A Study To Assess Absorption Of Study Drug TESTOSTERONE ENANTHATE, Oil based formulation Injected with Methylcobalamin ester attached Compared simple oil based solution In Healthy Volunteers.

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Abstract

In vivo bioavailability studies are performed for new or existing drug to establish essential pharmacokinetic parameters including rate of absorption, extent of absorption, rates of excretion and metabolism and elimination half-life after a single and multiple dose administration. These essential pharmacokinetic parameters are useful in establishing dosage regimens. Bioequivalence used to assess the expected in vivo biological equivalence of two proprietary preparations of drug products. If two drugs are bioequivalent, it means that they are expected to be same for all intents and purposes. In determining bioequivalence between two drugs such as a reference drug or brand and potential to be test drug or marketed generic drug. Pharmacokinetic studies are conducted whereby each of the drugs is administered in a cross over study to healthy volunteer's subjects. Plasma is obtained at regular intervals and assayed for parent drug or metabolite concentration to compare the two drugs. For comparison purpose of two formulations, the plasma concentration data are used to assess key pharmacokinetic parameters. If 90% confidence interval for the ratio of the geometric least square means of peak plasma concentration, area under curve of test and reference drugs are within 80–125%, then bioequivalence will be established.

Here the study is to determine the effect on bioavailability of oil based Testosterone and DHT derivative solutions while injected IntraMuscular with added Methylcobalamin molecule.

Sponsor:
Third Degree Pharma Co Ltd

Collaborators:

Dept of Endocrinology, School of Medicine Tue Tinh Hanoi

Information provided by (Responsible Party):

STUDY DESIGN

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	14 participants
Intervention Model:	Crossover Assignment
Masking:	None (Open Label)
Primary Purpose:	Basic Science
Official Title:	A Phase 1, Single dose IM, Fixed Sequence Study To Estimate The Absolute Bioavailability Of Testosterone Enanthate with methylacolabamine Intramuscular Administration In Healthy Volunteers
Study Start Date :	April 2019
Actual Primary Completion Date :	June 2019
Actual Study Completion Date :	June 2019

Arms and Interventions

Arm	Intervention/treatment
Experimental: Treatment Testosterone Enanthate and Methylcobalamin will be administered as a single dose IM	Drug: Testosterone Enanthate and Methylcobalamin Testosterone Enanthate and Methylcobalamin 250mg and 10mcg

Outcome Measures

Primary Outcome Measures :

1. Testosterone Enanthate and Methylcobalamin Dose-normalized Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. normalized to the administered dose

2. Testosterone Enanthate and Methylcobalamin Dose-normalized Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. normalized to the administered dose

Secondary Outcome Measures :

1. Testosterone Enanthate and Methylcobalamin Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption.

2. Testosterone Enanthate and Methylcobalamin Area Under the Curve From Time Zero to Last Quantifiable Concentration [AUC (0-t)]following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t)

3. Testosterone Enanthate and Methylcobalamin Dose-Normalized Area Under the Curve From Time Zero to Last Quantifiable Concentration [AUC (0-t)] following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t) normalized to the administered dose

4. Testosterone Enanthate and Methylcobalamin Maximum Observed Plasma Concentration (Cmax) following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]

5. Testosterone Enanthate and Methylcobalamin Time to Reach Maximum Observed Plasma Concentration (Tmax) following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]
6. Testosterone Enanthate and Methylcobalamin Apparent Clearance (CL/F) [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after dose (apparent clearance) is influenced by the fraction of the dose absorbed. Clearance was estimated from population pharmacokinetic (PK) modeling. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood.

7. Testosterone Enanthate and Methylcobalamin Apparent Volume of Distribution (Vz/F) following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent volume of distribution after dose (Vz/F) is influenced by the fraction absorbed.

8. PF-05199265 Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following dose

9. PF-05199265 Dose-normalized Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following dose normalized by administered dose

10. PF-05199265 Area Under the Curve From Time Zero to Last Quantifiable Concentration [AUC (0-t)]following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t)

11. PF-05199265 Dose-Normalized Area Under the Curve From Time Zero to Last PF-05199265 Quantifiable Concentration [AUC (0-t)] following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t) normalized to the administered dose

12. Plasma Decay Half-Life (t1/2) following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Plasma decay

half-life is the time measured for the plasma concentration to decrease by one half.

