Reviewer’s report

Title: Return to Fertility after Extended Chemical Castration with a GnRH Antagonist

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Reviewer: Cyril Bowers

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Accept without revision

1-The data support the conclusion.
2-The manuscript provides sufficient details for the data to be reproduced.
3-The data is analyzed well
4-The manuscript is well written.

The following is the basis for the answers to the above questions.

Evidence has been obtained which clearly demonstrates that the prolonged inhibitory action on the pituitary-gonadal axis is reversible. The potent decapeptide, orntide, was effectively incorporated into the 120 day depot microsphere formulation at a polymer load of 16% and 8.8 mg/kg of orntide. When this formulation was administered to normal adult male rats(n=6) basal serum testosterone levels were completely inhibited for 109 days and chemical castration persisted for 145 days(n=4) with testosterone levels of acute sc LHRH(10ug/kg) were completely inhibited and by day 173 they returned to normal.

On day 269 after the single injection of orntide these male and untreated female rats were bred. The reversibility of the orntide inhibition of the pituitary-gonadal axis and lack of adverse effects further support that the orntide treated male rats can sire normal litter size and offspring with normal morphology and behavior.

The pharmacokinetics of the serum orntide in these studies reveal that the RIA orntide levels had a Cmax of 52 ng/ml at +6h and a subsequent peak level of 20 ng/ml on day 8 which decreased to about 3 ng/ml by day 28 and
remained at this level until day 60. Between days 60 and 109, the level gradually decreased to These studies support the effectiveness of the long acting depot microsponge 120 day formulation of the LH antagonist, orntide, in inhibiting the pituitary-gonadal axis as well as the reversibility of this inhibition and the return of fertility.

Quality of written English: acceptable with correction of typographical/grammatical errors on page 7

**Competing interests:**

None declared.