Background

Androgen deprivation therapy (ADT) is the mainstay for the treatment of advanced prostate cancer. GnRH agonists are frequently used for ADT but these agents often result in initial surges in testosterone (T) levels. Although they do not result in initial T surge, current injectable GnRH antagonists are short term (1 month) subcutaneous (sc) depots that require a high volume loading dose followed by monthly high volume maintenance dosing. VERU-100 is a novel GnRH decapeptide antagonist 3-month depot formulation for long term suppression of T to below castrate levels and is administered as a low volume sc injection (<1 cc) without the requirement of a loading dose. Eight distinct GnRH antagonist formulations were evaluated in rats in order to select the best formulation, VERU-100.

Methods

Male Sprague Dawley rats (n=3 per group) were injected sc through a 21G needle, with approximately 200µl of each formulation at a dose level of 20 mg/kg. Eight groups consisting of the distinct test formulations were evaluated. Blood samples were drawn at weekly intervals until week 4 and then bi-weekly for pharmacokinetic (PK) (Integrated Analytical Solutions) and testosterone (T) level determinations (Cornell University Animal Health Diagnostic Center).

Results

Within approximately 24 hours after administration of the GnRH antagonist formulations, testosterone levels in the rats went from a mean of 7.36 ng/ml to undetectable. The T levels resulting from a single injection of the lead formulation VERU-100 were detectable for greater than 26 months. Administration of the GnRH antagonist formulations resulted in sustained, more than six months in men with advanced prostate cancer.

Materials and Methods

Testosterone levels decreased to undetectable within hours after injection without flare. The decreases in testosterone levels are associated with agonists but have a limitation in that the currently available agents are only approved for monthly injection. One of the biggest limitations to their use is the requirement of a loading dose. Eight distinct GnRH antagonist formulations, testosterone levels in the rats went from a mean of 7.36 ng/ml to undetectable. The T levels resulting from a single injection of the lead formulation VERU-100 were detectable for greater than 26 months. Administration of the GnRH antagonist formulations resulted in sustained, more than six months in men with advanced prostate cancer.

Conclusions

• With a single, subcutaneous injection, formulations of VERU-100 in rats resulted in >1 ng/ml blood levels of GnRH antagonist for more than six months.
• The single injection of VERU-100 is a low volume without obvious toxicity
• VERU-100 administration resulted in undetectable total testosterone levels for more than six months in almost all formulation variants.
• The decreases in testosterone levels are rapid (within hours)
• No surge/flare in testosterone levels were observed
• No testosterone escapes were identified

VERU-100-MATERIALS AND METHODS

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CONCLUSIONS

- The decreases in testosterone levels are associated with agonists but have a limitation in that the currently available agents are only approved for monthly injection. One of the biggest limitations to their use is the requirement of a loading dose. Eight distinct GnRH antagonist formulations, testosterone levels in the rats went from a mean of 7.36 ng/ml to undetectable. The T levels resulting from a single injection of the lead formulation VERU-100 were detectable for greater than 26 months. Administration of the GnRH antagonist formulations resulted in sustained, more than six months in men with advanced prostate cancer.

CURRENT/FUTURE CLINICAL TRIALS

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- FDA has agreed with plans for clinical development
  - Single phase 2 – open label, multicenter dose finding study of three doses of VERU-100 in men with advanced prostate cancer (n=60-80)
  - Single Phase 3 – open label, multicenter study in men with advanced prostate cancer (n=100)

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