Final Study Report

Study Title: *Myo-inositol versus clomiphene citrate as first line treatment for ovulation induction in PCOS*

EU reference number: *2018-004604-20*

Clinical Investigation identification number (CIV ID): *N.A.*

Study protocol/CIP code: *AGO/2018/007*

Investigational device / medicinal product: *N.A.*

ClinicalTrials.gov identifier: *NCT04306692*

Sponsor: *Ghent University Hospital*

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National Coordinator/ Coordinating Investigator: *Prof. Dr. Dominic Stoop*

Funder: *Gedeon Richter*

Author: *Sara Somers*

Date of report: *22 December 2023*

By signing this final study report, I acknowledge that the information is accurate and complete.

Name and signature Coordinating Investigator: .....

Date signature Coordinating Investigator: 21/12/23

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1. Introduction

Ovulation induction is mostly required in patients with polycystic ovary syndrome [PCOS] with a wish for a child. The etiopathogenesis of PCOS is multifactorial. One of the factors is insulin resistance. For this reason, the use of metformin was occasionally included in the decision tree about the treatment of ovulation induction (Figure 1).

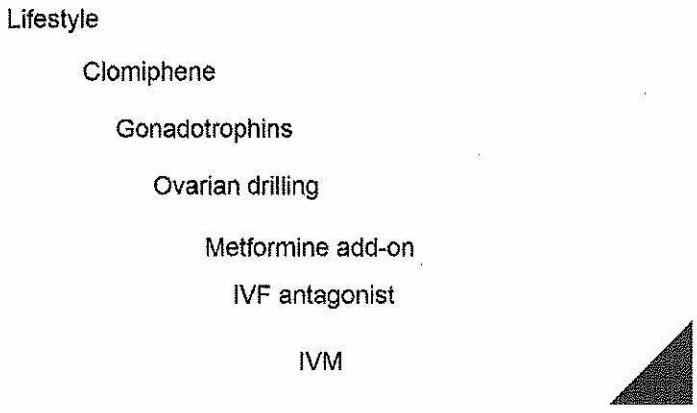

Figure 1 : Decision tree for ovulation induction in PCOS

In women with PCOS it is documented that a defect in the tissue availability of the changed metabolism of inositol and / or inositolphosphoglycan mediators (second messenger pathway in insulin signalling) contributes to insulin resistance.

Recently, a meta-analysis on the use of inositol in PCOS (1) was published. This study showed that inositol leads to a more regular menstrual cycle and recovery of ovarian function. Less data are present on pregnancy rates. No RCT was found on the comparison between inositol and the golden standard first line treatment of ovulation induction, namely clomiphene citrate. Another advantage of inositol is that it doesn't have side effects compared to metformin and that there is no elevated risk on multiple pregnancies, which is the case with clomiphene citrate.

2. Objectives of the study

2.1 Primary objective

We want to study if the pregnancy rates (COPR: cumulative ongoing pregnancy rate) after 3 treatment cycles with inositol are comparable to 3 cycles of ovulation induction with clomiphene citrate.

2.2 Secondary objective

To investigate whether the compliance for the patient is acceptable. Therefore, potential adverse events (e.g. ovarian hyperstimulation syndrome), the occurrence of ovulation, cancelling of treatment cycles, and multiple pregnancies are registered.

3. Investigational Medicinal Product

3.1 Food supplement (Gynositol)

The food supplement is taken at home.

Composition and dosing

- Myo-inositol 4000 mg
- Maltodextrin
- Anti-caking agent: silicon dioxide (E551)
- Folic acid 400 mcg

Dosing: 2 x 1 bag per day, per os (subjects can take Gynositol during the meal but it is not obliged).

Producer

Gynov SAS

5 Rue Salneuve

75017 Paris-France

Distributor

Gedeon Richter

Noordkustlaan 16A bus 5

1702 Groot-Bijgaarden

Packaging

Bags.

Administration way

Oral.

