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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-732

Clinical Pharmacology and Biopharmaceutics Review

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-732	Submission Date(s):	12/12/2003
		PDUFA Goal Date:	10/12/2004
Brand Name:		VANTAS™ (Histrelin acetate implant) 50 mg	
Generic Name		Histrelin acetate	
Reviewer		Sandhya Apparaju, Ph.D.	
Team Leader		Ameeta Parekh, Ph.D.	
OCPB Division		Division of Pharmaceutical Evaluation II	
OND division		Division of Reproductive and Urology Drug Products	
Sponsor		Valera Pharmaceuticals, Inc.	
Relevant IND(s)		40,772	
Submission Type; Code		Original NDA-505b(1); 3 S	
Formulation; Strength(s)		Non-biodegradable polymeric implant consisting of 50 mg histrelin acetate.	
Indication		Palliative treatment of advanced prostate cancer	

OCPB Briefing Date: July 26th 2004, 11 AM (Location: 13B17 conference room, Parklawn building)
Briefing attendees: Drs' Hank Malinowski, John Hunt, Ameeta Parekh, Mark Hirsch, Harry Handelsman, Suong Tran, Myong-Jin Kim and Sandhya Apparaju

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1 Executive Summary

Histrelin acetate is the active ingredient of VANTAS™ implants, developed by Valera Pharmaceuticals. It is a synthetic nonapeptide agonist of the gonadotropin releasing hormone (GnRH). Because testosterone is known to be a profound stimulator of malignant progression, GnRH agonists are often used in prostate cancer patients to achieve testosterone suppression to below castration levels (< 50 ng/dL), thereby alleviating bone pain, urinary problems and other symptoms associated with the disease.

The sponsor is seeking approval for the use of VANTAS™ (histrelin acetate implant) 50 mg for the palliative treatment of advanced prostate cancer. The proposed dose is one implant consisting of 50 mg of histrelin acetate, to be placed subcutaneously for 12 months. The implant is made of a non-biodegradable polymeric matrix that allows diffusion-controlled, sustained release of histrelin at a rate of ~ 50-60 µg/day over 12 months. The sponsor has adequately characterized the pharmacokinetics of histrelin released from the VANTAS™ implant in prostate cancer patients. In addition, the impact of renal impairment on histrelin pharmacokinetics was also characterized through subpopulation analyses of the pivotal trial data. The in vitro and in vivo release of histrelin from the dosage form was assessed and dissolution testing method & specifications are proposed to ensure product quality and assure in vivo performance.

The following comment regarding IVIVC has been conveyed to Valera pharmaceuticals in a letter dated 09/27/04:

- The development of the proposed IVIVC has limitations in that only mean data from the pivotal trial lots was employed in demonstrating the in vitro-in vivo correlation rather than individual lot data. More importantly, the correlation was not validated using either internal or external data for the determination of predictability error. The submitted data therefore, cannot be considered a validated and acceptable IVIVC.

1.1 Recommendation

NDA 21-732 is acceptable from a clinical pharmacology and biopharmaceutics perspective.

1.2 Phase IV Commitments

None.

2 Summary of clinical pharmacology and biopharmaceutics findings

The GnRH agonist, Histrelin was originally approved by FDA in 1991 as Supprelin injection for the treatment of central precocious puberty (NDA 19-836; Shire Laboratories). The NDA was later withdrawn in 2002. Because ADME information was lacking in that submission, the current sponsor Valera pharmaceuticals, Inc., attempted to address this issue by conducting a phase 1, single dose (SC) study in normal volunteers to characterize the human pharmacokinetics of histrelin.

Phase 1 study: The pharmacokinetics of histrelin following the administration of a single subcutaneous bolus dose (500 µg solution containing 10 % mannitol) was characterized in six fasted healthy male volunteers (18-65 years of age). Blood samples for pharmacokinetic analysis of histrelin serum concentrations were collected at 0 hour (pre-dose), 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours post-dose. Non-compartmental pharmacokinetic analysis of the histrelin concentration versus time data was conducted to determine the values of important PK parameters.

Table 1: Mean pharmacokinetic parameters of histrelin from six healthy male volunteers following a single bolus dose (500 µg, SC)

PK Parameter (units)	Average (mean ± s.d.)
C_{max} (ng/ml)	13.5 ± 3.0
T_{max} (hr)	1.17 ± 0.5
λ_z (hr^{-1})	0.19 ± 0.04
$T_{1/2}$ (hr)	3.92 ± 1.01
AUC_{0-t} (hr ng/ml)	50.47 ± 12.63
$AUC_{0-\infty}$ (hr ng/ml)	50.85 ± 12.69
CL/F (ml/min)	179.14 ± 37.79
MRT (hr)	4.31 ± 0.7
V_z/F (L)	58.40 ± 7.86

- The results of this study suggest that the pharmacokinetics of histrelin compare well to the other GnRH agonists with a mean half-life of 4 hours, an apparent clearance of 179 ml/min and an apparent volume of distribution of 58 L.

Phase 2 clinical trial: The pharmacokinetics of histrelin from the VANTAS™ implant were initially characterized in a dose-ranging study in prostate cancer patients (n =42). Subjects received 1, 2 or 4 implants, corresponding to histrelin acetate doses of 50, 100 or 200 mg. The duration of administration varied from 4 months to 30 months. Blood samples for analysis of histrelin and testosterone concentrations were obtained at pre-dose, 1, 2, 4, 8, 12, 16, 18, 20 weeks (testosterone only at week 20), then at 4, 5, 6, 7, 8, 9, 10, 11 and 12 months.

Table 2: Histrelin pharmacokinetics following administration of 1, 2 or 4 VANTAS™ implants (each implant containing 50 mg histrelin acetate) to male prostate cancer patients.

	No. of Implants	Weeks From Implant	AUC_{16} ng.week/ml	AUCall ng.week/ml	Cpav ng/ml
Mean(n=14)	1	36.99	3.69	5.90	0.19
SD		16.57	2.01	2.81	0.11
%CV		44.80	54.45	47.68	57.45
Min					
Max					
Mean(n=36)	2	42.20	12.09	19.73	0.52
SD		15.48	6.31	11.69	0.31
%CV		36.69	52.16	59.24	59.77
Min					
Max					
Mean(n=7)	4	50.99	21.73	50.21	0.99
SD		18.23	8.76	35.57	0.45
%CV		35.76	40.33	70.84	45.26
Min					
Max					

AUC_{16}: Partial area under the curve until 16 hours
AUCall: Area under the curve over the weeks of implants
Cpav: Average plasma concentration

- The average serum concentration (Cpav) and the partial $AUC_{0\text{-}16\ weeks}$ increased approximately in proportion to dose.
- Residual concentrations from previous implants did not alter the pharmacokinetics of histrelin released from a subsequent implant, suggesting the absence of accumulation, as could be expected owing to the removable nature of the drug product.
- Dose-Response: An assessment of the primary and secondary endpoints of efficacy (& safety) at various doses (1, 2 or 4) of the implant demonstrated the absence of a dose-response relationship. The change in serum testosterone caused by various doses of histrelin is shown below:

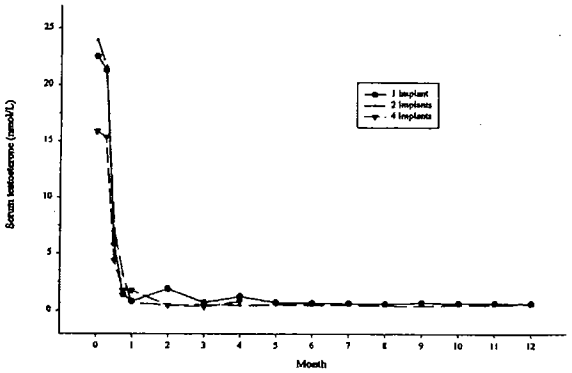


Figure 1: Changes in serum testosterone concentrations following various doses (1, 2 or 4) of VANTAS™ (histrelin acetate) implants.

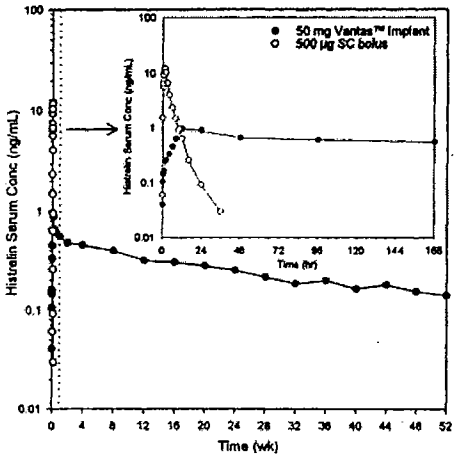
- One VANTAS™ implant was as effective as 2 or 4 implants in achieving testosterone suppression to below castration levels (by week 4) and maintenance of this suppression throughout the treatment (52 weeks). However, implants containing doses of histrelin lower than 50 mg were not studied and therefore the minimum effective dose of histrelin for achieving androgen ablation in prostate cancer patients was not identified in the true sense.
- The changes in the secondary endpoints of interest including the serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prostate-specific antigen (PSA) were also similar across all doses, suggestive of the absence of a dose-response relationship within the dose-range employed.
- In general adverse events were experienced by a larger percentage of patients who received two or four implants ($\geq$ 70 %) compared to patients who received only one implant (43 %). This is particularly apparent with cardiovascular related adverse events (vasodilatation). With respect to most other adverse events, dose-relationship is not obvious.
- In vitro/ in vivo release: The residual amount of histrelin in the implant was obtained for n = 15 implants over five patients and the amount delivered in vivo during the period of indwelling was estimated by difference. The average rate of

drug release was 51.39 µg/day in vivo, similar to the average in vitro release rate of approximately 54.33 µg/day.

- The results of the phase 2 dose-ranging study confirmed the safety and efficacy of VANTAS™ implants in pancreatic cancer patients. Dose-finding study supports the use of a single implant, as the use of higher number of implants was not associated with additional efficacy.

Phase 3 clinical trial: A pivotal clinical trial (# 301) in prostate cancer patients (n = 138) was conducted employing a dose of one VANTAS™ implant based on the findings of the phase 2 study. The pharmacokinetic parameters of histrelin released from the implant were adequately characterized through intensive sampling from 17 patients. Following 52 weeks of treatment, the first implant was removed and patients received a second implant. The pharmacokinetics of histrelin and the efficacy endpoints including testosterone concentrations were monitored for 8 weeks (week 52-60) during this second cycle of treatment, to assess the safety and efficacy of continued treatment with VANTAS™ implants.

- Serum histrelin concentration versus time data following the insertion of the first implant suggests that histrelin from the subcutaneous implant was immediately available for absorption (within 5 minutes).
- Following the observed peak of ~ 1.1 ng/ml (peak concentrations ranged from 0.603 to 1.91 ng/ml), mean histrelin serum concentration at the end of the 52 week treatment duration was ~ 0.13 ng/ml.
- Histrelin was released from the subcutaneous implant in a slow and controlled manner over the 52 week treatment period. Concentrations declined very slowly as indicated by the small value of the terminal elimination rate constant (λ_z=0.035 wk^{-1}), compared to a λ_z of 0.19 hr^{-1} following a subcutaneous bolus dose of histrelin. Therefore the elimination rate from the implant was limited by release from the implant (flip-flop kinetics).
- In addition, the T_{max} from the implant was considerably delayed (12 hours; ranging from 6 weeks to 36 weeks) compared to the T_{max} (1 hour) observed following a subcutaneous bolus administration of histrelin (500 µg solution).
- It is estimated that the relative bioavailability of histrelin from the hydrogel implant is high (> 80 %) relative to a SC bolus dose.



Parameter	All Patients (N=17)	
	Mean	SD
Cmax, ng/mL	1.10	0.375
Tmax, hr[a]	12.00	6 hr-36 wk
Cavg(0-96hr), ng/mL	0.697	0.226
Cavg(0-52wk), ng/mL	0.265	0.0685
AUC(0-96hr), ng·wk/mL	0.398	0.129
AUC(0-8wk), ng·wk/mL	3.99	1.24
AUC(0-16wk), ng·wk/mL	6.65	1.72
AUC(0-52wk), ng·wk/mL	13.8	3.55
SLP, wk^{-1}	0.0350	0.0193

Table 3: Histrelin pharmacokinetics following administration of a single subcutaneous implant to prostate cancer patients (n = 17).

Figure 2: Comparative plasma concentration versus time profiles following a single subcutaneous bolus (500 µg) and a single subcutaneous implant (50 mg VANTAS™)

- Important clinical observations from the pivotal clinical trial include: a) suppression of testosterone to below castration levels (i.e. < 50 ng/dL or 1.75 nmol/L) and LH by 4 weeks, b) maintenance of this suppression during the 60 weeks of treatment period (i.e. 52 weeks with first implant and 8 weeks with the second implant), and c) the absence of acute-on-chronic effect with repeated treatment cycles. [Acute-on-chronic refers to sudden increases in testosterone concentration to above castration levels at 48 hours and/or 7 days following insertion of a second implant, while it was previously below castration].
- Concentration-response: The relationship between serum testosterone and serum histrelin concentrations in prostate cancer patients was characterized by a clockwise hysteresis loop, indicating an indirect pharmacodynamic relationship. Initially, as serum histrelin concentration increased, testosterone concentration also increased over baseline due to the stimulation of pituitary gonadotropins. The Cmax for histrelin ("burst") occurred much earlier at ~ 12 hours than the Cmax for testosterone ("flare") at ~ 2 days. Following this initial stimulatory phase, testosterone concentrations fell rapidly below castration by ~ 4 weeks (resulting from desensitization of the pituitary receptors) and remained low even as histrelin concentrations continued to fall slowly throughout the 52 weeks.
- Minimum histrelin serum concentration required to maintain testosterone below castration levels could not be obtained from the data. Histrelin concentrations were not available for those patients who demonstrated occasional "breakthroughs" (i.e. T > 50 ng/dL).

