Determination of the ability of a novel, long-acting subcutaneous GnRH antagonist, VERU-100, to castrate without a testosterone surge in a rat model

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Background

Androgen deprivation therapy (ADT) is the mainstay for the treatment of advanced prostate cancer. LHRH 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 in these studies, VH-030-002, remained undetectable for greater than 26 weeks (6 months) as did the other formulations tested. The corresponding PK analysis demonstrated that the GnRH antagonist decapeptide levels were detectable for greater than 26 weeks and remained above 1 ng/ml for almost all of the study points. The T levels correlated to the exposure from the formulations, and PKPD was as consistent for GnRH antagonists.

Conclusions

VERU-100 is a novel GnRH antagonist formulation that in this rodent study, with a low injection volume, resulted in undetectable T for at least six months. No surge of T is observed after administration. An IND submission is anticipated in early 2020 for the dose finding Phase 2 trial in men with advanced prostate cancer.

Funding -This study was supported by Veru Inc.

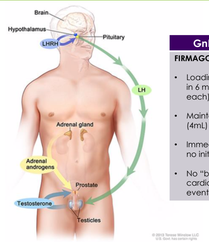
BACKGROUND

Opportunity for novel androgen deprivation therapy for advanced prostate cancer

LHRH Agonist

Long-acting products: LUPRON® Depot (IM) and ELIGARD® (SC) are leuprolide products

- Concern over initial T "surge" and micro-increases
- Convenient 4 and 6 month slow release
- "Buy and bill" model attractive to community Urologists
- Most popular is 3 month depot



GnRH Antagonist

FIRMAGON® (degarelix)(SC)

- Loading Injection of 240mg in 6 mL (2 injections of 3mL each)
- Maintenance dose: 80mg (4mL) every 1 month
- Immediate castration with no initial testosterone surge
- No "black box" warning for cardiovascular adverse events

GnRH agonists are commonly used for androgen deprivation therapy (ADT)

One of the biggest limitations to their use is the testosterone levels surge that can accompany their injection and result in tumor flare

GnRH antagonists do not result in the testosterone surge associated with agonists but have a limitation in that the currently available agents are only approved for monthly injection

MATERIALS AND METHODS

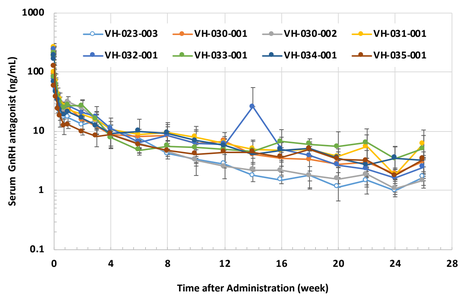
Male Sprague Dawley rats (n=3 per group) were injected subcutaneously through a 21G needle, with approximately 200µl of each formulation at a dose level of 20 mg/kg

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

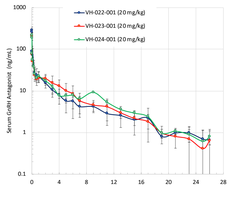
VERU-100 formulations resulted in sustained, clinically relevant levels of GnRH antagonist more than six months after single subcutaneous dosing

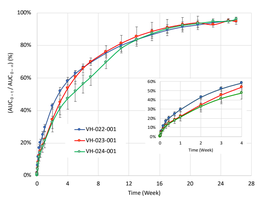


Pharmacokinetic (PK) analysis of VERU-100 formulations

ID	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-last} (ng/mL * hr)	$AUC_{0-\infty}$ (ng/mL * hr)	$AUC_{0-24hr}/AUC_{0-\infty}$	$AUC_{0-168hr}/AUC_{0-\infty}$	$AUC_{0-1344hr}/AUC_{0-\infty}$
VH-022-001	20	283.7	1	23,618.25	24,596.44	11.4%	29.4 %	42.6%
VH-023-001	20	218.7	1	26,714.19	27,411.38	8.1%	22.1 %	34.5%
VH-024-001	20	218.7	1	27,782.19	28,767.41	7.6%	21.3 %	32.7%

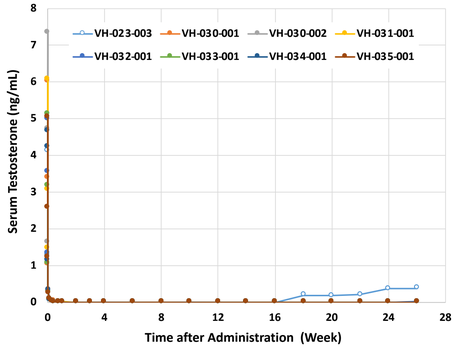
Data analyzed by PK Solver 2.0, Non-Compartmental Analysis



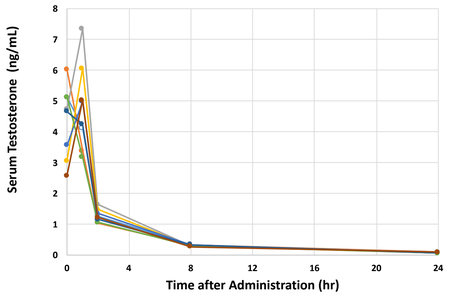


RESULTS

Administration of VERU-100 formulation variants resulted in undetectable testosterone levels which lasted more than six months



Testosterone levels decreased to undetectable within hours after injection without flare



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 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 DRUG PROPERTIES

- VERU-100 is a long acting 3-month depot GnRH antagonist
- Novel proprietary GnRH antagonist decapeptide formulation
- VERU-100 is a 3-month slow release subcutaneous depot (<1 cc SQ injection) with no loading dose
- Immediate testosterone suppression no initial testosterone surge
- Suppression of testosterone to less than 20ng/dL
- As with other GnRH antagonists, no black box warning for cardiovascular adverse effects

CURRENT/FUTURE CLINICAL TRIALS

- 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)