

Novel recombinant gonadotropin molecules in human reproductive dysfunction

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Org 36286 is a sustained follicular stimulant (SFS) inducing multiple follicular development in patients undergoing controlled ovarian stimulation. Due to its long half-life a single dose of Org 36286 may replace the first 7 injections of daily recFSH and after this one week interval, stimulation may be continued with daily recFSH up to the day of triggering ovulation (Org 36286 regimen). Ideally, recFSH should be started as soon as Org 36286 levels become too low to support multiple follicular growth. Observations in the clinical trials with Org 36286 suggested that follicular growth itself is not a good, immediate, marker for lack of follicular stimulation, as follicles (visualized by ultrasound) may still continue to grow when FSH-dependent hormones rapidly decline. Both inhibin-B and E2 are FSH-induced hormones and sensitive markers of follicular development and their premature decline indicates insufficient stimulation. To predict the pharmacodynamic effects of Org 36286, models have been developed including inhibin-B levels during stimulation. For this model inhibin-B was preferred over E2 as it is an LH-independent marker and it shows less variability than E2. The clinical importance of a decrease in inhibin-B levels was revealed in a subset analysis of subjects who were treated with a too low dose of Org 36286. The analysis revealed that when the time between a decrease in inhibin-B and the continuation of treatment with recFSH exceeded 1.5 days, the cancellation rate increased and the number of oocytes and number of good quality embryos decreased. The extent of this effect of a decrease of inhibin-B on clinical outcome parameters was further quantified in subsequent modeling. With this set of models, simulations of the outcome have been performed for a range of Org 36286 dose regimens. Taking into account the relevant variables, the simulation results could establish the lowest Org 36286 dose to obtain an optimal outcome in the desired one-week regimen.