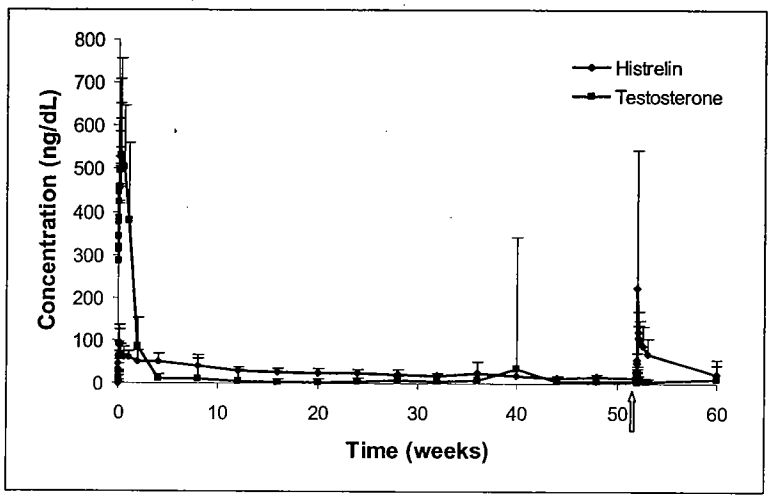


Figure 3: Serum histrelin and testosterone concentrations following first and second dosing with a single subcutaneous implant administered to prostate cancer patients. The arrow represents the time of insertion of the second implant (52 weeks) after removal of the first implant.

- Histrelin serum concentrations and the associated pharmacokinetic parameters following insertion of a second implant (studied from week 52 through week 60) were comparable to the observed concentrations and pharmacokinetics of histrelin following the first implant. This observation together with the observed maintenance of testosterone suppression with continued treatment (as shown in figure 3) supports the use of VANTAS^{TM} implant beyond the first year of treatment.

- Effect of renal impairment: A trend for higher histrelin exposure was apparent in mild to severe renal-impaired patients (CL_{cr}: 15-60 ml/min) of the pivotal clinical trial compared to normal renal function patients. Within the PK subgroup, renal impairment patients (n = 10) had slightly higher C_{max} (1.28 ng/ml) and $AUC_{0\text{-}52\ weeks}$ (15.2 ng.wk/ml) values compared to normal renal/hepatic function patients (n =5) with C_{max} and AUC values of 0.856 ng/ml and 12.8 ng.wk/ml, respectively. When histrelin concentrations available from the entire pivotal study population (n = 138) were considered, the average serum concentration of histrelin (C_{pav}) in the renal impairment subgroup (n = 42) again demonstrated ~ 50 % increase compared to the calculated unimpaired average (n = 92) (0.392 ng/ml compared to 0.264 ng/ml). However, the observed increases are not considered clinically relevant and therefore changes to dosing are not anticipated for this subpopulation.

- Effect of hepatic impairment: Within the pivotal study population, there were no patients with clinically significant hepatic impairment. Therefore no conclusions can be made regarding the effect of hepatic impairment on histrelin exposure.

- Effect of race: In the pivotal clinical trial, Blacks (n = 30), Caucasians (n = 77) and Hispanics (n = 7) did not exhibit any demonstrable differences in histrelin pharmacokinetics.

- Effect of age: The median age of the prostate cancer patients in the pivotal study # 301 was 75 years, with a range of 53-92 years. The vast majority of these patients (89.9 %) were of age 65 years or over. Age did not appear to have an impact on histrelin pharmacokinetics within the range studied.
- In vitro/in vivo release rates: The in vivo release rate from the histrelin implants was estimated by determining the residual amount of histrelin remaining in 41 explants over 38 patients. The average in vivo release of histrelin from the VANTAS™ implants was 56.7 µg/day and compares well with the average in vitro release of 56.43 µg/day.
- The reported value for apparent clearance of histrelin from the implant in patients with unimpaired renal or hepatic function was 173.84 ± 56.53 ml/min (calculated as the quotient of in vivo delivery rate and the average serum concentration). This value compares well with the apparent clearance value for histrelin determined during the ADME study in normal volunteers (179.14 ± 37.79 ml/min).
- Dissolution testing: The sponsor has proposed the in vitro release testing method and elution specifications for VANTAS™ (histrelin acetate) implants. The method consists of release testing individual implants placed in serum vials containing

  The method is deemed acceptable. Based on the observed ranges of histrelin release from individual implants, changes were suggested for the proposed release specifications after discussion with Dr. Parekh, Dr. Tran and Dr. Rhee (HFD 580). The sponsor has agreed to the suggested changes and the final proposed elution specifications incorporating these changes are shown below (as per Valera pharmaceuticals letter dated August 19, 2004):

Table 4: Proposed release rate specifications for VANTAS™ implants.

This table contains the revised Specifications of Elution Rate for Finished drug product **(Bolded).**

- Protein binding: In vitro determination of the extent of protein binding of histrelin in human plasma suggests that the mean ± SD fraction unbound is 29.5 ± 8.9 %.
- Drug metabolism: Circulating metabolites of histrelin have not been specifically identified. However, as the structure of histrelin is very similar to other GnRH agonists such as leuprolide, nafarelin, goserelin etc, the metabolism is also likely to be similar, with hydrolysis of amino acids resulting in peptide fragments, in addition to the dealkylated product resulting from hepatic microsomal metabolism, identified in vitro.
- Although no specific drug-drug interaction studies have been conducted for the histrelin subdermal implant, the sponsor claims that given the minimal involvement of hepatic microsomal enzymes in the metabolism of GnRH agonists, induction or inhibition of drug metabolism of other drugs is unlikely. As the protein binding is not very extensive (average fraction unbound is 29.5 %), protein binding interactions are unexpected. Also, no pharmacokinetic drug-drug interactions are reported for any other GnRH agonists. In addition, the pivotal clinical trial patients (n = 138) were older men with various ailments and simultaneously on several different prescription and over the counter medications while on treatment with VANTAS^{TM} implant. However, no drug-drug interaction based adverse events were reported in this study.

3 QBR

3.1 General Attributes

Regulatory history: Histrelin was originally approved by FDA in 1991 as Supprelin injection for the treatment of central precocious puberty (NDA 19-836; Shire Laboratories). The NDA was later withdrawn in December, 2002. Roberts Laboratories completed the phase 2 dose-ranging study of the histrelin 12-month implants and initiated a phase 3 trial in prostate cancer patients under IND 40,772. The current sponsor Valera Pharmaceuticals (formerly Hydro med Sciences, HMS) obtained rights for the drug product development while the phase 3 studies were underway. The sponsor submitted the current NDA 21-732 for VANTAS^{TM} (histrelin acetate) implants for the palliative treatment of prostate cancer in December 2003.

Chemistry: Histrelin acetate is a synthetic nona peptide derived from the structure of luteinizing hormone-releasing hormone (LHRH) by [redacted] The amino acid sequence and chemical name for histrelin is as follows: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Nt-benzyl-D-histidyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide. The molecular formula is $C_{66}H_{86}N_{18}O_{12}$ and it has a molecular weight of 1323.52

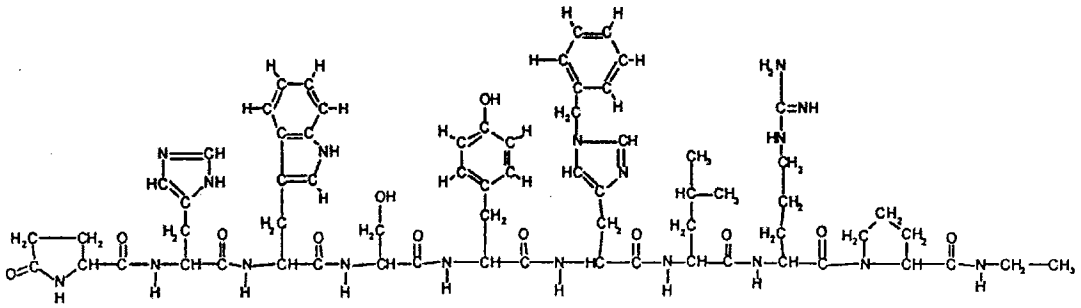


Figure 1: Structure of Histrelin.

Physical and chemical characteristics: Histrelin acetate is a white to off-white powder that is very slightly soluble (~ 0.5 mg/ml) in water at pH 6-7.5 and sparingly soluble (~ 13 mg/ml) at pH 5. Stability data show that the stability of histrelin acetate decreased as pH and temperature increased. It is most stable at pH 5. It has a λmax of 281 nm.

Drug Product: VANTAS™ is a sterile, non-biodegradable, diffusion-controlled, miniature implantable drug delivery system designed to deliver histrelin for 12 months at a controlled rate. The hydrated cylindrical implants (3 cm long and 3.5 mm in diameter) are made up of a hydrophilic polymer matrix (hydrogel®; crosslinked copolymer of hydroxypropyl methacrylate and hydroxyethyl methacrylate) and contain histrelin acetate pellets (50 mg) in the core. The in vitro release rate is approximately 55-60 µg daily over one year. A trocar type device is used to insert the cartridge subcutaneously and the implant can be removed if needed (Trocar #3 was reviewed by CDRH and deemed acceptable).

Following the loading of histrelin pellets into the polymer cartridge and sealing, the implant is subjected to hydration process for four weeks to allow leaching of impurities, following which implants are stored individually in 1.8 % saline. Therefore by the end of storage, the histrelin pellets within the core are reduced to aqueous slurry and the walls of the implant are fully saturated with the drug solution. When an implant is first introduced into the body, release of the drug from the "fully loaded" walls causes the initial "burst". Following this, dissolved histrelin acetate is continuously released from the implant via diffusion through the polymer cartridge. The design of the polymer cartridge controls the rate of diffusion, which is measured as the elution rate.

Mechanism of action: Histrelin has the actions of a classical luteinizing hormone releasing hormone (LHRH) agonist, otherwise known as gonadotropin-releasing hormone (GnRH) agonist. It is 200 times more potent than LHRH itself. Upon acute administration, histrelin causes the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. However, if administered in large doses or continuously, the LHRH receptors on the pituitary gonadotrophs undergo downregulation and desensitization, leading to a suppression of LH concentrations well below the normal. In addition, the pulsatile pattern of LH concentration in the blood required for the end organ response is lost. In the male, the end target is the Leydig cells of the testes where LH is required to stimulate testosterone production. Castrate serum

levels of testosterone (< 50 ng/dL or 1.75 nmol/L) are achieved after 3 to 4 weeks with agonist treatment.

Therapeutic Indication: The proposed indication for VANTAS™ implants is palliative treatment of advanced prostate cancer. Testosterone is necessary for prostate growth and development, and it also serves as a profound stimulator of malignant progression. Decrease in testosterone to castrate levels (< 50 ng/dL) helps in reducing bone pain, urinary problems and other symptoms associated with prostate cancer.

Proposed dosage and route of administration: The recommended dose of VANTAS™ is one implant every 12 months. Each implant consists of 50 mg of histrelin. The implant is inserted subcutaneous into the inner aspect of the upper arm. The device should be removed at the end of the 12-month period and can be replaced with a new device at that point for continued therapy. The device is expected to release histrelin at a controlled rate of 50-60 μg/day, over a period of 12 months. Approximately 20 mg of drug is released during the 12 month treatment period.

3.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The following clinical and clinical pharmacology studies were conducted to assess safety, efficacy and pharmacokinetics of histrelin hydrogel implants:

Phase 1 study (# 07-03-100): A single-center, open-label, pharmacokinetic study in 6 healthy male volunteers in order to characterize the ADME of histrelin following a single, subcutaneous bolus dose (500 μg aqueous solution).

Phase 2 clinical trial (Study # BAR-002-0591A-USA): A multi-center, open-label, randomized parallel group, dose-ranging study employing 1, 2 or 4 implants in 42 prostate cancer patients in order to investigate the effectiveness of histrelin hydrogel implant in suppressing testosterone production and to identify the effective dose (50, 10 or 200 mg).

Pivotal clinical trial (study # 301): A Phase 3, multi-center, open-label study was conducted to evaluate the safety and efficacy of histrelin implants in patients with advanced prostate cancer (n = 138). The pharmacokinetics and pharmacodynamics of histrelin hydrogel implant were investigated following administration of one implant.

A second implant was inserted at 52 weeks after the first one was removed and the PK/PD was investigated for an additional 8 weeks. No placebo or active comparators were used in this study.

Supportive clinical trials:

Study # 302: Open-label, randomized, parallel, active-control study was conducted to evaluate safety and efficacy of histrelin hydrogel implants in patients (n = 59) with metastatic prostate cancer. Zoladex 3-month (10.8 mg goserelin acetate implant) was used as the active control.

Study # 301E: Open-label, extension study was conducted to evaluate the continued safety and efficacy of histrelin implant in prostate cancer patients. 21 patients were monitored during their second year of treatment to study the continued treatment with histrelin implants.