Labelling

VOEDINGSSUPPLEMENT – Food Supplement - Nahrungsergänzungsmitte

EudraCT N° 2018-004604-20 - TRIAL subject ID nr: _____ Initialen: _____ Datum/ Date visite: _____

ENKEL VOOR STUDIEGEBRUIK

Gebruiksaanwijzing: 2 x 1 zakje per dag, oplossen in water – 60 zakjes – Elk zakje bevat 2000 mg myo-inositol en 0.2 mg foliumzuur - Voor oraal gebruik - Buiten het zicht en bereik van kinderen houden – Koel en droog bewaren, vermijd directe warmte en licht.

UNIQUEMENT POUR UTILISATION DE L'ESSAI CLINIQUE

Mode d'emploi: 2 x 1 sachet par jour, dissoudre dans l'eau – 60 sachets - Chaque sachet contient 2000 mg myo-inositol et 0.2 mg acide folique - Voie orale - Tenir hors de la vue et de la portée des enfants - A conserver dans un endroit frais et sec à l'arbri de la lumière et de la chaleur.

NUR STUDIENGEBRAUCH KLINISCHER

Gebrauchsanweizung: 2 x 1 Beutel pro tag, in Wasser auflösen – 60 Beutel – Jede Tasche enthält 2000 mg myo-inositol und 0.2 mg Folsäure – Orale anwendung – Artznemittel für Kinder unzugänglich aufbewahren – An einem kühlen, trockenen Ort lagern, vor direkter Hitze und Licht schützen.

Exp: XX/XXXX

Prof. Dr. Stoop Tel: 09 332 49 03

SPONSOR: UZ Gent, C. Heymanslaan 10, 9000 GENT

Storage conditions

Store in a cool, dry place, away from direct heat and light.

3.2 Medication (Clomiphene citrate, Clomid®)

The medication is taken at home.

Composition and dosing

Each tablet contains 50 mg of clomiphene citrate which means 33,9 mg of clomiphene. Other constituents are sucrose, lactose monohydrate, corn starch, pregelatinized starch, yellow iron oxide (E172) and magnesium stearate (E470b).

Dosing: 1 tablet per day from cycle day 3 until 7 (extremes included), stepping up until a maximum dose of 3 tablets per day for 5 consecutive days.

Producer

Sanofi Belgium

Leonardo Da Vincilaan 19

1831 Diegem

Treatment regimens allow different combinations of marketed products used according to local clinical practice.

Distributor

Sanofi Belgium

Leonardo Da Vincilaan 19

1831 Diegem

Packaging
Tablets.

Administration way
Oral.

Labelling

Clomid 50mg tablet/comprimé/Tablette
EudraCT N°: 2018-004604-20
TRIAL subject ID nr: _____ Initialen: _____ Datum/ Date visite: _____
ENKEL VOOR STUDIEGEBRUIK
Gebruiksaanwijzing: 1 tablet per dag gedurende 5 dagen – 10 tabletten - Elke tablet bevat 50 mg clomifeencitraat - Voor oraal gebruik - Buiten het zicht en bereik van kinderen houden - Bewaren beneden 25°C in de oorspronkelijke verpakking.
UNIQUEMENT POUR UTILISATION DE L'ESSAI CLINIQUE
Mode d'emploi: 1 comprimé par jour pendant 5 jours – 10 comprimés - Chaque comprimé contient 50 mg de citrate de clomifène - Voie orale - Tenir hors de la vue et de la portée des enfants - A conserver dans l'emballage extérieur d'origine à moins de 25°C.
NUR STUDIENGEBRAUCH KLINISCHER
Gebrauchsanweizung: 1 Tablette pro tag während 5 Tage – 10 Tabletten - Jede Tablette enthält 50 mg clomifencitrat – Orale anwendung – Artznemittel für Kinder unzugänglich aufbewahren - In der Originalverpackung aufbewahren, unter 25°C.
Exp: XX/XXXX
Prof. Dr. Stoop Tel: 09 332 49 03
SPONSOR: UZ GENT C. Heymanslaan 10 9000 GENT

Storage conditions
Below 25°C.