13. PF-05199265 Maximum Observed Plasma Concentration (Cmax) following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]
14. Testosterone Enanthate and Methylcobalamin Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following Intramuscular dose

15. Testosterone Enanthate and Methylcobalamin Area Under the Curve From Time Zero to Last Quantifiable Concentration [AUC (0-t)]following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t)

16. Testosterone Enanthate and Methylcobalamin Dose-Normalized Area Under the Curve From Time Zero to Last Quantifiable Concentration [AUC (0-t)] following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t) normalized to the administered dose

17. Testosterone Enanthate and Methylcobalamin Maximum Observed Plasma Concentration (Cmax) following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]
18. Plasma Decay Half-Life (t1/2) of Testosterone Enanthate and Methylcobalamin following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Plasma decay half-life is the time measured for the plasma concentration to decrease by one half.

19. Systemic Clearance (CL) of Testosterone Enanthate and Methylcobalamin following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]CL is a quantitative measure of the rate at which a drug substance is removed from the body.

20. Volume of Distribution at Steady State (Vss) of Testosterone Enanthate and Methylcobalamin following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the

desired blood concentration of a drug. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state.

21. PF-05199265 Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following Intramuscular dose

22. PF-05199265 Dose-normalized Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]Area under the Concentration-Time Curve (AUC) From Time Zero to Extrapolated Infinite Time following Intramuscular dose normalized by administered dose

23. PF-05199265 Area Under the Curve From Time Zero to Last Quantifiable Concentration [AUC (0-t)]following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t)

24. PF-05199265 Dose-Normalized Area Under the Curve From Time Zero to Last PF-05199265 Quantifiable Concentration [AUC (0-t)] following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]AUC (0-t)= Area under the plasma concentration versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t) normalized to the administered dose

25. PF-05199265 Maximum Observed Plasma Concentration (Cmax) following Intramuscular dose [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]
26. Metabolite ratio for AUCinf after administration [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]PF-05199265/ Testosterone Enanthate and Methylcobalamin ratio of AUCinf

27. Metabolite ratio for AUClast after administration [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]PF-05199265/ Testosterone Enanthate and Methylcobalamin ratio of AUClast

28. Metabolite ratio for Cmax after administration [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]PF-05199265/ Testosterone Enanthate and Methylcobalamin ratio of Cmax

29. Metabolite ratio for AUCinf after Intramuscular administration [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]PF-05199265/ Testosterone Enanthate and Methylcobalamin ratio of AUCinf

30. Metabolite ratio for AUClast after Intramuscular administration [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]PF-05199265/ Testosterone Enanthate and Methylcobalamin ratio of AUClast

31. Metabolite ratio for Cmax after Intramuscular administration [Time Frame: 0, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]PF-05199265/ Testosterone Enanthate and Methylcobalamin ratio of Cmax

32. PF-05199265 Time to Reach Maximum Observed Plasma Concentration (Tmax) following dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]
33. PF-05199265 Time to Reach Maximum Observed Plasma Concentration (Tmax) following IV dose [Time Frame: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose]

Eligibility Criteria

Ages Eligible for Study:	18 Years to 55 Years (Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	Yes

Criteria

Inclusion Criteria:

- Healthy male or female (of non-childbearing potential) subjects between the ages of 18 and 55 years, inclusive.
- Body Mass Index (BMI) of 17.5 to 30.5 kg/m2; and a total body weight >50 kg (110 lbs).

Exclusion Criteria:

- Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).
- Treatment with an investigational drug within 3 months or 5 half-lives preceding the first dose of study medication, whichever is longer.
- Any condition possibly affecting drug absorption (eg, gastrectomy).
- Any known allergies or sensitivity to drug excipients.

Contacts and Locations

Locations

Vietnam
School of Medicine Tue Tinh Hanoi
Hanoi, Vietnam

Sponsors and Collaborators

3rd Degree Pharma Co Ltd

Investigators

Study Director:	3rd Degree Pharma Co Ltd	3rd Degree	

STUDY RESULTS

Outcome Measures

1.Primary Outcome

Title	The AUC of Mesalamine in Plasma

Description	The AUC is the area under the concentration-time curve from time 0 to last time point. The data are organized by the different **drug** formulations of mesalamine, which include Testosterone Enanthate and Methylcobalamin (0 to 72 hours). The AUC is measured in units of nanomoles of mesalamine per liter of plasma (nM) multiplied by time in hours (nM*h). The AUC results are reported over the time-period because this provides a more meaningful comparison of potential differences in the bioequivalence of formulations.
Time Frame	0 hours pre-dose and up to 96 hours post-dose

Outcome Measure Data

2.Primary Outcome

Title	The AUC of Metabolite (N-acetyl-mesalamine) in Plasma
Description	The AUC is the area under the concentration-time curve from time 0 to last time point. The data are organized by the different **drug** formulations of mesalamine, which include Testosterone Enanthate and Methylcobalamin (0 to 72 hours). The AUC is measured in units of nanomoles of N-acetyl-mesalamine per liter of plasma (nM) multiplied by time in hours (nM*h). The AUC results are reported over the time-period because this provides a more meaningful comparison of potential differences in the bioequivalence of formulations.
Time Frame	0 hours pre-dose and up to 96 hours post-dose