What is the basis for selecting the response end points i.e., clinical or surrogate endpoints, or biomarkers (PD) and how are they measured in clinical pharmacology and clinical studies?

The *primary* clinical efficacy measure is the proportion of patients whose serum testosterone levels indicate chemical castration (<50 ng/dL or 1.75 nmol/L) at week 4 and the proportion of patients whose serum testosterone levels indicate the maintenance of chemical castration for 52 weeks. The 4-week time point although arbitrary to some extent, is also based upon the fact that most people receiving Lupron depot ("gold standard" for LHRH agonist therapy) achieve castration level by week 4 and also because 4 weeks is a reasonable amount of time for these patients to wait for purposes of treatment.

Secondary efficacy measures include serum concentrations of testosterone, luteinizing hormone (LH), and prostate specific antigen (PSA). While decrease in serum testosterone and LH demonstrate histrelin-mediated suppression of steroidogenosis (thus confirming the drug-response relationship), PSA levels act as surrogate marker for disease progression. The concentration of serum testosterone (T) was determined by a radioimmunoassay (RIA) with a lower limit of quantitation (LLOQ) of 12.4 pg/ml. LH was determined by a time-resolved fluoroimmunoassay with a practical detection limit of 0.50 mIU/ml.

Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Serum histrelin was the only assessable active moiety in this study. The metabolic pathway of histrelin is not known and no circulating metabolites were identified in the study. Exposure-response relationships have been assessed by correlating histrelin dose and/or serum concentrations with the serum concentrations of testosterone and luteinizing hormone obtained at identical time points. Serum histrelin was quantified using a competitive radioimmunoassay (RIA).

3.2.1 Exposure-Response

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Dose-response: The relationship between the dose of histrelin to the response was evaluated in a phase 2 dose-finding study of histrelin implants in prostate cancer patients (n =42). Subjects received 1, 2 or 4 implants, corresponding to total dose of 50, 100 or 200 mg histrelin acetate.

As shown in the table below there was no clear dose-response relationship between one or two implants and the proportion of patients (92 % and 90 %, respectively) who

achieved testosterone suppression by week 4. However, 100 % of patients who received 4 implants had testosterone below castration levels by week 4.

Table 1: Percentage of responders (patients with testosterone < 50 ng/dL by week 4) in relation to number of implants received.

			Responders, Number (Percentage)			
			One implant	Two implants	Four implants	Overall
Month	Center	Responder	n = 13	n = 20	n = 8	n = 41
1	Austria	Yes	6 (86)	8 (89)	1 (100)	15 (88)
		No	1 (14)	1 (11)	0 (0)	2 (12)
	Israel	Yes	6 (100)	8 (100)	0 (0)	14 (100)
		No	0 (0)	0 (0)	0 (0)	0 (0)
	USA	Yes	0 (0)	2 (67)	7 (100)	9 (90)
		No	0 (0)	1 (33)	0 (0)	1 (10)
	Overall	Yes	12 (92)	18 (90)	8 (100)	38 (93)
		No	1 (8)	2 (10)	0 (0)	3 (7)

Patients in all dose groups maintained testosterone suppression throughout the duration of treatment (4-12 months or more). The secondary endpoints including the reduction from baseline in the serum testosterone (to < 1.75 nmol/L or 50 nmol/dL), and LH concentrations following one year treatment with 1, 2 or 4 histrelin implants are consistent among all dose groups as seen below:

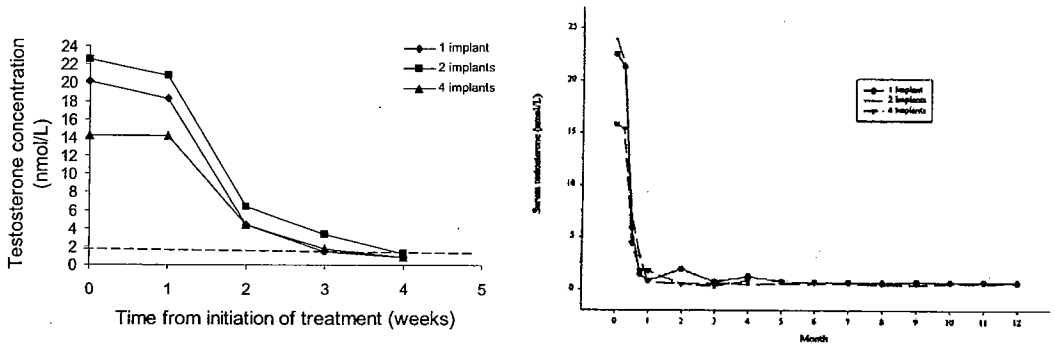


Figure 2: Mean testosterone values over 4 weeks (panel 1) and over 12 months (panel 2) for assessable patients treated during an initial cycle of therapy with one, two or four histrelin hydrogel implants.

Table 2: Testosterone concentrations (nmol/L) during the first four months of treatment with various doses of histrelin implants:

Initial Treatment (Implant)	Month	Result (nmol/L) N	Result (nmol/L) Mean	Result (nmol/L) S.D.	Result (nmol/L) Min	Result (nmol/L) Max	Change from Baseline N	Change from Baseline Mean	Change from Baseline S.D.	Change from Baseline Min	Change from Baseline Max	% Change from Baseline N	% Change from Baseline Mean	% Change from Baseline S.D.	% Change from Baseline Min	% Change from Baseline Max
1	0	13	20.1	13.8												
	0.25	13	18.3	12.6			13	-1.8	3.7			13	-8.3	20.3		
	0.5	6	4.4	3.6			6	-19.1	16.7			6	-77.6	8.2		
	0.75	5	1.5	0.5			6	-13.6	3.8			6	-89.9	4.3		
	1	7	0.8	0.4			7	-23.7	17.7			7	-92.6	7.6		
	2	13	1.7	3.7			13	-18.4	14.8			13	-86.1	27.6		
	3	13	0.7	0.2			13	-19.4	13.8			13	-93.2	6.6		
	4	13	1.2	1.9			13	-18.9	14.1			13	-90.1	12.8		
2	0	20	22.5	18.2												
	0.25	16	20.9	13.4			16	-2.8	10.1			16	-1.4	31.3		
	0.5	11	6.4	6.5			11	-21.5	21.0			11	-72.5	20.5		
	0.75	7	3.3	5.2			7	-15.0	10.5			7	-82.4	22.6		
	1	14	1.3	1.6			14	-23.3	20.6			14	-92.0	8.1		
	2	20	0.8	1.2			20	-21.7	18.3			20	-94.1	6.4		
	3	20	0.6	0.2			20	-22.0	18.2			20	-95.5	3.6		
	4	20	0.5	0.2			20	-22.0	18.2			20	-95.7	3.2		
4	0	8	14.2	4.8												
	0.25	7	14.2	8.4			7	-0.6	4.6			7	-8.2	30.5		
	0.5	6	4.4	2.1			6	-10.2	5.1			6	-67.8	20.7		
	0.75	1	1.8				1	-14.5				1	-89.0			
	1	7	0.8	0.2			7	-13.2	5.1			7	-94.2	1.7		
	2	8	0.8	0.2			8	-13.4	4.9			8	-93.7	2.9		
	3	8	0.7	0.1			8	-13.6	4.9			8	-94.8	1.8		
	4	8	1.0	0.9			8	-13.2	4.0			8	-93.2	3.2		

Table 3: Testosterone concentrations (nmol/L) during the two years of treatment with various doses of histrelin implants:

Initial Treatment (Implant)	Month	Result (nmol/L) N	Result (nmol/L) Mean	Result (nmol/L) S.D.	Result (nmol/L) Min	Result (nmol/L) Max	Change from Baseline N	Change from Baseline Mean	Change from Baseline S.D.	Change from Baseline Min	Change from Baseline Max	% Change from Baseline N	% Change from Baseline Mean	% Change from Baseline S.D.	% Change from Baseline Min	% Change from Baseline Max
1	0	9	16.2	10.3												
	1	5	0.8	0.5			5	-15.8	14.1			5	-90.4	8.1		
	4	9	1.5	2.3			9	-14.7	10.5			9	-87.4	14.7		
	12	9	0.5	0.4			9	-15.6	10.3			9	-93.7	6.4		
	24	9	0.6	0.4			9	-15.5	10.3			9	-93.4	5.9		
2	0	15	23.1	20.2												
	1	9	0.9	0.5			9	-25.8	24.3			9	-93.0	5.6		
	4	10	0.5	0.1			10	-28.7	23.3			10	-95.8	4.1		
	12	13	0.6	0.2			13	-22.5	21.7			13	-94.8	4.6		
	24	15	0.5	0.2			15	-22.6	20.2			15	-96.0	3.4		
4	0	7	12.7	2.5												
	1	6	0.8	0.2			6	-11.4	1.9			6	-93.7	1.3		
	4	6	0.7	0.2			6	-11.4	2.1			6	-93.9	1.9		
	12	6	0.6	0.3			6	-11.9	2.8			6	-94.7	3.4		
	24	7	0.6	0.1			7	-12.2	2.4			7	-95.6	1.3		

Table 4: Serum LH levels (IU/L) during the first year of treatment with various doses of histrelin implants:

	1 implant	2 implants	4 implants
Baseline	5.9 ± 4.0	8.2 ± 4.8	6.9 ± 4.1
1 month Post-dose	0.5 ± 0.4	0.5 ± 0.3	0.3 ± 0.1
12 months Post-dose	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1

Reviewer's comments:

1. While all doses achieved testosterone suppression to below castration threshold (< 1.75 nmol/L or 50 ng/dL) by week 4, the dose group employing one-implant achieved this desired endpoint as early as week 3.
2. However, testosterone values at the end of one month, 12 months and even at the end of the second year of treatment i.e. 24 months were similar across all dose groups. Therefore, it appears that the ability to achieve testosterone suppression

to below castrate levels at one month and maintenance of this suppression was uniform among all patients and was not dependent upon the dose of histrelin administered i.e. 1, 2 or 4 implants, corresponding to 50, 100 or 200 mg.

3. No statistically significant differences in serum testosterone, LH and FSH levels were observed between the groups of patients treated with a different number (1, 2 or 4) of histrelin implants.
4. There is no apparent advantage of using 2 or 4 implants over 1 histrelin implant for achieving the desired endpoints.
5. Although, this study provides demonstrative evidence of the clinical efficacy of 1, 2 or 4 histrelin implants (corresponding to 50mg, 100 mg and 200 mg) and the lack of dose-response relationship within the dose range employed, the clinical efficacy of histrelin doses lower than 50 mg was not investigated.

What are the characteristics of the exposure-response relationships for safety?

The frequency and type of adverse events associated with the use of various doses of histrelin implants are summarized below in order to correlate dose-response relationship with respect to safety.

Table 5: Frequency and type of adverse events related to the use of histrelin implants:

Table 30. Patients Experiencing Adverse Events Judged to be Related to Treatment

	Number (%) Patients Initial Histrelin Treatment			
Body System/ Preferred Term	1 implant n = 14	2 implants n = 20	4 implants n = 8	Overall n = 42
ANY ADVERSE EVENT	6 (43)	14 (70)	6 (75)	26 (62)
BODY AS A WHOLE	1 (7)	3 (15)	0 (0)	4 (10)
Asthenia	1 (7)	2 (10)	0 (0)	3 (7)
Headache	0 (0)	1 (5)	0 (0)	1 (2)
CARDIOVASCULAR	4 (29)	12 (60)	4 (50)	20 (48)
Vasodilatation	4 (29)	12 (60)	4 (50)	20 (48)
METABOLIC AND NUTRITIONAL	0 (0)	2 (10)	3 (38)	5 (12)
Gout	0 (0)	1 (5)	0 (0)	1 (2)
Peripheral edema	0 (0)	1 (5)	3 (38)	4 (10)
MUSCULOSKELETAL	0 (0)	0 (0)	1 (13)	1 (2)
Myalgia	0 (0)	0 (0)	1 (13)	1 (2)
NERVOUS	2 (14)	1 (5)	1 (13)	4 (10)
Hyperesthesia	0 (0)	0 (0)	1 (13)	1 (2)
Libido decreased	1 (7)	1 (5)	0 (0)	2 (5)
Thinking abnormal	1 (7)	0 (0)	0 (0)	1 (2)
SKIN AND APPENDAGES	1 (7)	1 (5)	1 (13)	3 (7)
Application site reaction	1 (7)	1 (5)	0 (0)	2 (5)
Sweating	0 (0)	0 (0)	1 (13)	1 (2)
UROGENITAL	0 (0)	3 (15)	2 (25)	5 (12)
Gynecomastia	0 (0)	2 (10)	0 (0)	2 (5)
Testicular atrophy	0 (0)	3 (15)	2 (25)	5 (12)

Reviewer's comments: In general, a larger proportion of patients who received two (70 %) or four (75 %) implants appear to have experienced adverse events compared to patients who received one implant (43 %). This was particularly apparent with cardiovascular related adverse events (vasodilatation). With respect to most other adverse events, no apparent dose- relationship was observed.