4. Investigational Medical Device

N.A.

5. Study Protocol Summary

5.1 Study design

This study is a multicenter, non-inferiority, randomized clinical trial. Ghent University Hospital is the primary center.

Only subjects with PCOS according to the Rotterdam criteria (2) are eligible for the trial.

In case of a wish for a child, they can be included once.

The primary outcome variable is COPR after 3 treatment cycles of inositol (study group) or 3 ovulation induction cycles with clomiphene citrate (starting dose of 50 mg during 5 days with

a maximum of 150 mg during 5 days), the control group. In case no ovulation occurs after treatment with clomiphene citrate, a higher dose can be prescribed after provoking a withdrawal bleeding (see infra).

Secondary outcome variables are live birth rate, the number of gestational sacs at the time of the first ultrasound (around 7 weeks), the number of cancelled treatment cycles and persistent anovulation during the study.

Both study groups will be compared demographically (female age, duration of the wish for a child, ethnicity, cycle regularity, PCO morphology, AFC, AMH, hyperandrogenism, phenotype, endometriosis, male factor infertility, type of subfertility, BMI, smoking status, alcohol).

5.2 Inclusion criteria

Subject eligibility is determined according to the following criteria at enrolment:

Rotterdam criteria for PCOS: at least 2 out of 3 criteria should be fulfilled:

- irregular cycle (shorter than 21 days or longer than 35 days);
- clinical (modified Ferriman-Gallwey score ≥ 6) or biochemical signs (elevated free testosterone) of hyperandrogenism (www.eshre.eu/Guidelines-and-Legal/Guidelines/Polycystic-Ovary-Syndrome.aspx);
- PCO ovaries on ultrasound (www.eshre.eu/Guidelines-and-Legal/Guidelines/Polycystic-Ovary-Syndrome.aspx): multiple small cysts (≥ 20 per ovary) and/or an ovarian volume ≥ 10 ml, measured with a probe >8 MHz in both ovaries.

Age: 18 until 40 years old (extremes included).

A treatment cycle, possibly combined with intra uterine insemination (IUI) and this for (one of) the following reasons:

- mild male factor (as defined by each local center)
- endometriosis AFS score 1 or 2

Use of own or donor sperm.

5.3 Exclusion criteria

- Tubal factors
- Uterine factors
- Endometriosis AFS score 3 or 4
- Moderate to severe male factor (as defined by each local center)
- BMI > 35

5.4 Primary endpoint

Pregnancy rates (COPR) after 3 treatment cycles of inositol (study group) or 3 ovulation induction cycles with clomiphene citrate (starting dose of 50 mg during 5 days with a maximum of 150 mg during 5 days) in the control group.

5.5 Secondary endpoints

Live birth rate (32-42 weeks after conception), the number of gestational sacs at the time of the first ultrasound (around 7 weeks), the number of cancelled treatment cycles (3 cycles) and persistent anovulation during the study (3 cycles).

5.6 Procedures

Procedures before entering the study (standard of care)

- Blood test to diagnose PCOS
- AMH, TSH and TPO antibodies
- HSG, HyFoSy or laparoscopy to exclude tubal factors. This is not necessary in lesbian couples without a specific indication.
- Sperm analysis according to WHO criteria (3), MAR included (= a test to investigate the sperm on the presence of antibodies against sperm cells).

Procedures

Start

A first treatment cycle starts at the time of the spontaneous menstruation or at the time of a withdrawal bleeding, evoked by taking a progestativum during 5 days:

- Inositol group: inositol 2 x 1 bag daily p.o.
- Clomiphene citrate 50 mg daily p.o. from cycle day 3 until 7 (extremes included).

