Phase IIa, Double-Blind, Placebo-Controlled, Study of ESN364 Administered for 12 Weeks to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Women Presenting With Polycystic Ovarian Syndrome

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The primary objective of the study is:To evaluate efficacy of two doses of ESN364 versus placebo when administered for 12 weeks to decrease total testosterone (TT) levelsThe Secondary objectives are:To evaluate effect of two doses of ESN364 versus...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON43634

Source
ToetsingOnline

Brief title
ESN364-PCO-201

Condition

- Lipid metabolism disorders
- Gonadotrophin and sex hormone changes

Synonym

Stein–Leventhal syndrome; PCO

Research involving
Human

Sponsors and support

Primary sponsor: Ogeda S.A
Source(s) of monetary or material Support: Euroscreen SA

Intervention

Keyword: Double-Blind, ESN364, Phase IIa, Polycystic Ovarian Syndrome

Outcome measures

Primary outcome

Change in TT levels from baseline to end-of-treatment visit (Week 12).

Secondary outcome

Changes in menstrual cycle as measured by frequency menses, spotting,

inter-menstrual bleedings

Change in endometrium thickness, ovarian volume, number of follicles (cysts),

and dominant follicle development (Y/N) assessed by 2D transvaginal ultrasound

from baseline to Week 6 and Week 12 (end-of-treatment visit)

Change from baseline in the PCOS Q score (total and subcategories) at Week 6

and Week 12 (end-of-treatment visit)

Change in sex hormone levels (LH, free and TT levels) from baseline to Week 6,

Week 12 (end-of-treatment), and Week 18 (Follow-up)

Change in sex hormone levels (P4 and E2 levels) from baseline to Week 6, Week

12 (end-of-treatment), and Week 18 (Follow-up)

Change in sex hormone levels (FSH and LH/FSH ratio) from baseline to Week 6,

Week 12 (end-of-treatment), and Week 18 (Follow-up)

Change in total testosterone (TT) levels from baseline to Week 9 (at trough PK

levels).

Study description

Background summary

PCOS) is a condition that is characterized by overproduction of luteinizing hormone and the subsequent imbalance results often in an increased Testosterone production.

The excessive production of these two hormones is causing ovulatory dysfunction, irregular menstruations and very often infertility. The excess of testosterone often causes the development of male secondary sex characteristics such as acne, loss of cranial hair and/or excessive hair growth elsewhere on the body.

ESN364, is an experimental oral drug that works by influencing the regulation of sex hormones, like testosterone, in the body. The mechanism works via the regulation of the abnormal luteinising hormone production.
In theory, a decrease in circulating levels of luteinising hormone and testosterone can normalise ovarian function and restore fertility.

This is the first phase II study of ESN364 in patients presenting with PCOS to evaluate the preliminary efficacy, safety and tolerability, pharmacokinetics, and pharmacodynamics of two doses of ESN364 versus placebo administered for 12 weeks in women presenting with polycystic ovarian syndrome.

Study objective

The primary objective of the study is:

To evaluate efficacy of two doses of ESN364 versus placebo when administered for 12 weeks to decrease total testosterone (TT) levels

The Secondary objectives are:
To evaluate effect of two doses of ESN364 versus placebo to decrease luteinizing hormone (LH), free and total testosterone (TT) at Week 6, Week 12 (end-of-treatment), and Week 18

To evaluate effect of two doses of ESN364 versus placebo to change progesterone (P4) and estradiol levels (E2) at Week 6, Week 12 (end-of-treatment), and Week 18

To evaluate effect of two doses of ESN364 versus placebo to change follicle stimulating hormone (FSH) levels and LH/FSH ratio at Week 12 (end-of-treatment), and Week 18

To evaluate changes in menstrual cycle of two doses of ESN364 versus placebo when administered for 12 weeks

To evaluate efficacy of two doses of ESN364 versus placebo to improve quality of life (assessed by PCOS questionnaire [PCOSQ]) at Week 6 and Week 12 (end-of-treatment)

To evaluate efficacy of two doses of ESN364 versus placebo to change ovarian volume, endometrial thickness, number of follicles, and dominant follicle development (assessed by transvaginal ultrasound [TVU])

To evaluate efficacy of two doses of ESN364 versus placebo when administered for 9 weeks to decrease total testosterone (TT) levels at trough PK levels