Concentration-response: The relationship between serum testosterone concentration and serum histrelin concentration in prostate cancer patients was characterized by a clockwise hysteresis loop, indicating an indirect pharmacodynamic relationship consistent with the mechanism of action. The lack of a direct relationship is due to the time delay between the achievement of pharmacokinetic Cmax (at 12 hours) and the desired pharmacodynamic endpoint (i.e. T suppression below 50 ng/dL occurring at ~ 28 days). This temporal delay is caused by the sensitization of pituitary receptors by histrelin during the initial time points which raises the serum testosterone above baseline concentrations. The non-typical shape of the clockwise hysterisis loop (the secondary loop on the right side) is due to the observed time delay between the Cmax (at 12 hours) and the initial testosterone peak that doesn't occur until day 2 when histrelin levels are already on the decline.

Following the initial surge in testosterone concentrations (376 ± 150 ng/dL at baseline to 530 ± 225 ng/dL on day 2), continuous exposure of the pituitary gonadotropin receptors to histrelin caused the decrease of serum testosterone concentrations to below castration levels (< 50 ng/dL) by day 28. Testosterone concentrations were then maintained at these low levels during the life of the implant in most cases, even while histrelin concentrations continued to fall.

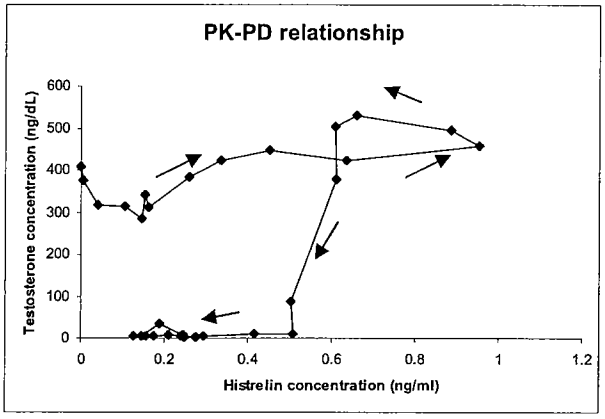


Figure 3: Indirect pharmacodynamic relationship between histrelin serum concentration and testosterone concentration as demonstrated by a clockwise hysteresis loop.

How long is the time of onset and offset of the pharmacological response or clinical endpoint?

In general, the observed time of onset of the desired pharmacological response i.e. testosterone suppression to castrate levels in the phase 2 and phase 3 trials was 3 to 4 weeks. This suppression was then maintained in most patients as long as the implant remained in the body causing sustained release of histrelin.

In the phase 2 study, **reversibility** of the observed clinical effect upon discontinuation of treatment was documented, with 4 out of 8 subjects showing the return of testosterone concentrations within 2 weeks of no treatment after a 4-month treatment period. The return of testosterone to baseline after use of histrelin implants for 29 to 37 months was somewhat slower than after 4 months of treatment, but a clear return was observed by 42 days in most patients.

Pivotal clinical study (Phase 3): All patients within the PK subset (n = 17) achieved testosterone suppression to below castration levels (< 50 ng/dL) within 4 weeks of implantation and maintained this suppression throughout the duration of the implant (52 weeks). In the overall study population (n = 138), castration at 4 weeks was not achieved in one patient and was not maintained in 4 patients over the entire 52 weeks, with occasional breakthroughs. Testosterone suppression was adequately maintained, with no acute-on-chronic occurrences, when a second implant was inserted after the removal of the first implant at the end of 52 weeks. Testosterone levels started to rise above castration levels by one month after implant removal.

Mean Serum Testosterone Values for All Patients Included in Study 301.

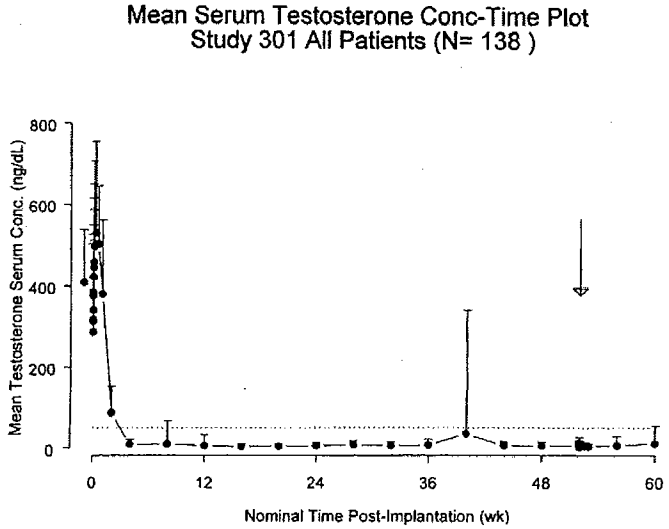


Figure 4: Mean serum testosterone concentrations (ng/dL) for all patients included in the pivotal clinical trial (# 301). The dashed line indicates castrate levels of testosterone. The arrow at 52 weeks represents timing of second dose.

Does this drug prolong the QT or QTc interval?

No in vitro data is available regarding the QTc prolongation potential of histrelin acetate (as per Dr. Krishan Raheja, pharmacology/toxicology reviewer). The sponsor also did not submit the QT data from the clinical trials in the NDA volumes (as per the medical officer, Dr. Harry Handelsman). The sponsor has not addressed the QTc prolongation potential of VANTAS (histrelin acetate implant) through a definitive study. In response to a clinical pharmacology comment reminding the sponsor to address the QT prolongation issue of histrelin at higher exposure in a definitive study, Valera pharmaceuticals has submitted a letter from cardiology consultant [ ] The following are the highlights of Dr. [ ]s preliminary correspondence to Valera:

- VANTAS™ (histrelin acetate) implants prolonged the QTcB by a mean of 6.4 msec and QTcF by 5.2 msec, when week 24 and week 60 on-treatment ECG's

were compared to baseline QTc measurements. The observed QTc increase occurs when serum testosterone levels fall to castrate levels (< 50 ng/dL). 4/97 patients had at least one QTc of > 500 msec in patients who did not have such a value at baseline. None were supposedly associated with arrhythmic events.

- A consistent QTc increase has been documented for all four approved treatment strategies producing androgen deficiencies (abarelix, goserelin, leuprolide and bicalutamide).
- The magnitude of QTc increase documented for VANTAS (~ 6 msec) is lower than the currently available options for the same indication (10-20 msec).
- The 10 adverse events experienced by 8 of the pivotal trial patients translates to a rate of 7.6 events of interest per hundred patient years and is comparable to the rates in the abarelix SBA report and the other available treatments.
- There is no direct evidence available that VANTAS™ or other drugs in this class are IKr blockers. The induction of androgen deficiency with each of these alternative therapies of advanced prostate cancer results in QTc prolongation.
- The relative cardiac safety of VANTAS is comparable to other available therapies and therefore further studies to investigate the magnitude of QT prolongation by VANTAS™ implants are not necessary.

Note: These comments were discussed with the MO/TL (Dr. Mark Hirsch) and a prospective study was not deemed critical. Clinical pharmacology agrees with the decision.

Are the dose and dosing regimen consistent with known relationship between dose-concentration-response, and are there unresolved dosing or administration issues?
The findings of Phase 2 dose-ranging study suggest that the use of 2 or 4 VANTAS™ implants in prostate cancer patients offers no additional advantage over the use of a single implant (although the % of initial responders was high in patients who received 4 implants, the statistical significance of this observation is not known). Pivotal clinical trial using a single implant containing 50 mg histrelin acetate has provided demonstrative evidence regarding the safety and efficacy of this dose. Therefore, the dosage recommendation i.e. one implant over 12 months, is consistent with the findings of the phase 2 and 3 clinical trials.

3.2.2 Pharmacokinetics

What are the basic PK parameters?
Phase 1 pharmacokinetic study: A phase 1 study to provide ADME information for histrelin was conducted as per the agency's request during the EOP2 (July 14, 1999) meeting. A Single center, open-label pharmacokinetic study of histrelin in n = 6 normal, healthy, white, male volunteers (mean age 27.7 years, mean BW 73.9 kg) was conducted to evaluate histrelin pharmacokinetics following a single subcutaneous bolus dose. Subjects received a single bolus dose of histrelin (500 μg; 10 % Mannitol solution, SC) under fasting conditions. Serum samples were collected for histrelin bioanalysis at

predose, at 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours post-dose. Urine samples were also collected but were deemed unreliable due to exceptionally high pre-dose concentrations in all six subjects ranging from 0.236 to 8.920 ng/ml (> 10 x greater than the LOQ) probably due to interference from some endogenous substance in urine.

Table 6: Individual and mean pharmacokinetic parameters of histrelin in healthy, male volunteers following a single bolus dose (500 µg, SC).

Subject	C_{max} (ng/mL)	T_{max} (hr)	λ_z (1/hr)	$T_{1/2}$(hr)	AUC_{0-t} (hr·ng/mL)	$AUC_{0-\infty}$ (hr·ng/mL)	%Extrap	CL/F (mL/min)	MRT (hr)	V_z/F (L)
1	17.90	0.75	0.13	5.31	73.73	73.95	0.31	117.87	5.05	54.21
2	10.30	2.03	0.20	3.52	40.99	41.34	0.84	210.87	4.72	64.23
3	12.20	1.50	0.21	3.36	48.20	48.42	0.47	180.02	4.08	52.43
4	14.90	1.00	0.14	5.09	54.46	55.59	2.03	156.79	4.94	69.02
5	15.20	0.75	0.23	2.99	46.26	46.45	0.41	187.64	3.35	48.58
6	10.50	1.00	0.21	3.23	39.17	39.33	0.41	221.65	3.69	61.97
N	6	6	6	6	6	6	6	6	6	6
Mean	13.50	1.17	0.19	3.92	50.47	50.85	0.74	179.14	4.31	58.40
SD	3.00	0.50	0.04	1.01	12.63	12.69	0.66	37.79	0.70	7.86
Min	[									]
Median	13.55	1.00	0.20	3.44	47.23	47.44	0.44	183.83	4.40	58.09
Max	<									>
CV%	22.20	42.85	22.80	25.81	25.02	24.95	88.20	21.10	16.31	13.46
Geometric Mean	13.22	1.09	0.18	3.82	49.31	49.68	0.59	175.46	4.26	57.96

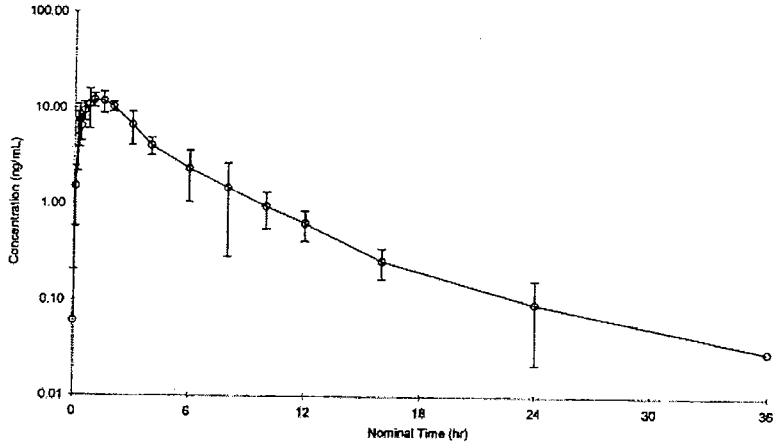


Figure 5: Mean Histrelin concentration-time profile in healthy, male volunteers following a single bolus dose (500 µg, SC).

Reviewer's comments:

1. Histrelin was detectable in serum within 5 minutes following subcutaneous administration. The peak serum concentration (C_{max}) had a mean value of 13.5 ± 3.0 ng/ml, the median time to T_{max} was 1 hour with a range of 0.75 to 2.03 hours.
2. The observed apparent volume of distribution (V_z/F) had a mean value of 58.4 ± 7.86 L and the apparent clearance, Cl/F had a mean value of 179 ± 37.8 ml/min.

3. The pharmacokinetic parameters of histrelin following administration of a single SC dose of 500 µg compare well with other GnRH agonists with a mean half-life of 4 hours, an apparent clearance of 179 ml/min and an apparent volume of distribution of 58 L.
4. The variability of the PK parameters of histrelin was moderate (< 30 %).

Phase 2 dose-finding study: A Multi-center, open-label, parallel group, dose finding, phase II study in N = 42 adult prostate cancer patients (58 to 88 years; mean age 74.2 years) was conducted to investigate the dose(s) required to adequately suppress pituitary gonadotropin and indirectly, testosterone levels and to assess the pharmacokinetics of the histrelin hydrogel implant in this patient population. Subjects received one, two, or four histrelin implants (corresponding to 50, 100 or 200 mg histrelin). The duration of administration varied from 4 months to 30 months. Blood samples for analysis of histrelin and testosterone concentrations were obtained at pre-dose, 1, 2, 4, 8, 12, 16, 18, 20 weeks (testosterone only at week 20), then at 4, 5, 6, 7, 8, 9, 10, 11 and 12 months.

Table 7: Pharmacokinetic parameters of histrelin disposition in human serum following administration of 1, 2, or 4 implants. (Values represent mean ± SD of all observations in that treatment group. N represents the number of treatment sequences that employed the specified number of implants.)