Monitoring

Monitoring of ovulation induction with clomiphene citrate is done according to the standard of care (follicle measurement via ultrasound and hormonal follow-up as from day 10 of the cycle). In case there is no dominant follicle visible via ultrasound or oestradiol is lower than 50 ng/l on day 10 (+/- 2 days) of the cycle a new appointment for ultrasound and hormonal follow-up must be made after 7 days (+/- 2 days). In case the oestradiol is lower than 50 ng/l and there is no dominant follicle on day 17 (+/- 2 days) of the cycle Clomid should be restarted during 5 days. The dose of Clomid should then be elevated with 50 mg/day. In case the oestradiol is higher than 50 ng/l and there is no dominant follicle a progestativum should be taken to evoke menstruation. hCG 5000 will be administered as ovulation trigger or a spontaneous LH surge can occur. The cycle needs to be cancelled in case there are more than two mature follicles on the day of ovulation trigger or spontaneous LH surge. Another reason for cycle cancellation is an endometrium thickness of less than 6 mm on the day of the ovulation trigger or spontaneous LH surge.

In the inositol study group, the cycle monitoring can be done via LH tests or via the classical monitoring as explained above for the clomiphene citrate group. This monitoring starts on day

10 of the spontaneous cycle or on day 10 after the start of a menstruation that was evoked with a progestativum.

Intra uterine insemination

The intra uterine insemination will be performed on the day of ovulation when indicated. The day of ovulation will be determined by LH tests or after monitoring and admission of hCG 5000.

Diagnosis of pregnancy

hCG in serum to diagnose a pregnancy (guideline, timing can differ per center): from day 16 after ovulation (if day 16 is a Saturday, the blood test can be performed on day 15.)

hCG in urine to diagnose a pregnancy: day 18 after ovulation (at the earliest)

The 1st pregnancy ultrasound will be performed between week 6+3 and week 8 of pregnancy or sooner when clinically necessary (blood loss, abdominal pain, slowly ascending hCG in serum). The follow-up of the live birth rate will occur 4-5 weeks after delivery (+ 1 week).

Absent menstruation (not pregnant)

When no menstruation has occurred on day 21 after the LH surge/hCG 5000, a withdrawal bleeding will be evoked with a progestativum.

Flow chart

Intake: Discussion of the results of previous fertility tests:

Blood test to diagnose PCOS

AMH, TSH and TPO antibodies

Exclusion of a tubal factor by HSG, HyFoSy or laparoscopy. This is not necessary in lesbian couples without a specific indication

Sperm analysis according to WHO criteria, MAR included (= a test to investigate the sperm on the presence of antibodies against sperm cells).

An explanation about the starting procedure of a first treatment cycle:

Spontaneous menstruation or evocation of a withdrawal bleeding

Cycle 1 Day 10:

Clomiphene citrate group:

Cycle monitoring via ultrasound and biochemical (estradiol, LH and progesterone)

Inositol group:

LH monitoring (urine test)

or

Cycle monitoring via ultrasound and biochemical (estradiol, LH and progesterone)

Day 15 or 16 after ovulation (at the earliest):

Pregnancy test (serum hCG)

OR from day 18 after ovulation:

Pregnancy test (urine)

When pregnant:

Ultrasound between week 6+3 and week 8

Follow-up live birth rate 4 - 5 weeks after delivery (+ 1 week)

When not pregnant:

Restart the next cycle with the first day of the menses as day 1. An ultrasound on

day 1, 2 or 3 can be performed according to the standard of care of the site (not required and only applicable to the clomiphene citrate group).

When no menstruation occurs: consultation with monitoring via ultrasound and biochemical

and evocation of withdrawal bleeding.

cycle 2	Idem to cycle 1
cycle 3	Idem to cycle 1

5.7 Randomisation and blinding

Randomisation via envelopes. The randomisation list is made by the principal investigator of the study, through an online randomisation system (www.sealednevelope.com). The sealed envelopes will be prepared by a fellow worker of the Women's Clinic who is not involved in the study. The envelopes will be kept in the office of the study team. Randomisation will be done by someone of the study team.
The study is not blinded.

