GnRH Receptor Antagonist KLH-2109 dose-dependent E2 suppression in Japanese and Caucasian women

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Introduction:
KLH-2109 (a.k.a. OBE2109) is a novel, potent, oral GnRH receptor antagonist being developed for the treatment of sex-hormone-dependent diseases in women by lowering estradiol levels. Our objectives were to evaluate the safety, pharmacokinetics, and inhibitory effects on gonadotropins and estradiol of single-dose and 7-day KLH-2109 administration to healthy Caucasian and Japanese women.

Methods:
This was a first-in-human, double-blind, placebo-controlled, single- and multiple-dose study with sequential dose escalation in healthy women. In part 1, participants received a single oral dose between 12.5 and 400mg or placebo. In part 2, participants received placebo or 100, 200, or 400mg/d under fed and fasted conditions. We evaluated safety, tolerability, pharmacokinetics, and serum LH, FSH, and estradiol concentrations.

Results:
KLH-2109 was well tolerated and presented favorable pharmacokinetic properties with high bioavailability, low variability, suitable for daily dosing (t1/2 = Approx.15.5h) with or without food. LH was reduced by >50% within 8h in subjects receiving at least 50mg. In part 2, estradiol was dose-dependently suppressed within 12h at all doses and daily mean trough levels after repeated dosing remained below 35pg/mL at 100mg/d and below 25pg/mL at 200 and 400mg/d during the late follicular phase. Pharmacokinetics and pharmacodynamics were similar in Caucasian and Japanese women.

Conclusions:
KLH-2109 at doses up to 400mg is safe, has favorable pharmacokinetic characteristics and provides controlled suppression of LH and estradiol. Our results suggest that KLH-2109 may reduce estradiol in a way that efficacy and hypoestrogenic side effects may be balanced thus being suitable for long-term treatment of sex-hormone-dependent diseases.

Keywords :
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