	No. of Implants	Weeks From Implant	AUC_{16} ng.week/ml	AUCall ng.week/ml	Cpav ng/ml
Mean(n=14)	1	36.99	3.69	5.90	0.19
SD		16.57	2.01	2.81	0.11
%CV		44.80	54.45	47.68	57.45
Min		[			]
Max					
Mean(n=36)	2	42.20	12.09	19.73	0.52
SD		15.48	6.31	11.69	0.31
%CV		36.69	52.16	59.24	59.77
Min		[			]
Max					
Mean(n=7)	4	50.99	21.73	50.21	0.99
SD		18.23	8.76	35.57	0.45
%CV		35.76	40.33	70.84	45.26
Min		[			]
Max					

AUC_{16}: Partial area under the curve until 16 hours
AUCall: Area under the curve over the weeks of implants
Cpav: Average plasma concentration

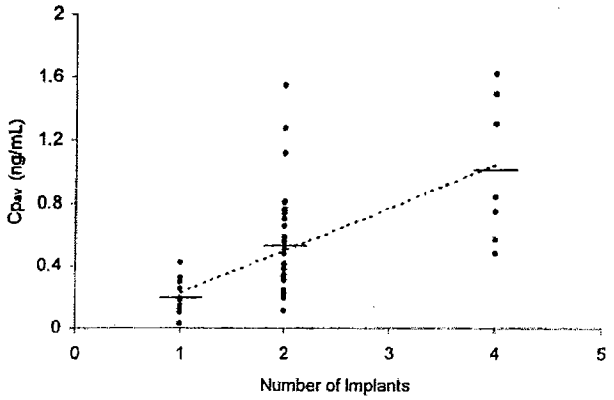


Figure 6: Change in the average serum concentration (Cpav) of histrelin with increasing number of implants. The solid lines indicate mean data.

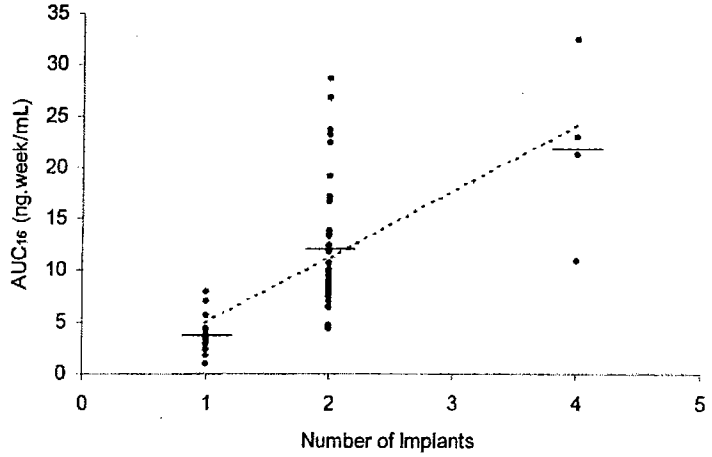


Figure 7: Change in area under the curve to 16 weeks (AUC_{16}) of histrelin with increasing number of implants. The solid lines indicate mean data.

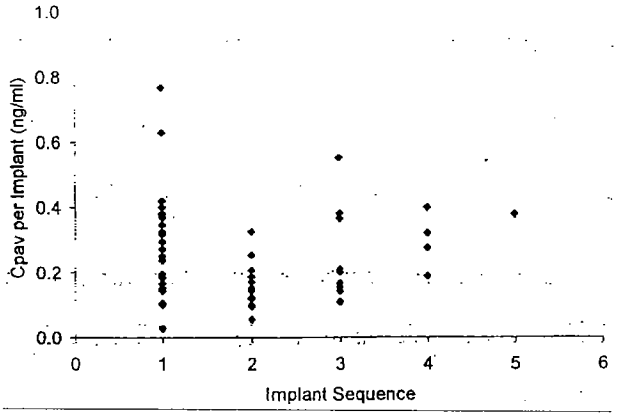


Figure 8: Effect of implant sequence on average plasma concentrations (Cpav) of histrelin.

Reviewer's comments:

1. The pharmacokinetic parameters of histrelin released from the implants (AUC_{all}, AUC_{16} and Cpav) exhibited moderate to high variability (CV 40-70 %).

2. Dose-proportionality: Assuming that the actual drug content (50 mg per implant) and the in vivo release rate (~50 μg/day) were fairly consistent among all the implants, the pharmacokinetic parameters AUC_{16} and Cpav appear to increase approximately in proportion to the dose. With doses of 1 (50 mg), 2 (100 mg) and 4 (200 mg) histrelin implants, the AUC_{16} was 3.7, 12.1 and 21.7 ng/week/ml, respectively.
3. The implant sequence did not appear to have any influence over the average plasma concentrations (Cpav) of histrelin. This suggests that the contribution of residual concentrations from previous implants was minimal and there is no change in pharmacokinetics with multiple treatment cycles.

Pivotal study # 301 (Phase 3): A Multi center, Phase III, open-label study was conducted in 138 male prostate cancer patients, aged 53 to 92 years (median age 75 years; 32 black, 99 Caucasian and 7 Hispanic). Patients had histological confirmed advanced or metastatic adenocarcinoma of the prostate, disease staging III or IV. All subjects received one VANTAS™ implant containing 50 mg of histrelin acetate on day 1. This dose was selected because it was well tolerated and effective in phase 2 dose-ranging study. Histrelin serum concentrations were quantified in a pharmacokinetic subgroup of 17 patients, at pre-dose, 5, 15, 30, 45 min, 1, 2, 4, 6, 8, 12, 24, 48, 96 hours following implantation, weeks 1, 2 and monthly thereafter until week 52. Serum samples for histrelin analysis were obtained at each monthly visit in renal (n = 42) and hepatic failure (n = 1) patients identified at baseline. For renal (n = 14) or hepatic (n = 12) insufficiency patients identified post-baseline, serum samples for histrelin analysis were obtained at each monthly visit thereafter. Histrelin concentrations were not obtained from unimpaired patients who were not part of the PK subset. Due to high pre-dose histrelin urinary concentrations observed in the phase 1 study suggesting interference in the RIA from endogenous substances, urine from the phase 3 trial was not analyzed as agreed during a pre-NDA meeting with the division on August 12th, 2003.

After 52 weeks, the first implant was removed and a new one inserted and patients were monitored for an additional 8 weeks for testosterone suppression with continued treatment. The total duration of treatment was therefore 60 weeks (14 months). Out of approximately 113 patients who received a second implant, histrelin concentrations were obtained from 15 PK patients. Only 4 of these patients had intensive pharmacokinetic (histrelin) data following the second implant, while ~ 13 patients had infrequent sampling at 48 hours, 1, 4 and 8 week time points. Testosterone concentrations were obtained from 57 patients at 48 h and 7 days for the assessment of acute-on-chronic effects.

The following parameters were determined for the first implant (52 weeks) as well as the second implant (8 weeks): Cmax, Tmax, Cavg (0-96 h), Cavg (0-52 wk), AUC (0-96h), AUC (0-8 wk), AUC (0-16 wk), AUC (0-52 wk) and SLP, which is the terminal log-linear regression slope associated with the decline of histrelin serum concentrations versus time data. Some of the removed implants were analyzed for residual histrelin content in order to estimate the amount delivered in vivo.

Serum histrelin concentration after the first implant: Pharmacokinetic evaluation

Table 8: Pharmacokinetics of histrelin release from the initial 50 mg VANTAS implant.

Parameter	All Patients (N=17)	
	Mean	SD
Cmax, ng/mL	1.10	0.375
Tmax, hr[a]	12.00	6 hr-36 wk
Cavg(0-96hr), ng/mL	0.697	0.226
Cavg(0-52wk), ng/mL	0.265	0.0685
AUC(0-96hr), ng·wk/mL	0.398	0.129
AUC(0-8wk), ng·wk/mL	3.99	1.24
AUC(0-16wk), ng·wk/mL	6.65	1.72
AUC(0-52wk), ng·wk/mL	13.8	3.55
SLP, wk^{-1}	0.0350	0.0193

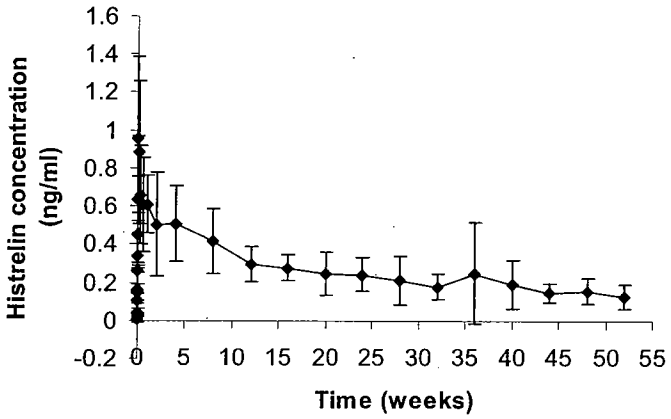


Figure 9: Histrelin serum concentration versus time profile following release from one VANTAS™ subdermal implant containing 50 mg histrelin acetate (n = 17).

Reviewer's comments:

1. Following insertion of the single 50 mg implant, histrelin was rapidly absorbed into the systemic circulation (within 5 minutes) in 12 out of 17 PK patients.
2. The mean histrelin serum concentration was 1.1 ± 0.17 ng/ml and the levels declined gradually over the 52 weeks, with a terminal elimination rate constant of 0.035 ± 0.02 wk^{-1} that corresponds to a elimination half-life of 20 weeks.
3. The peak concentrations of histrelin (C_{max}) occurred at a median value of 12 hours, with a T_{max} range of 6 hours to 36 weeks. The observed delay in T_{max} in two patients (10/006, 10/021) at 36 and 8 weeks respectively did not affect the timely achievement of the pharmacodynamic endpoints in these patients. Both

patients achieved castration by week 4 and maintained suppression throughout the duration of implant.

4. The overall inter-subject variability in the serum histrelin concentrations and pharmacokinetics for the first histrelin implant (n =17) was moderate with CV ranging from 26-34 % for the various observed concentrations and 26-32 % for the various AUCs. The variability in pharmacokinetics was much lower in this phase 3 study compared to the phase 2 dose-finding study.

5. The $AUC_{0\text{-}16\ weeks}$ values (mean 3.69 ± 2.01 ng.wk/ml; n =14) observed in the phase 2 study were significantly lower than the results of the phase 3 study (mean 6.65 ± 1.72 ng.wk/ml; n = 17); p=0.0001 for all patients and p = 0.03, when renal impaired patients' data is excluded). The observed differences in serum histrelin concentrations during the phase 2 and 3 studies may be due to several reasons including physiological status of the patients, specificity of the bioanalysis method employed etc.

Serum histrelin concentration after the second implant: Pharmacokinetic evaluation

Table 9: The average serum histrelin concentrations obtained following the first and second implants are tabulated below:

Post-Implantation Time Point	**First Implant (ng/ml)**	**Second Implant (ng/ml)**
48 hours	0.66 (n = 17)	0.692 (n =43)
1 week	0.557 (n = 64)	0.557 (n = 40)
4 weeks	0.457 (n = 46)	0.387 (n = 25)
8 weeks	0.399 (n = 41)	0.265 (n = 16)

Table 10: Summary table of mean histrelin pharmacokinetics in **four** patients with advanced prostate cancer who received both first and second 50 mg histrelin subdermal implants (0-8 week data only) and had intensive PK sampling (note that all 4 patients had renal impairment identified at baseline):

Parameter	First Implant (Week 1 to 52)		Second Implant (Week 52 to 60)	
	Mean	SD	Mean	SD
Patient Subgroup	Renal	Renal	Renal	Renal
Cmax, ng/mL	1.19	0.177	2.66 (1.20)[c]	2.94 (0.336)[c]
Tmax, hr[b]	12.00	12 hr-36 wk	18.00 (24.0)[c]	8-48 hr (12-48 hr)[c]
Cavg(0-96hr), ng/mL	0.749	0.203	1.00 (0.895)[c]	0.393 (0.405)[c]
AUC(0-96hr), ng·wk/mL	0.429	0.117	0.573 (0.512)[c]	0.225 (0.233)[c]
AUC(0-8wk), ng·wk/mL	4.78	1.90	3.85 (3.92)[c]	1.90 (2.32)[c]
SLP, wk^{-1}	0.0533	0.0316	0.279 (0.227)[c]	0.186 (0.190)[c]

[a] Patients 10/003, 10/005, 10/006, and 17/001.

[b] Expressed as median and range.

[c] Values in parentheses represent results from patients 10/003,10/006, and 17/001, only.

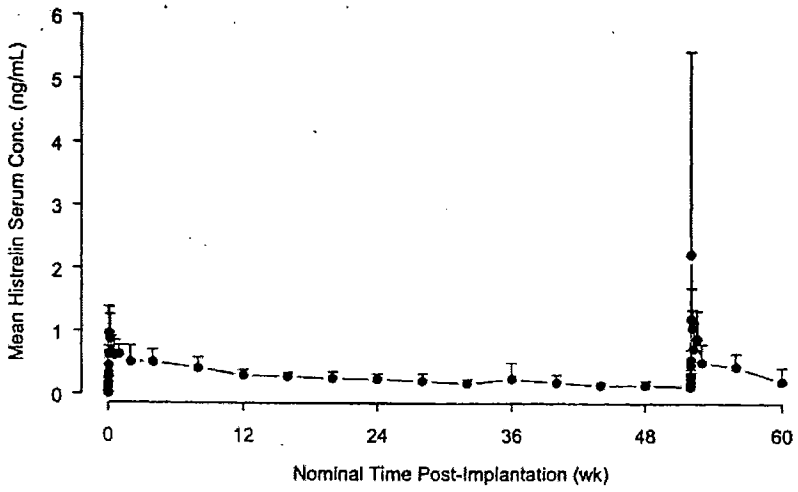


Figure 10: Mean histrelin concentration versus time profiles obtained from n=17 patients (PK subset) of study # 301, following insertion of the first and second VANTAS ™ implants (note that only 4 out of 17 patients had intensive sampling during the first 96 hours following the second implant).

