insurance

(10.A) Regulatory Authority approval

Approval by the Greek Regulatory Agency (Hellenic Organization for Medicines, EOF) and National Ethics Committee.

(10.B) Data collection – Quality control

Paper Case Report Form will be used for this study
The study person should keep accurate files to record study conduction.

(11) Ethics

(11.A) Informed Consent

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.

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(11.B)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).

(11.C)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. Paper CRFs and other documents will be identified by an identification code (e.g., identification number).

Personal medical information will always be treated as confidential.

(11.D)Study Termination

The end of study will be when the last subject complete the last scheduled visit.

During this interventional study, any changes and/or additions to the concomitant medications are allowed according to the investigator's criteria. All concomitant medications will be recorded on the CRF.

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