PROFILE

Sant Joan de Déu Hospital is one of the main references within and outside of Catalonia in pediatrics, obstetrics, gynecology and highly specialized areas. The Institut de Recerca Sant Joan de Déu (IRSJD) is a research and innovation center in biomedicine. The IRSJD was created in 2015 through a collaboration agreement between the SJD Barcelona Children's Hospital, the Universitat de Barcelona, the Universitat Politècnica de Catalunya, the Parc Sanitari Sant Joan de Déu and the Fundació de Recerca Sant Joan de Déu.

SPEAKER

Professor Lourdes Ibáñez, Chair of Pediatrics, University of Barcelona; Director of the Endocrinology Research Program, Hospital Sant Joan de Déu; Group leader, CIBERDEM, ISCIII, Madrid (will present scientific rationale & proof of concept).

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PRODUCT

SPIOMET: low-dose combination of 3 compounds in a single pill, for treating PCOS

MECHANISM OF ACTION

The 3 low-dose components of SPIOMET act through different pathways. Spironolactone (50 mg/d) is a mixed anti-androgen and anti-mineralocorticoid that was recently found to activate brown adipose tissue (BAT) thereby raising the energy expenditure of PCOS patients toward normal. No safety concerns have been raised, when spironolactone is given in low dose.

Pioglitazone (7.5 mg/d) has the capacity to drive adipogenesis in white adipose tissue (via PPAR-gamma agonism) and to raise high-molecular-weight (HMW) adiponectinemia (via cdk5 antagonism) without causing weight gain. HMW adiponectin is a key adipokine that can reverse liver & muscle insulin resistance by reducing ectopic lipid storage in these organs. No safety concerns have been raised, when pioglitazone is given in low dose.

Metformin (850 mg/d) improves insulin sensitivity via complex mechanisms, and may decrease appetite via growth-and-differentiation factor 15 (GDF15) which is a peptide hormone that acts via a specific receptor in the brainstem, and that may also reduce liver fat in the absence of weight loss. No safety concerns have been raised, when metformin is given in low dose.

SPIOMET appears to be more effective than each of the components in monotherapy, and to be devoid of side effects at the proposed doses. At present, the 3 medications have to be administered separately, and the commercially available preparations have different dosages and contain also different numbers of pills.

TARGET INDICATIONS

PCOS (Polycystic ovary syndrome) in adolescent girls & young women.

Potentially additional indication: hepatic and/or visceral fat excess.

CURRENT STATUS

- The effects of SPIOMET versus those of an OC were assessed in two consecutive, open-label, single-centre studies. Adolescents with PCOS (n=62) were randomized to receive an OC or SPIOMET for 1 year and were followed for another year without intervention.

- The primary endpoint was post-treatment ovulation rate. Key secondary endpoints were androgens, insulin, lipids, C-reactive protein, HMW-adiponectin, body composition (DXA), and abdominal fat partitioning (MRI).
- SPIOMET had more broadly normalizing effects than the OC, as well on treatment as thereafter. SPIOMET – but not OC – reduced hepatic fat toward normal, and this effect extended beyond active treatment, without changing body weight. Post-treatment ovulation rate was nearly 3-fold higher after SPIOMET than after OC; more loss of liver fat was followed by more ovulations.

INNOVATIVE ASPECTS

SPIOMET is an apparently simple combination of 3 generics, namely spironolactone, pioglitazone and metformin. However, behind this apparent simplicity, there are several layers of complex novelty:

- The basis for SPIOMET treatment of PCOS is the novel concept that PCOS may not be a disorder of the gonadotropic axis (or the ovaries) but rather an endocrine mode ensuing from ectopic adiposity, notably from liver steatosis; accordingly, SPIOMET aims at reducing PCOS features by reducing ectopic fat, in particular, liver fat.
- Neither of the 3 compounds has been licensed to treat PCOS. Neither of the 3 compounds has been licensed to reduce liver steatosis. Neither of the 3 compounds is commonly used by young women in doses as low as those inside SPIOMET; there are no safety concerns in such low dose ranges.
- When the 3 compounds are given together in low doses, then at least 3 newly discovered mechanisms of action have been shown to be operational: Activation of brown adipose tissue (with a key role for spironolactone); Doubling of HMW adiponectinemia (with a key role for pioglitazone); Tripling of circulating GDF15 (with a key role for metformin).
- Traditional off-label treatment consists of an oral estro-progestagen contraceptive (OC) which reduces the androgen excess and generates a pseudo-normalization of menstrual cyclicity but does not reduce the ectopic adiposity, and is thus typically followed by an alarming rebound of androgen excess and oligo-anovulatory subfertility. Costly and cumbersome techniques of reproductive assistance may then be needed to induce a pregnancy which, in turn, is at double or triple risk of major complications, potentially with lifelong sequelae in the offspring.
- The future of PCOS therapy is to target the root cause (= ectopic fat) at an early stage, thereby not only preventing reproductive and obstetric complications, but also avoiding their psychological and financial burdens at the individual and societal levels.

IPR

In 2021, patents for SPIOMET treatment of PCOS have so far been granted in regions as diverse as EU, Russia, Australia, Mexico, UK. The patent owners are the Universities of Leuven and Barcelona. Patent applications are active worldwide.

PARTNERING OPPORTUNITIES

Looking for a pharma partner who is keen to develop SPIOMET beyond Phase 2b..