Reviewer's comments:

1. Histrelin concentrations following first and second implants were comparable (especially when patient 10/005 was excluded) indicating that there is no change in histrelin pharmacokinetics upon repeated treatment with the implant.
2. A single occurrence of a large variability observed during the second treatment cycle was due to patient 10/005, who demonstrated a Cmax value of 7.05 ng/ml, which was almost six-fold higher than the mean obtained for the three other patients. The reason for the observed high concentrations of histrelin in this patient is not clear, although variations in drug release from the implant (dose dumping) cannot be ruled out. However, the testosterone concentrations in this patient remained suppressed below castration.

What are the characteristics of drug absorption?

Subcutaneous Bolus: Following administration of a single subcutaneous bolus dose (500 μg), histrelin was detectable in serum within 5 minutes in all six volunteers. The peak serum concentration (C_{max}) was observed at a median T_{max} of 1 hour (0.75-2.03 hours) and had a mean value of 13.5 ± 3.0 ng/ml.

Subcutaneous Implant: Following insertion of the single 50 mg VANTAS™ implant, histrelin was rapidly absorbed into the systemic circulation (within 5 minutes) in 12 out of 17 PK patients. Peak concentrations (1.1 ± 0.17 ng/ml) were however, achieved more slowly following the VANTAS™ subcutaneous implant, with C_{max} occurring at ~12 hours. Due to the continuous release of histrelin from the implant, serum histrelin concentrations were sustained throughout the life of the implant, in contrast to the bolus dose administration that demonstrated rapid decline in concentrations, as shown below.

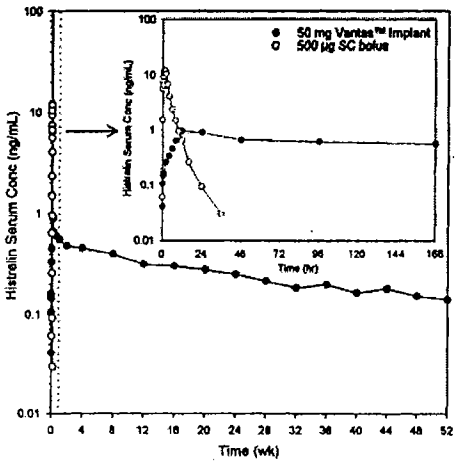


Figure 11: Serum histrelin concentration versus time profile observed after a single subcutaneous VANTAS™ implant. Histrelin concentrations after the implant are shown in comparison to the concentrations after a single subcutaneous bolus dose.

What are the characteristics of drug distribution?

Following a single subcutaneous bolus dose of histrelin, the observed apparent volume of distribution (V_z/F) was of 58.4 ± 7.86 L. The fraction of drug unbound in plasma as measured in vitro was 29.5 ± 8.9 %.

What are the characteristics of drug metabolism?

The in vitro metabolism of histrelin was investigated by incubating the drug (50 µM) for 60 minutes with cryopreserved human hepatocytes. Sample analysis was performed on an [redacted] with separation of drug and metabolites using [redacted] chromatography. A single metabolite resulting from the C-terminal dealkylation was identified as shown below:

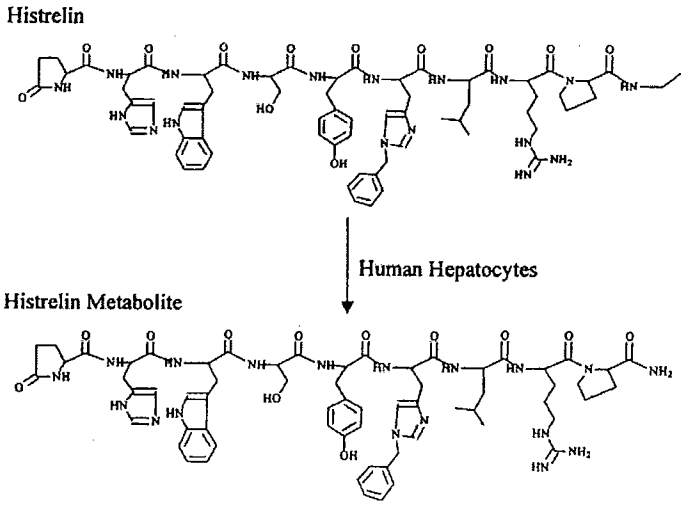


Figure 12: In vitro metabolism of histrelin

Circulating metabolites of histrelin have not been specifically identified. However, as the structure of histrelin is very similar to other GnRH agonists such as leuprolide, nafarelin, goserelin etc, the metabolism is also likely to be similar, with hydrolysis of amino acids resulting in peptide fragments, in addition to the dealkylated product resulting from hepatic microsomal metabolism, identified in vitro.

Following a subcutaneous bolus dose in healthy volunteers, the apparent clearance of histrelin was 179.14 ± 37.79 ml/min and the terminal half-life was 3.92 ± 1.01 hours. The estimated clearance value following administration of the 50 mg VANTAS™ implant in 17 prostate cancer patients with intensive PK sampling was 173.84 ± 56.53 ml/min.

What are the characteristics of drug excretion?
No formal drug excretion studies were conducted with histrelin.

Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Histrelin exposure appeared to increase linearly with dose as shown previously in Table 7. The linear relationship between the dose of histrelin (i.e. number of implants) and the exposure parameters ($AUC_{0\text{-}16\ weeks}$ and C_{pav}) is also demonstrated in figures 6 and 7.

What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The pharmacokinetics of histrelin in healthy male volunteers was characterized by low to moderate variability for the various concentrations and AUCs obtained (13.5 - 42.3 %). In prostate cancer patients, the overall inter-subject variability in the serum histrelin concentrations and pharmacokinetics for the first histrelin implant was moderate, ranging from 26 to 34 % CV for the various calculated serum concentrations and AUC parameters. The variability may be partly due to the physiological status of the patients. Patients with renal impairment tended to have slightly, but fairly consistently higher histrelin serum concentrations and AUC values, compared to normal renal function patients as will be further discussed below.

3.3 Intrinsic Factors

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the efficacy or safety responses?

Effect of renal and hepatic impairment on histrelin pharmacokinetics:

Data from the PK subgroup: Within the subset of 17 PK patients of the pivotal study # 301, 10 were classified as renal-impaired and 2 as hepatic-impaired. This group of patients had intensive sampling over the first 96 hours post-implant, weekly for the first 2 weeks and monthly thereafter.

Non-compartmental analysis of the PK patient data demonstrated that the renal impairment patients had slightly, but fairly consistently higher histrelin concentrations and AUC relative to the normal renal and hepatic function patients. The pharmacokinetic parameters of individuals within the PK subset (n = 17) of the pivotal clinical trial are presented below according to their renal/hepatic function category.

Table 11: Mean histrelin pharmacokinetics in patients with prostate cancer following the first 50 mg histrelin subdermal implant, classified according to their renal/hepatic function status.

Summary of Mean Histrelin Pharmacokinetics in Patients with Advanced Prostate Cancer Following First 50 mg Histrelin Subdermal Implant

Parameter	All Patients (N=17)		Normal Renal and Hepatic Function (N=5)		Renal Impairment (N=10)		Hepatic Impairment (N=2)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cmax, ng/mL	1.10	0.375	0.856	0.294	1.28	0.337	0.832	0.323
Tmax, hr[a]	12.00	6 hr-36 wk	12.00	12-24 hr	12.00	6 hr-36 wk	677.75	12 hr-8 wk
Cavg(0-96hr), ng/mL	0.697	0.226	0.576	0.114	0.802	0.178	0.472	0.438
Cavg(0-52wk), ng/mL	0.265	0.0685	0.247	0.0837	0.292	0.0527	0.193	0.0417
AUC(0-96hr), ng·wk/mL	0.398	0.129	0.329	0.0654	0.459	0.102	0.270	0.251
AUC(0-8wk), ng·wk/mL	3.99	1.24	3.36	0.692	4.58	1.31	2.91	0.127
AUC(0-16wk), ng·wk/mL	6.65	1.72	5.77	1.18	7.48	1.72	5.07	0.375
AUC(0-52wk), ng·wk/mL	13.8	3.55	12.8	4.35	15.2	2.71	10.0	2.20
SLP, wk^{-1}	0.0350	0.0193	0.0259	0.00711	0.0426	0.0227	0.0232	0.00325

[a] Expressed as median and range.

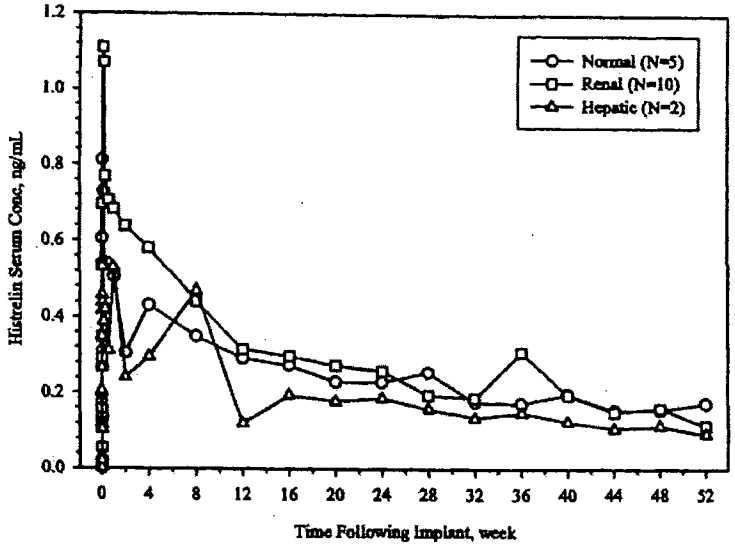


Figure 13: The histrelin serum concentration versus time profiles for the PK subset of patients plotted according to the renal/ hepatic function classification.

Reviewer's comments:

1. PK subgroup patients who had mild to moderate degree of renal impairment (Cl_{cr}: 30-60 ml/min) exhibited higher histrelin concentrations and AUCs relative to the normal renal function patients.

2. The mean values for C_{max}, $AUC_{0\text{-}96\ hours}$, $AUC_{0\text{-}8\ weeks}$, $AUC_{0\text{-}16\ weeks}$ were 49 %, 39 %, 36 % and 29 % higher in impaired renal function patients relative to the normal patients.
3. The observed difference was more pronounced in the earlier time points as seen for the C_{max} and $AUC_{0\text{-}96\ hours}$ values in renal-impaired patients ($p = 0.03$ and 0.01, respectively, compared to normal patients).
4. These differences appear to diminish with time and at the end of 52 weeks of duration, the AUC0-52 weeks was approximately 18 % *($p = 0.23$)* higher in renal impaired patients compared to normal patients. It is important to note that because there are insufficient numbers of subjects in each subgroup, the above analysis should be used to understand the general trend but should not be used for making conclusive quantitative comparisons.

Data from the entire study population: Within the entire study population (n=138), 55 patients were classified as renal-impaired (41 at baseline and a further 14 during the course of treatment), 13 were hepatic-impaired (1 at baseline and 12 post-baseline) and the remaining 73 had no impairment of renal or hepatic function (normal function). 39 out of 41 renal-impaired patients had creatinine clearance values between 30 and 60 ml/min (mild to moderate impairment). Two patients had severe renal impairment with creatinine clearance values between 15 and 30 ml/min.

The sponsor uses the NCI common toxicity criteria (shown below) to classify patients according to the severity of hepatic impairment. Under the protocol for this study, patients with any value for AST that exceeded 54 U/L or a value for ALT that exceeded 52.5 U/L (patients older than 68 years) or 64.5 U/L (patients younger than 68) or a value for bilirubin that exceeded 3.0 mg/dL were classified as "hepatic impaired".

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Bilirubin	WNL	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Effect of renal impairment: In the entire pivotal study population, renal impairment appeared to result in higher histrelin serum concentrations compared to unimpaired patients. As seen in the box and whisker Plots, this trend is most apparent for patients (n = 2) with severe renal impairment i.e. creatinine clearance < 30 ml/min (sponsor incorrectly labels this as moderate impairment).