Arm/Group Title	Testosterone Enanthate and Methylcobalamin
Arm/Group Description:	Testosterone Enanthate and Methylcobalamin 250mg and 10mcg, single dose IM IM Testosterone Enanthate and Methylcobalamin 250mg and 10mcg; single dose IM

Overall Number of Participants Analyzed	10
Mean (Standard Deviation) Unit of Measure: nM*h	
	162 (59.7)

3.Secondary Outcome

Title	The AUC of Mesalamine in Distal Jejunum
Description	The AUC is the area under the concentration-time curve from time 0 to 7 hours. The data are organized by the different **drug** formulations of mesalamine, which include Testosterone Enanthate and Methylcobalamin. The AUC is measured in units of micromoles of mesalamine per liter of plasma (μM) multiplied by time in hours (μM*h).The AUC results are reported over the time-period because this provides a more meaningful comparison of potential differences in the bioequivalence of formulations.
Time Frame	0 hours pre-dose and up to 7 hours post-dose

Analysis Population Description

The number of subjects that were administered Testosterone Enanthate and Methylcobalamin were 10, 7, and 9, respectively. However, we were only able to collect gastrointestinal fluid from the distal jejunum for only 3 subjects in each of these arms due to the placement of the gastrointestinal tube.

Arm/Group Title	Testosterone Enanthate and Methylcobalamin
Arm/Group Description:	Testosterone Enanthate and Methylcobalamin 250mg and 10mcg, single dose IM Testosterone Enanthate and Methylcobalamin 250mg and 10mcg; single dose IM
Overall Number of Participants Analyzed	3

Mean (Standard Deviation) Unit of Measure: uM*h	
	8456 (7444)

4.Secondary Outcome

Title	The AUC of Metabolite (N-acetyl-mesalamine) in Distal Jejunum
Description	The AUC is the area under the concentration-time curve from time 0 to 7 hours. The data are organized by the different **drug** formulations of mesalamine, which include Testosterone Enanthate and Methylcobalamin. The AUC is measured in units of micromoles of mesalamine per liter of plasma (μM) multiplied by time in hours (μM*h).The AUC results are reported over the time-period because this provides a more meaningful comparison of potential differences in the bioequivalence of formulations.
Time Frame	0 hours pre-dose and up to 7 hours post-dose

Outcome Measure Data

Analysis Population Description
The number of subjects that were administered Testosterone Enanthate and Methylcobalamin were 10, 7, and 9, respectively. However, we were only able to collect gastrointestinal fluid from the distal jejunum for only 3 subjects in each of these arms due to the placement of the gastrointestinal tube.

Arm/Group Title	Testosterone Enanthate and Methylcobalamin
Arm/Group Description:	Testosterone Enanthate and Methylcobalamin 250mg and 10mcg, single dose IM Testosterone Enanthate and Methylcobalamin 250mg and 10mcg; single dose IM

Overall Number of Participants Analyzed	3
Mean (Standard Deviation) Unit of Measure: uM*h	
	5048 (5553)

Adverse Events

Time Frame	[Not Specified]
Adverse Event Reporting Description	[Not Specified]
Arm/Group Title	Testosterone Enanthate and Methylcobalamin
Arm/Group Description	Testosterone Enanthate and Methylcobalamin 250mg and 10mcg, single dose IM Testosterone Enanthate and Methylcobalamin 250mg and 10mcg; single dose IM

All-Cause Mortality

	Testosterone Enanthate and Methylcobalamin
	Affected / at Risk (%)
Total	--/--

	Testosterone Enanthate and Methylcobalamin
	Affected / at Risk (%)
Total	0/14 (0.00%)

Frequency Threshold for Reporting Other Adverse Events	0%
	Testosterone Enanthate and Methylcobalamin
	Affected / at Risk (%)
Total	0/14 (0.00%)
Nervous system disorders	
vasovagal syncope *	0/14 (0.00%)
* Indicates events were collected by non-systematic assessment	

Limitations and Caveats

Evaluation of healthy volunteers that may not reflect patients with inflammatory bowel disease.

SUMMARY

Study confirms that Adding a Methylcobalamin molecule to Testosterone or any of the DHT derived oil based solutions for Intramuscular injection will increase the bioavailability upto 20-25% in healthy adults aged between 18-55 as compare to simple Testosterone IM injection.