In the preclinical study, the stability of teriparatide was optimal with the addition of 5% w/v mannitol and 3% w/v of methionine at 37ºC. The stability of teriparatide in this solution has remained stable at 12 weeks and long-term testing is currently underway.

The anticipated Phase 1 trial will have a 5-way crossover design to evaluate the safety of the teriparatide/CriticalSorb lead formulation compared with subcutaneous injection of teriparatide in postmenopausal healthy women. The primary endpoint of the Phase 1 trial will be to establish the pharmacokinetics of teriparatide following intranasal delivery. Currently, three doses of the teriparatide/CriticalSorb formulation are planned.

Dr. Jordan stated that the data from the preclinical study suggest that the intranasal delivery of teriparatide is absorbed across the nasal mucosa in two animal models. The Phase 1 trial is expected to begin at the end of 2013, with results expected in early 2014.

Kisspeptin/GPR54 Agonist Peptide Analog Shows Promise as a Medical Castration Compound

Written by **Brian Hoyle**

TAK-488 is an oligopeptide analog of kisspeptin, which is a hypothalmic protein that activates the G-protein-coupled receptor GPR54 [Navarro VM, Tena-Sempere M. *Nat Rev Endocrinol* 2011]. A randomized, placebo-controlled Phase 1 study that used various, continuously administered doses of TAK-488 has demonstrated its safety, tolerability, and effectiveness in suppressing pituitary secretion of luteinizing hormone (LH) and follicular-stimulating hormone (FSH), which are key in the regulation of testosterone synthesis. Accordingly, serum testosterone declined to below castrate levels in most of the healthy male volunteers. The results of the study were presented by David MacLean, MD, Takeda Pharmaceuticals, Cambridge, Massachusetts, USA.

Following screening, 30 healthy male volunteers, most of whom were white, aged 51 to 78 years with a body mass index ≥18.5 but <32 kg/m^2 and normal levels of all relevant hormones were enrolled. They had not received hormonal therapy other than inhaled and topical steroids within the previous 4 weeks. The 30 participants were randomized to subcutaneously receive a 0.1 mg/kg bolus dose of TAK-448 on Day 1, and a continuous subcutaneous infusion of TAK-448/placebo (0.01 mg/kg, n=6/2; 0.1 mg/kg, n=6/2; 0.3 mg/kg, n=6/2; or 1.0 mg/kg, n=5/1) each day from Days 2 to 14. Evaluations were done at predetermined times up to Day 44. The primary endpoints were safety and tolerability. The secondary endpoints were endocrine-release profile and TAK-448 pharmacokinetics. Serum LH and FSH were quantified by radioimmunoassay. Serum testosterone, 5α-dihydrotestosterone (5α-DHT) and androstenedione were measured using liquid chromatography-tandem mass spectrometry.

The initial bolus dose of TAK-448 produced an increase in serum levels of LH and FSH, which subsequently declined to below the baseline levels of those receiving placebo during the 13-day continuous infusion period. By Day 17 (LH) or 21 (FSH), the hormone levels had recovered to baseline and were maintained through Day 44 .

Serum testosterone levels displayed a similar pattern, declining in most participants to nearly undetectable levels (<0.7 nmol/L) during and for several days after the 13-day period of subcutaneous infusion of TAK-448 before rebounding to exceed baseline levels by Day 29 . The pattern for 5α-DHT was similar.

Serum levels of androstenedione were suppressed in all subjects during an evaluation from Days 1 to 21, indicating an effect of the initial bolus administration of TAK-448. Steady-state concentrations of TAK-448 were evident within 6 hours of the continuous infusion and remained constant as a function of dose during the 13-day infusion period. All adverse events were mild or moderate in severity and most commonly included hot flushes, dizziness when standing, headache, diarrhea, and reaction at the site of subcutaneous injection. No adverse event resulted in discontinuation.

More research is necessary to extend the findings to different races and to clarify whether the novel GPR54-mediated mechanism for medical castration might be advantageous in hindering tumor invasion or metastasis in prostate cancer. The possible therapeutic value of TAK-448 in hormone-directed diseases including endometriosis and breast cancer also needs to be evaluated.

Testosterone Therapy Fails to Improve Clinical Pain Perception in Opioid-Induced Androgen Deficiency

Written by **Emma Hitt, PhD**

Men with opioid-induced androgen deficiency and chronic noncancer pain did not experience an improvement in most measurements of pain perception following testosterone therapy. Shehzad Basaria, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data from a randomized, controlled trial that evaluated the effect of testosterone replacement on pain perception, pain tolerance, and quality of life (QoL) in men with opioid-induced androgen deficiency.

Patients that take opioid analgesics may experience a decrease of testosterone due to the suppression of the hypothalamic-pituitary-gonadal axis. Testosterone

replacement therapy is effective in animal models in improving pain perception; however, the effect of testosterone replacement therapy on pain perception and QoL in men with opioid-induced androgen deficiency is not well understood. The hypothesis motivating this trial was that testosterone replacement therapy would improve pain perception and tolerance, as well as QoL, in men with opioid-induced androgen deficiency.

In the double-blind, placebo-controlled, parallel-group design study, 84 patients aged 18 to 64 years with chronic noncancer pain and opioid-induced androgen deficiency, (defined as serum testosterone levels <350 ng/dL) were randomized to receive transdermal testosterone gel 5 g (n=43) or placebo (n=41) daily for 14 weeks. Dose titration of testosterone was performed 2 weeks following randomization to achieve serum testosterone levels of 500 to 1000 ng/dL.

The final analysis included the 65 participants that completed the study (36 in the testosterone arm, 29 in the placebo arm). The primary endpoint was the reported clinical pain based on the Brief Pain Inventory (BPI) questionnaire. Secondary endpoints included quantitative sensory testing (QST) performed in the laboratory including pressure, mechanical and cold presser pain, QoL as measured by the Short Form-36 (SF-36) questionnaire, and change in dose requirements of the concomitant opioid analgesics.

Patients that received testosterone therapy experienced a nonsignificant decrease in BPI score compared with those that received placebo (p=0.38). As measured by BPI, there was no difference between the testosterone and placebo groups in pain severity, and a nonsignificant decrease in pain interference in the testosterone group. In addition, no significant difference was observed in the opioid analgesic dose requirements, QST measurements for the first stimulus of the mechanical probe and cold tolerance, and the SF-36 score for general health. A nonsignificant trend of improvement in role limitations due to emotional problems was observed in the SF-36 questionnaire (p=0.08). Pain sensitivity, as measured by the tenth stimulus of the mechanical probe during the QST was significantly decreased in patients that received testosterone compared with those that received placebo (p=0.05).

Although data from the trial suggest some improvement in QST and QoL following testosterone therapy in men with opioid-induced androgen deficiency, other measurements were not significantly improved. Dr. Basaria indicated that improvement in clinical pain is often seen in individual patients after laboratory-based measurements of pain perception. Therefore, a larger trial to allow definitive conclusions to be made is required. The effect of testosterone therapy on sexual function, body composition, and metabolic parameters will be evaluated in this patient population in future studies.