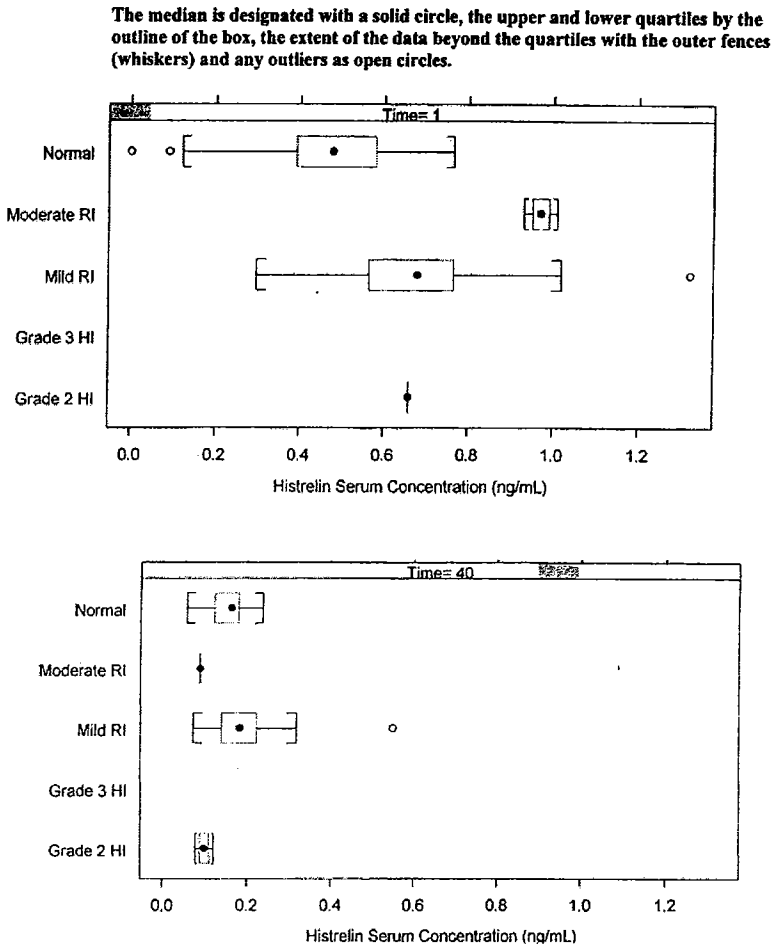


Figure 14: Impact of renal impairment on histrelin serum concentrations during week 1 and week 40 post-implantation.

- It was apparent from the box and whisker plots that after ~ 40 weeks following implantation, the observed differences in exposure were considerably smaller compared to normal RH population, probably due to the lower serum histrelin concentrations at these later time points.
- A comparison of the frequency of adverse events between normal, renal and hepatic impaired patients did not show any discernible differences between these subgroups.

Table 12: Classification of adverse events based on renal or hepatic function status

Adverse event category	Normal (%)	Renal (%)	Hepatic (%)	Total % ADR
Blood & Lymphatic system	13	6	15	**10**
Cardiac	20	22	8	**20**
Eye	4	6	8	**5**

Gastrointestinal	27	28	31	28
Hepatobiliary	0	4	31	4
Immune system	1	9	0	4
Infections	44	44	46	44
Investigations	18	19	38	20
Metabolism & nutritional	20	20	23	20
Musculoskeletal	58	37	54	49
Neoplasms	11	9	31	12
Nervous system	35	28	8	30
Psychiatric	14	20	23	17
Renal & urinary	25	43	38	33
Reproductive & breast	25	19	8	21
Respiratory/thoracic	31	15	46	26
Skin	17	9	38	16
Vascular disorders	82	61	46	70

- In order to quantify the impact of renal and hepatic impairment within the entire population (not just PK patients), the average concentration was determined by pooling all data for the particular subpopulation. This calculation assumes that the sampling time points are well-distributed over the profile. When only the baseline identified (i.e. prior to dosing) renal impaired patients (n = 40) were considered, the average serum concentration of histrelin was 0.363 ng/ml compared to 0.260 ng/ml in unimpaired patients (n = 53) i.e. ~ 30 % higher in renal impairment.
- In n = 13 post-baseline identified (i.e. at some point after dosing) renal impairment patients, the mean value for C_{pav} was lower (0.223 ng/ml). Because renal impairment in these patients was identified later in the study, concentration data from earlier time points was not available. Because concentrations at these earlier time points (surrounding C_{max}) would be the highest during any given dosing period, absence of these values in the calculation of C_{pav} will result in apparently lower concentrations in these patients.
- When patients were categorized into renal impairment categories based on the laboratory values obtained at each sampling time points (i.e. changing renal function status for each patient at each visit as opposed to one pre-set status identified prior to dosing), average histrelin serum concentration in the renal impairment subgroup was approximately 50 % higher than the calculated unimpaired average, with a value of 0.392 (n = 42) compared to 0.264 ng/ml (n = 92).
- The C_{pav} of histrelin in a patient classified at baseline as hepatic-impaired (n = 1) was 0.220 ng/ml compared to 0.260 ng/ml in unimpaired patients. The C_{pav} of histrelin in post-baseline identified hepatic-impaired patients (n = 10) was 0.252 ng/ml. When hepatic function status associated with each patient visit was considered (data points from n = 7 patients), the average histrelin concentration in the hepatic impairment subgroup was again slightly lower (0.237 ng/ml) compared to unimpaired average (data from n = 92 patients) of 0.264 ng/ml.

Reviewer's comments:

1. An overall trend for a higher histrelin exposure is apparent in renal-impaired patients compared to normal renal function patients. This trend was apparent for patients with all degrees of renal impairment (mild to severe i.e. CL_{cr} ranging from 15-60 ml/min). Due to the observed safety and efficacy profile of histrelin implants in the renal impairment patients, no changes in dosing are anticipated.
2. Although 13 patients were documented by the sponsor to have elevated hepatic enzyme or bilirubin levels (NMT 3x ULN) at one or more visits, these values returned to the normal range by the patient's next visit. The sponsor concludes that there was no evidence of clinical hepatic impairment in the pivotal study patients and the occasional elevations in the hepatic enzymes are believed to be random anamolous laboratory results that commonly occur when studying older patients with various underlying diseases and who are on a variety of concomitant medications. DRUDP medical reviewer Dr. Handelsman also confirmed that there were no cases of clinically significant hepatic impairment within the study population. Based on these observations, no conclusions can be made regarding the effect of hepatic impairment on histrelin exposure.

Effect of race on histrelin pharmacokinetics: The pivotal study population consisted of 99 Caucasian, 32 black and 7 Hispanic patients. At least one histrelin measurement was available for 30 black, 77 Caucasian and 7 Hispanic patients. The impact of race was investigated by constructing box and whisker plots at various time points during the treatment. A representative plot is shown below:

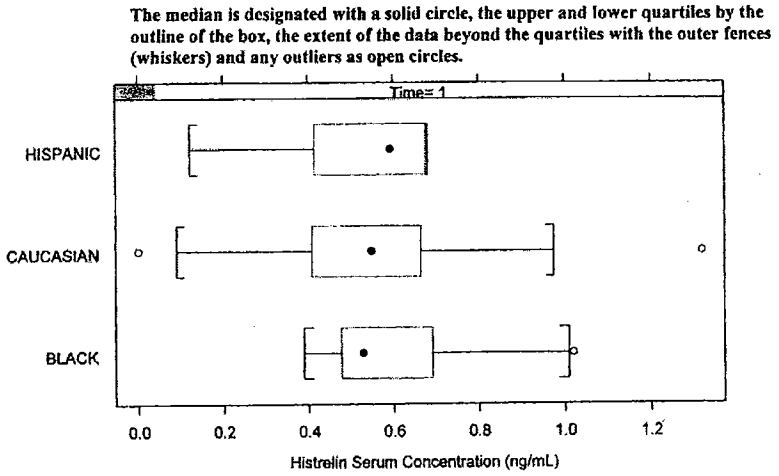


Figure 15: Impact of race on histrelin serum concentration.

Reviewer's comments:

Blacks, Caucasians and Hispanics did not exhibit any demonstrable differences in histrelin pharmacokinetics.

Effect of age on histrelin pharmacokinetics: The median age of the prostate cancer patients in the pivotal study # 301 was 75 years, with a range of 53-92 years. The vast majority of these patients (89.9 %) were of age 65 years or over. Within the age group studied, no impact of age on histrelin pharmacokinetics was discernible from the available data.

What dosage regimen adjustments, if any, are recommended for each of these groups?

Despite the observed increases in histrelin concentrations with renal impairment, the due to the wide safety margin of histrelin, no implications for drug dosing are anticipated (also particularly difficult considering the nature of the drug delivery system).

3.4 Extrinsic Factors

What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

None.

Is there an in vitro basis to suspect in vivo drug-interactions?

No specific drug-drug interaction studies have been conducted for the histrelin hydrogel implant. However, the sponsor claims that given the minimal involvement of hepatic microsomal enzymes in the metabolism of GnRH agonists, induction or inhibition of drug metabolism of other drugs is unlikely. As the extent of protein binding is not extensive (average fraction unbound is 29.5 %), protein binding interactions are unexpected. Also, no pharmacokinetic drug-drug interactions are reported for any other GnRH agonists. In addition, the pivotal clinical trial patients (n = 138) were older men with various ailments and who were simultaneously on several different prescription and over the counter medications while on treatment with VANTAS™ implant. However, no drug-drug interaction based adverse events were reported in this study.

Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Although in vitro metabolism study demonstrated presence of a dealkylation product suggesting involvement of hepatic microsomal enzymes, the specific involvement of a particular class of enzymes has not been investigated. Furthermore, the role of genetics in the metabolism of histrelin is not known.

Is the drug an inhibitor and/or inducer of CYP enzymes?

Enzyme induction/inhibition potential of histrelin has not been investigated.

Are there other metabolic pathways that may be important?

Other possible route of metabolism of histrelin may include formation of peptide fragments due to peptidase mediated hydrolysis of C-terminal amino acids. Although circulating metabolites of histrelin have not been identified, due to structural similarity

with other GnRH agonists such as goserelin, nafarelin and leuprolide that are predominantly metabolized via peptidases, it is likely that similar metabolic pathway may exist for histrelin.

What other co-medications are likely to be administered to the target patient population?

Subjects are old men with a variety of co-morbidities involving all organ systems and requiring a large number of varied medications.

3.5 General Biopharmaceutics

Is the proposed to-be-marketed (TBM) formulation similar to the clinical trial formulation?

The clinical trial and TBM formulations are identical. Hence no bridging studies are necessary.

3.5.1 Dissolution

Proposed in vitro dissolution method for VANTAS™ implants:
Apparatus:
Temperature:
Shaker speed: RPM
Elution medium: Physiological Saline
Volume: 10 ml
Sampling: Day 1, Day 7, Day 14, Day 21 and Day 28.
Analysis: HPLC with UV detection
At the above mentioned time points, implants are transferred to new vials containing fresh saline and the saline from which the implant was removed is retained for analysis. Only samples from Day 1, Day 21 (week 3) and Day 28 (Week 4) are analyzed for histrelin content using HPLC method, while the Day 7 and Day 14 samples are discarded. The amount of histrelin released during that week is obtained by multiplying the concentration by the saline volume. The elution rate of histrelin from the implant is expressed as µg /day.

Proposed release specifications: The sponsor is proposing combined specifications for the initial and stability release testing.

Table 13: Proposed dissolution specifications for VANTAS™ histrelin acetate implants.

The average release rate over 52 weeks was determined for n = 10 implants from clinical Lots 508 and 510. The observed release rates were 55.95 and 56.91 µg/day, respectively. For Lot # 511, in vitro release data is available only until week 30. The average histrelin release rate from Lot # 508 over 30 weeks was 72.36 µg/day and this compares well to the average release over 30 weeks for lots 508 and 511 (67.9 and 70.5, respectively), suggesting uniformity of histrelin release from the implants across various lots.

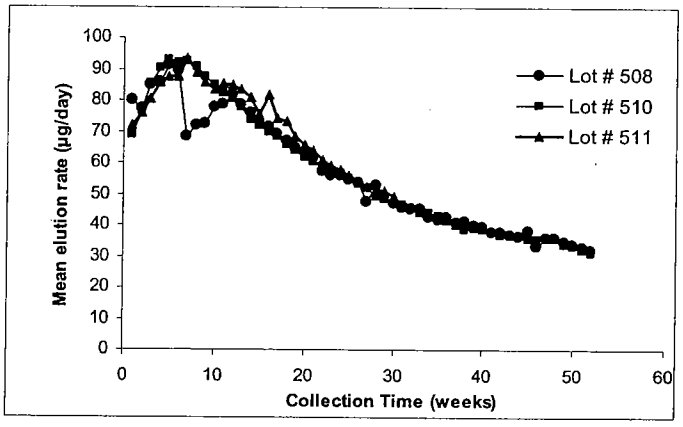


Figure 16: In vitro release profile of histrelin from various clinical lots used in the pivotal study.

Day 1 elution:

Table 14: Day 1 elution rate data for implants with a shelf-life [ ]

Elution Rate Data Lot #510			
Implant	*Day 1 (µg)*	*Week 3 (µg/day)*	*Week 4 (µg/day)*
510-1	367	80	78
510-2	388	79	77
510-3	391	88	83
510-4	619	96	88
510-5	380	83	80
510-6	368	80	77
510-7	375	80	77
510-8	386	82	80
510-9	395	86	84
510-10	375	81	78

Week 3 and Week 4 release:

Table 15: Histrelin elution rate data for week 3 and week 4 for product stored at 2-8°C for up to 24 months.

	Description		
	Week 3 (n=78)	Week 4 (n=78)	Week 3 and Week 4 Combined (n=156)
Average Elution Rate, ug/day	86.6	87.4	87.0
Standard Deviation	15.3	12.8	14.1
RSD	17.7%	14.6%	16.2%
Range	[ ]		
Xbar +/- 3s	40.7 – 132.5	49.0 – 125.8	44.7 – 129.3
Natural Tolerance Limits[1]	[ ]		

Table 16: Histrelin elution rate data from fresh batches of implants (month 0) during week 3 and week 4

Histrelin Initial Release Elution Rate Data – Weeks 3 and 4

	Summary Statistics - All Data Combined (Lots 508, 510, & 511)	
	Elution Rate Data, ug/day	Percentage of Avg.
Avg:	84.8	100%
SD:	12.4	14.60%
Min:		
Max:		

Reviewer's comments:

1. The Day 1 specification of NMT [ ]µg/day appears to have been based on data from only one implant (# 510-4; 619 µg/day) in the elution study. All other implants studied had a day 1 elution rate of < 400 µg/day. **Therefore, the Day 1 release specification can be modified to [ ]µg/day, with NMT [ ] implants [ ] µg/day.**
2. The observed range for initial release from all lots of histrelin implants is [ ] and the observed release range for all data combined (initial plus stability) is [

] µg/day. The range proposed by the sponsor is [ ] µg/day and is intended to allow for 3 standard deviations (mean ± 3s). Based on the observed in vitro release data, the release rate proposed by the sponsor for weeks 3 and 4 appears very broad. However, because the proposed dissolution testing criteria are stringent in that they require each individual implant to satisfy the proposed release rate, **the week 3 and week 4 release could be modified to [ ] µg/day**.

