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SPIOMET4HEALTH: a 4-Arm Trial to Test the Effects of Lifestyle Intervention plus either Placebo, or Pioglitazone (PIO), or Spironolactone-Pioglitazone (SPIO), or Spironolactone-Pioglitazone-Metformin (SPIOMET) in Adolescent Girls and Young Women with PCOS

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Introduction: PCOS in adolescent girls and young women is nowadays thought to be, in essence, an epiphenomenon of ectopic fat accumulation. By definition, "adolescent PCOS" is characterized by androgen excess (as well clinical as biochemical) and oligo-anovulation (often judged by oligo-amenorrhea) (1) presenting between 2 and 8 years after menarche. There is no FDA-approved treatment for "adolescent PCOS". In SPIOMET4HEALTH (a project funded by the European Commission under Grant Agreement 899671), we aim at reducing ectopic fat in an early phase of PCOS, with a standardized lifestyle intervention plus a pharmacological addendum consisting of either placebo, or PIO, or SPIO, or SPIOMET. In "adolescent PCOS", low-dose pioglitazone (7.5 mg/d) may exert insulin-sensitizing and gonadotropin-normalizing effects, in part by raising the circulating concentrations of high-molecular-weight adiponectin; low-dose spironolactone (50 mg/d) may not only act as an anti-androgen but also exert anti-mineralocorticoid effects that raise energy expenditure by activating brown adipose tissue; low-dose metformin (850 mg/d) is known to act through multiple mechanisms and was recently shown to be capable of changing the relative deficit of GDF15 into an abundance that is thought to contribute to reduce liver fat.

Subjects & Methods: In the SPIOMET4HEALTH trial, patients with "adolescent PCOS" (age range 12.0–23.9 years; BMI <35 kg/m 2) will be recruited in seven centers across Europe. A total of 364 patients are expected to engage into a lifestyle intervention, and to receive either placebo, or PIO, or SPIO, or SPIOMET once daily (1: 1: 1: 1 randomization; single tablets; double blinding) for 12 months. Post-treatment follow-up will span 6 months. The primary endpoint is ovulation rate, as judged by a combination of menstrual data and progesterone concentrations in saliva; the analysis will start by testing for superiority between placebo and SPIOMET. Secondary endpoints include pre-treatment, on-treatment and post-treatment measures of androgen excess, body composition and insulin sensitivity, as well as measures of quality of life, and of adherence to treatment. The design of this trial has been endorsed by the European Medicines Agency, as part of a "Paediatric Investigation Plan". Expected Results/Discussion: The SPIOMET4HEALTH project is expected to deliver the first results of an international, randomized, double-blind, active-controlled/placebo-controlled trial evaluating the safety, efficacy, and tolerability of the fixed dose combination SPIOMET in adolescent girls and young women with PCOS. Favorable results of this Phase 2 trial may advance SPIOMET into Phase 3. Reference: Ibáñez L, et al. An International Consortium Update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. Horm Res Paediatr 2017;88: 371-395.

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