To asses overall safety and tolerability of ESN364 after 12 weeks of treatment in subjects with polycystic ovarian syndrome (adverse events, physical exam, vital signs, ECG, clinical lab safety, and Columbia-Suicide Severity Rating Scale [C-SSRS])

To evaluate levels of the bone density markers, bone alkaline phosphatase (BALP) and beta carboxy-terminal peptide of type I collagen (CTX), after 12 weeks of treatment with ESN364 in subjects with PCOS

To evaluate pharmacodynamics of ESN364 in subjects with polycystic ovarian syndrome (PCOS) at Week 12 (end-of-treatment) and Week 18

Study design

This study is a phase II, randomized, double-blind, placebo-controlled, multicenter study to evaluate the preliminary efficacy, safety and tolerability, pharmacokinetics, and pharmacodynamics of two doses of ESN364

versus placebo administered for 12 weeks in women presenting with polycystic ovarian syndrome.

Intervention

Two doses of ESN364 (60mg and 180mg) and a placebo group will be studied. Each participant will receive one oral dose of ESN364 (60 mg/180 mg) or identical placebo during 12 weeks.

Subjects will be assigned to one of 3 treatments: 60 mg ESN364, 180 mg ESN364 or placebo

Study burden and risks

The study will last for 19 to 22 weeks and the patients will have to come for 7 visits to the hospital.
Each visit will take 1 to 4 hours depending on the procedures that have to be performed.

The following procedures will be performed:
5x Physical examination/ body weight and waist circumference
7x Blood pressure, heart rate and body temperature
7x ECG
4x Transvaginal ultrasound
7x Clinical laboratory tests
5x Urinalysis
3x Blood sample for BALP/CTX
1x Serology
2x Urine drug screen
7x Pregnancy test (1st time on serum afterwards on urine)
5x PK blood sample
7x Blood sample for sex hormones
4x Blood sample for exploratory hormones
6x PCOSQ questionnaire
6x menses diary
3x C-SSRS questionnaire

See protocol page 35 section 1.5 Risk Benefit Analysis:
Prolonged administration of ESN364 at the highest dose might induce anovulation in an important fraction of the participating subjects. This anovulation has shown to be reversible upon treatment discontinuation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Pre-menopausal woman between 18 and 45 years inclusive at screening;;2) Diagnosed with PCOS according to the Rotterdam criteria with the following modification: biochemical hyperandrogenism is mandatory (TT > 50 ng/dL [1.7 nmol/L] at screening and at least one of the following two other Rotterdam criteria are additionally required for diagnosis of PCOS:;* Oligomenorrhea (*6 menses per year) or oligo-ovulation and/or ;* Polycystic ovaries on ultrasound (*12 antral follicles in at least one ovary or ovarian volume *10 cm3);;3) Normal thyroid function (thyroid stimulating hormone [TSH] compatible with normal thyroid function); mild hypothyroidy treated with stable hormone replacement therapy is allowed if TSH is normal;;4) FSH and E2 within normal limits as judged by the investigator;5) Normal prolactin (PRL) levels as judged by the investigator;;6) 17-hydroxy-progesterone levels compatible with normal 21-hydroxylase activity (<200 ng/dL (<6.1 nmol/L),In case of a sample taken in luteal phase levels < 286 ng/dL [<8.7 nmol/L] are acceptable.) ;;7) In good physical and mental health as determined on the basis of medical history and general physical examination performed at screening; hematology and chemistry parameters, heart rate (HR) and/or blood pressure, and electrocardiogram (ECG) within the reference range for the population studies,

or showing no clinically relevant deviations, as judged by the investigator;;8) Has a negative (normal or atypical squamous cell of uncertain significance) cervical smear (Papanikolaou test [PAP], cytobrush or equivalent) within 36 months prior to screening or at screening and available before randomization;;9) Negative urine test for selected drugs (amphetamines benzodiazepines, cannabinoids, cocaine, tetrahydrocannabinol, barbiturates or opiates) of abuse at screening and before first administration of study drug;;10) Negative pregnancy test at screening and before randomization; not have been pregnant within 6 months prior to screening;;Note: pregnancy testing will consist of a serum pregnancy test at screening and urine pregnancy tests at other visits. ;11) Women of childbearing potential agrees not to get pregnant and willing to be abstinent or to use adequate highly effective contraception (failure rate less than 1% per year) during the trial and for at least 42 days after end of treatment;;The following non-hormonal contraceptive methods are defined as acceptable: ;* Partner with a vasectomy performed at least 3 months prior to the study and with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. (The vasectomized male partner should be the sole partner for that subject).;* True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptom-thermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception);* Hormone-free intrauterine device (copper intrauterine device) in combination with a condom;* The subject is homosexual/has no intercourse with the opposite sex;* Partner is using condoms in combination with spermicidal cream or gel;Women of childbearing potential are defined as any female who has experienced menarche and are not post-menopausal or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy);;12) Willing to adhere to the prohibitions and restrictions specified in the protocol;;13) Informed Consent Form (ICF) signed voluntarily before any study-related procedure is performed; indicating that the subject understands the purpose of and procedures required for the study and is willing to participate in the study.

