**27.An irreversible inhibitor of 17β-hydroxysteroid dehydrogenase type 1 inhibits estradiol synthesis in human endometriosis lesions and induces regression of the non-human primate endometriosis**

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**Abstract**

Endometriosis is a gynecological disorder affecting about 10% of women and can lead to invalidating painful symptoms and infertility. Since there is no current definitive cure for this disease, new therapeutic options are necessary. 17β-Hydroxysteroid dehydrogenase type 1 (17β-HSD1) is involved in the production of estradiol (E2), the most potent estrogen in women, and of 5-androstene-3β,17β-diol (5-diol), a weaker estrogen than E2, but whose importance increases after menopause. 17β-HSD1 is therefore a pharmacological target of choice for the treatment of estrogen-dependent diseases such as endometriosis. We developed a targeted-covalent (irreversible) and non-estrogenic inhibitor of 17β-HSD1, a molecule named PBRM, and herein evaluated its efficiency for the treatment of endometriosis. In a cell-free assay containing estrone (E1), the natural substrate of 17β-HSD1, PBRM was able to block the formation of E2 in a collection of 50 human endometriosis lesions

from a different clinical feature type, location, and phase. When given orally by gavage at 15 mg/kg to baboons, the resulting plasmatic concentration of PBRM was found to be sufficiently high (up to 125 ng/mL) for an efficacy study in a non-human primate (baboon) endometriosis model. After 2 months of treatment, the number of lesions/adhesions decreased in 60% of animals (3/5) in the PBRM-treated group, compared to the placebo group which showed an increase in the number of lesion/adhesions in 60% (3/5) of animals. Indeed, the total number of lesions/adhesions decreased in treated group (-6.5 or -19% when excluding one animal) while it increased in the control group receiving a placebo (+11%). Analysis of specific endometriotic lesions revealed that PBRM decreased the number of red lesions (-67%; 8/12) and white lesions (-35%; 11/31), but not of blue-black lesions. Similarly, PBRM decreased the surface area of dense adhesions and filmy adhesions, as compared to placebo. Also, PBRM treatment did not significantly affect the number of menstrual days. Finally, this targeted covalent inhibitor showed no adverse effects and no apparent toxicity for the duration of the treatment. These data indicate that 17β-HSD1 inhibitor PBRM is a promising candidate for therapy targeting endometriosis and supports the need of additional efforts toward clinical trials.

**Keywords:** 17β-HSD1 inhibitor; Endometriosis; Estrogen; Hormone; Steroid; Treatment.