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P279. EC313-a tissue selective SPRM reduces the growth and proliferation of uterine fibroids in a human fibroid tissue xenograft model

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Background: Human uterine fibroids (UF) or uterine leiomyoma are benign tumors of the myometrial layers of the uterus that represent a major underestimated health burden for women worldwide. Uterine fibroids are often associated with irregular or excessive uterine bleeding, pelvic pain or pressure, or infertility. Uterine fibroids require endocrine support from the ovarian steroid hormones. The standard of care include GnRH agonists that block estrogen production, starving uterine fibroids of estrogen and causing them to shrink. More recently ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM) has been approved to treat UFs. However, recent liver toxicity concerns over UPA, diminished the enthusiasm and reinstate the critical need for a safer yet efficacious SPRM to treat uterine fibroids. In the current study, we have tested the efficacy of new SPRM, EC313 as a novel agent for the treatment for uterine fibroids.

Methods: We have rationally designed and synthesized a library of SPRMs and selected EC313 based on the prudential properties including progesterone receptor-agonist /antagonist binding. PR agonist/ antagonist binding was confirmed by transactivation assays, guinea pig model to assess PR agonist/antagonist screening. The efficacy of EC313 was tested in the fibroid xenograft NOD-SCID mouse model and the markers were analyzed by immunohistochemistry (IHC).

Results: EC313 treatment reduced the fibroid xenograft weight dose dependently ($p>0.01$). When compared to the control animals, E2 induced proliferation was blocked significantly in EC313 treated xenograft fibroids ($p>0.0001$). The uterine weight was reduced by EC313 treatment when compared to UPA. The fibroid PDX preserved the histology of human uterine fibroids on collected samples. Levels of ER and PR was reduced in IHC on EC313 treated groups versus control ($p>0.001$) and with UPA ($p>0.01$). The uterine fibroid markers such as desmin and collagen were markedly reduced in IHC upon treatment with EC313- 0.1 and 1mg/kg doses. UF consist of interwoven bundles of smooth muscle cells and areas of hyalinized stroma marked by desmin and collagen in IHC.

Conclusion: EC313 is a novel SPRM with tissue selectivity. EC313 has distinct pharmacologic advantageous of oral bioavailability and invivo stability. EC313 showed superior efficacy when compared to ulipristal acetate in the fibroid model. EC313 is a potential candidate for the long-term treatment for UF and endometriosis.

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