Exclusion criteria

1) Evidence of diabetes diagnosed on any of the following World Health Organization (WHO) criteria:;- Fasting plasma glucose (FPG) *7.0 mmol/l (126 mg/dl) or,;- Glycated hemoglobin (HbA1c) *6.5% /48 mmol/mol or,;- Random plasma glucose *11.1 mmol/l (200 mg/dl) in the presence of classical diabetes symptoms;;2) Concomitant use of insulin sensitizers is not allowed, if taken, they should be stopped at screening;;3) Use of anti-androgens within 3 months prior to screening;;4) Have been treated within 3 months of screening with any of the following drugs: GnRH agonist/antagonist, selective estrogen receptor modulator (SERM), selective progesterone receptor modulator (SPRM), dienogest, danazol aromatase inhibitors, glucocorticoids, mineralocorticoids, androgens, and depot contraceptive preparations;;5) Treatment with hormonal contraceptives (oral, transdermal, coated intrauterine device) should be stopped 1 month prior to screening;;6) Has undergone bariatric surgery within 6 months prior to screening;;7) Has undergone ovarian surgery (drilling, wedge resection,*) within 6 months prior to screening;;8) Has undergone hysterectomy or bilateral oophorectomy or both;;9) Has Cushing*s syndrome;;10) Has a history of or currently ongoing pelvic inflammatory disease;;11) Has a known severe allergy, hypersensitivity, or intolerance to drugs in general, including the study drug and any of its excipients;;12) Has a history of or

a currently ongoing malignant tumor (except for basal cell carcinoma of the skin that has been treated with no evidence of recurrence);;13) Has active liver disease or jaundice, or values for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >1.3 times the upper limit of normal (ULN); or total bilirubin >1.3 times the ULN; or creatinine >1.25 times the ULN at screening;;14) Has any psychological disorder according to criteria indicated in the Diagnostics and Statistical Manual of Mental Disorders, 4th edition within one year before screening. Such disorders include, but are not limited to, alcohol (more than 3 glasses of wine, beer, or equivalent/day) and substance abuse/dependence within 2 years prior to the initial study medication administration;;15) Hemoglobin level <10 g/dL;;16) Has symptoms of clinically relevant acute or chronic illness in the 3 months before the initial study administration;;17) Judged by investigator to be inappropriate to participate in this study based on findings on the ECG regarding rhythm or conduction. A first degree AV block will not be considered as a significant abnormality;;18) Had a significant blood loss (including blood donation [>500 mL]) or had a transfusion of any blood product within 12 weeks prior to the initial study medication administration;;19) Has a medical condition or chronic disease (including neurological [including cognitive], hepatic, renal, cardiovascular, gastrointestinal, pulmonary, or endocrine disease), or malignancy that could confound interpretation of the study outcome as judged by the investigator (e.g., condition requiring chronic treatment with valproic acid);;20) Has a history of poor compliance in clinical research studies;;21) Concurrent participation or participation within 3 months prior to screening in a drug/device or biologic investigational research study;;22) Subject is the investigator oor any sub-investigator, research assistant, pharmacist, study coordinator, or other staff or relative thereof who is directly involved in the conduct of the study;;23) Has a positive hepatitis panel (including hepatitis B surface antigen [HBsAg] or anti-hepatitis C virus [HCV] antibodies) or positive human immunodeficiency virus (HIV) antibody at screening;;24) Presence or sequellae of gastrointestinal, liver, kidney or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs as judged by the investigator.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2015
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ESN-364
Generic name:	NAP

Ethics review

Approved WMO Date:	25-02-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-07-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-004409-34-NL
CCMO	NL51955.041.15