5.8 Monitoring and quality measures

The study will be conducted according to the quality norms of each fertility center involved.
The data that will be analyzed for this study will be taken out of the electronic patient files.
Monitoring of this study will be organized by HIRUZ CTU from Ghent University Hospital.
The nature and extent of the monitoring will be discussed in the monitoring plan.

6. Study analysis

The study was ended prematurely. The collected data will not be analyzed because clomiphene citrate is no longer the standard treatment for PCOS.

7. Independent Ethics Committee and Competent Authority

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - *Protocol version 1, dd. 28AUG19* - *Protocol summary version 1, dd. 28AUG19* - *ICF version 2, dd. 25NOV19* - *Leaflet Gynositol* - *SmPC Clomid*	***Approval date Central EC:*** *3DEC19*	***Approval date FAMPH:*** *3DEC19*
Amendment 1: - *Protocol version 2, dd. 11FEB20* - *Protocol summary version 2, dd. 11FEB20* - *ICF version 3, dd. 11FEB20* - *Recruitment text version 1, 2JUN20* - *Patient card version 1, 11FEB20* - *AE log and concomitant medication log, version 1, 11FEB20*	***Approval date Central EC:*** *4MAY20*	***Approval date FAMPH:*** *17MAR20*
Amendment 2: - *Protocol version 3, dd. 7SEP20* - *Protocol summary version 3, dd. 7SEP20*	***Approval date Central EC:*** *27OCT20*	***Approval date FAMPH:*** *12NOV20*
Amendment 3: - *Protocol version 4, dd. 28JUL21* - *Protocol summary version 4, dd. 28JUL21* - *ICF version 4, dd. 28JUL21*	***Approval date Central EC:*** *17NOV21*	***Approval date FAMPH:*** *N.A.*

8. Results

8.1 Subject enrollment and demographics

Site	Number of Subjects included ?	TIV	Date of first inclusion ?	Number of Subjects randomized ?	Number of Subjects completed ?	Number of subjects prematurely discontinued	date of site closure (LPLV)
UZ Gent	4	3 MAR 20	2 JUL 20	4	1	3	20 APR 21
UZA	4	22 OCT 20	5 JAN 21	4	2	2	18 SEP 21
AZ Jan Palfijn	0*	24 JUL 20	NA	NA	NA	NA	NA
OLV Waregem	4	15 SEP 20	22 SEP 20	4	2	2	4 JAN 21

* Low study staff due to COVID-19.

The number of subjects exposed are as follows:

Treatment	Number of subjects
Investigational product: Myo-inositol	3
Active Comparator: Clomiphene citrate	9

The available demographic data are shown below:

Age range	No of female subjects	No of male subjects	Total No of subjects
21 – 31 y.o.	12	N.A.	12

The study was ended prematurely. The collected data will not be analyzed because clomiphene citrate is no longer the standard treatment for PCOS.

8.2 Study specific results

The study was ended prematurely. The collected data will not be analyzed because clomiphene citrate is no longer the standard treatment for PCOS.

9. Safety

There have been no Serious Adverse Events.

10. Device deficiencies

N.A.

11. Protocol deviations

- UZ Gent: No protocol deviations were detected by the monitor or reported by the site.
- UZA: No protocol deviations were detected by the monitor or reported by the site except for the early termination of subject 02-002.
- AZ Jan Palfijn: Since no subjects were enrolled at this site, no protocol deviations occurred.
- OLV Waregem:
    - Deviation storage temperature
    - Drop-out of subjects 04-003 and 04-004 + reason

12. Discussion and overall conclusions

The study was ended prematurely. The collected data will not be analyzed because clomiphene citrate is no longer the standard treatment for PCOS.

13. References

1. Pundir J, Psaroudakis D, Savnur P, Bhide P, Sabatini L, Teede H, et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG : an international journal of obstetrics and gynaecology. 2017.
2. Rotterdam EA-SPcwg. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human reproduction (Oxford, England). 2004;19(1):41-7.
3. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231-45.