Note: The above suggestions were conveyed to the sponsor in a CMC letter and the sponsor has agreed to incorporate all the suggested changes into the final elution specifications (letter dated 08/19/2004). The final specifications are shown in the table below:

Table 17: Final revised elution rate specifications for VANTAS implants.
This table contains the revised Specifications of Elution Rate for Finished drug product **(Bolded).**

[

]

In vitro/in vivo correlation (IVIVC): The cumulative in vivo input from the histrelin hydrogel implant was estimated by deconvolution for comparison to the in vitro release profile. For deconvolution, the mean serum histrelin concentration data for all patients in study 301 were used employing mean data from SC bolus dose (study 07-03-100) as a reference for construction of the unit impulse response function (UIR = $0.107\ e^{-130t} + 0.00796e^{-25.5t} - 0.155e^{-209t}$, where t is in units of wk and UIR has units of L^{-1}).

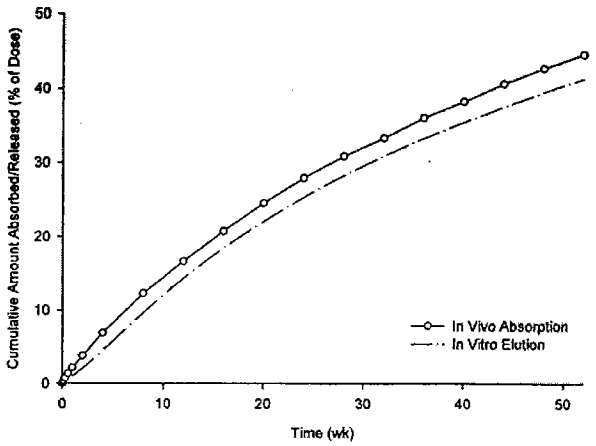


Figure 17: Comparison of cumulative in vitro release and cumulative absorption as a function of time.

The cumulative amounts released in vitro and in vivo are very similar, with a value of 41.4 % in vitro and 44.7 % in vivo after 52 weeks. Throughout the profile, the in vivo release slightly exceeded the in vitro release.

Reviewer's comments:

Valera has proposed an IVIVC model for VANTAS™ implants, employing a single formulation. Although this data was submitted as part of the NDA submission, no formal claim for an IVIVC was made by the sponsor. Because IVIVC was discussed by the sponsor with the division during a pre-NDA meeting (August 12, 2003), this issue was further discussed in DPE 2 (Drs Malinowski, Parekh and Apparaju) and the following points ensued:

- The development of the proposed IVIVC has limitations in that only mean data from the pivotal trial lots was employed in demonstrating the in vitro-in vivo correlation rather than individual lot data.
- More importantly, the correlation was not validated using either internal or external data for the determination of predictability error.
- The submitted data therefore, cannot be considered a validated and acceptable IVIVC.

Note: This will not be an approvability issue as the sponsor did not make any changes to the TBM formulation. The comments were conveyed to the sponsor (09/27/04).

3.6 Analytical methods

Histrelin, testosterone and LH serum concentrations were quantified using validated analytical techniques. The major metabolites of histrelin are not known and have not been quantified in this study.

Serum histrelin concentrations: Serum samples from studies # 07-03-100 (Phase 1 ADME) and # 301 (Phase 3) were assayed for histrelin by [redacted]

[redacted] Samples from study # BAR-002-0591A-USA (phase 2 study conducted by Roberts) are reported to have been assayed for histrelin by [redacted]

[redacted] Detailed data are available regarding the

validation and qualification of the method used for the phase 1 and phase 3 studies. Limited information is available for the phase 2 study conducted by Roberts.

Method: Histrelin concentrations in human serum extracts were quantified using a validated radioimmunoassay (RIA). The method was . [ ] antibody RIA that utilized a delayed tracer and rabbit antiserum.
Method: Serum samples were first purified using [ ] extraction techniques (96-well plate format employing a ^{3}H internal standard for extraction efficiency correction) then incubated with the tracer (^{125}I-Histrelin) and antibody (rabbit anti-histrelin). The histrelin (antigen)-antibody complex was precipitated using a [ ] second antibody and polyethylene glycol and the radioactivity in the precipitate was counted on a [ ] counter.
In addition to the assay precision and accuracy, antiserum cross-reactivity [ability of an antibody to bind heterologous antigens (non-target analytes)] was also determined.

Results of the bio analytical assay method validation:

- LLOQ: ~ 16 pg/ml; ULOQ: 2500 pg/ml
- Accuracy and Precision:

	Inter Assay		Intra Assay	
	Accuracy (% error)	Precision (% CV)	Accuracy	Precision
Ultralow	93.6	16.7	85.0	16.4
Low	90.6	11.3	86.2	14.2
Mid	97.4	10.7	93.9	11.2
High	91.0	11.4	92.2	9.22

- The long-term stability for histrelin assay samples is approximately 35 months when stored at less than -15°C.
- The analyte was stable through at least — freeze/thaw cycles
- Samples can be diluted safely up to 1:64
- The cross reactivity potential was evaluated and is outlined below:

Cross-Reactant	Structure	[ ] Ref #	Mfg. Lot #	% Cross-Reactivity
Histrelin	PGlu-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt	1262-17-2B	522584	100%
2-9 Amino acid fragment	H-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt	1262-3-D1	524717	180%
3-9 Amino acid fragment	H-Trp-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt	1262-3-D6	524716	96.0%
4-9 Amino acid fragment	H-Ser-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt	1262-3-D10	524718	75.0%
5-9 Amino acid fragment	H-Tyr-D-His(Bzl)-Leu-Arg-Pro-NHEt	1262-3-D2	524715	5.0%
	H-D-His(Bzl)-Leu-Arg-Pro-NHEt - Acetate	1262-3-D5	523152	95.0%
	H-Arg-Pro-NHEt - 2HCl	1262-3-D4	524578	0.4%
1-7 Amino acid fragment	Pyr-His-Trp-Ser-Tyr-D-His(Bzl)-Leu-OH	1262-3-D9	524619	<0.1%
LHRH (=GnRH)	pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2	1262-53	36833	<0.1%
	Pyr-His-Trp-Ser-OH trifluoroacetate salt	1262-3-D7	524618	<0.1%
	Pyr-His-OH	1262-3-D3	524631	<0.1%
	Pyr-His-Trp-OH	1262-3-D8	504338	<0.1%

Note: Crossreactivity calculations are approximate

Reviewer's comments:

1. The bioanalytical method had values for precision (< 15 %) and accuracy (% CV between 85 – 115%) within the FDA recommended limits.
2. An investigation of antiserum cross-reactivity, employing eleven potential cross-reactants (ten different histrelin fragments and LHRH) demonstrated high cross-reactivity with at least 3 different peptide fragments.
3. The metabolites of histrelin in human serum have not been identified. The only identified (in vitro) dealkylated metabolite of histrelin has not been tested for crossreactivity. Therefore, the in vivo relevance of the fragments tested for crossreactivity is not known. According to the CMC reviewer, these fragments do not occur in the drug or formulation as impurities.
4. For the GnRH agonists with known metabolism, goserelin and nafarelin (both decapeptides), the major metabolites are the 1-7 and 5-10 fragments resulting from hydrolysis of C-terminal amino acids. Given this pattern of metabolism for structurally similar GnRH agonists, the 2-9, 3-9 and 4-9 fragments are unlikely to be important (sponsor's response to IR letter dated 03/09/04). *Histrelin (nonapeptide) demonstrated ~ 5 % and < 0.1 % crossreactivity with the 5-9 and 1-7 fragments, respectively.*
5. In addition, Valera intends to test the duplicate samples from clinical study # 07-03-100 (500 μg SC bolus dose study) tested using the LC/MS/MS method currently under development for the assay of histrelin in serum and urine.
6. The clinical pharmacology review team considers the histrelin radioimmunoassay acceptable based on the above arguments supporting the absence of in vivo relevance for the observed in vitro crossreactivity employing hypothetical peptide fragments.

Phase II Study Histrelin bioanalysis: The phase II study (conducted by Roberts pharmaceuticals) employed a similar Radioimmunoassay (RIA) for histrelin analysis. The working standard curve range is 0.03 to 3.0 ng/ml. The lower limit of quantitation was 30 pg/ml. However the method and the validation procedures are not described in detail in the submission.

Serum testosterone bioanalysis: Serum samples from the phase 3 pivotal trial were assayed for testosterone by [ ] The radioimmunoassay employed was validated over the range of 7.8 to 1000 ng/dL with a lower limit of quantification of ~ 12 ng/dL. Testosterone is isolated from the human serum matrix by ethyl ether extraction. The serum extract is further purified by [ ] chromatography to separate potential interfering endogenous steroids from the testosterone fraction. Final quantitation is by RIA. The RIA employs rabbit anti-testosterone-11HS: BSA antiserum, 1, 2, 6, 7-^{3}H testosterone tracer and a Dextran-coated charcoal separation step.

Results of the bio analytical assay method validation:

Estimates of the percent coefficients of variation (% CV) of intra-day and inter-day precision were ≤ 15.8 % and ≤ 14.8 %, respectively.
The intra-day and inter-day accuracy (% nominal) ranged from 84.1 to 95 % and 87.6 to 111 %, respectively.
The samples were found to be stable after —reeze/thaw cycles.
Storage stability was not determined.
Antiserum crossreactivity: Some crossreactivity with dihydrotestosterone (12 %).

Cross Reactivity

Testosterone	100%	Pregnenolone	0.65%	11-Deoxycorticosterone	0.001%
Dihydrotestosterone	12.0%	Dehydroepiandrosterone	0.05%	Estrone	0.002%
17β-estradiol	0.002%	Cortisone	0.001%	16-Epi-Estriol	0.001%
Pregnanediol	0.05%	12α-Estradiol	0.002%	6-Keto-Estradiol	0.001%
Estriol	0.002%	11-Hydroxyprogesterone	0.002%	Androstenedione	0.70%

Phase 2 study: A radioimmunoassay was used for the quantitation of testosterone in human serum. The method is a conventional radioimmunoassay similar to that employed by Valera for testosterone bioanalysis of the phase 1 and 3 samples. The working standard curve range is 1 to 125 pg/100 µl and the lower limit of quantitation is 0.3 nmol/l (0.09 ng/ml). The intra-assay coefficients of variations (CV) varied from 2 % to 15 % and the inter-assay %CV in males was 14 %. Antiserum against testosterone showed some cross-reactivity with dihydrotestosterone (14 %) and Δ4-androstene-dione (8.2 %) and few other endogenous molecules (up to 3 %). Cross-reactivity potential suggests that testosterone concentrations in serum might have been overestimated. In an indication in which androgen ablation is the desired pharmacodynamic endpoint, overestimation of testosterone levels is not of a concern as lower testosterone concentrations are always desirable.

Lutenizing hormone (LH) bioanalysis: Serum samples from the phase 3 study were assayed for LH by [ ] The method employs [ ] assay that uses microparticle enzyme immunoassay (MEIA) technology [ ] Sample and anti-LH coated microparticles are incubated, allowing the LH in the sample to bind with the antibody-coated microparticles forming an antigen-antibody complex. The sample mixture containing the complex is transferred to a glass fiber matrix cell where the microparticles bind to the matrix. The matrix is washed to remove unbound components. The anti-α LH subunit specific alkaline phosphatase conjugate is added to bind with the antigen-antibody complex, and then the matrix is again washed to remove unbound components. The substrate, 4-methylumbelliferyl phosphate is added to the matrix, and the resulting fluorescent reaction is measured by the MEIA optical assembly [ ] The LLOQ and ULOQ were 0.5 and 250 mIU/mL. % CV of intra- and inter-day precision were ≤ 3.91 % and ≤ 6 %, respectively. The accuracy was ≥ 88.2 %. % Crossreactivity was less than 3.5 % for TSH and less than 0.02 % for hCG and FSH.

In the Phase 2 study, LH was quantified before treatment, at 1 and 2 weeks, 1 month and then each month thereafter. The concentration of LH was determined by a time-resolved fluoroimmunoassay with a practical detection limit of 0.05 U/L. Validation procedure employed for this assay method is not provided in the interim report.

4 Appendix

4.1 Labeling

Please refer to the approved labeling in DFS.

4.2 Cover sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-732**	**Brand Name**	**VANTAS™**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Histrelin acetate**
Medical Division	**Division of Reproductive and Urology Drug Products (DRUDP; HFD 580)**	**Drug Class**	**GnRH agonist**
OCPB Reviewer	**Sandhya Apparaju, Ph.D.**	**Indication(s)**	**Palliative treatment of prostate cancer**
OCPB Team Leader	**Ameeta parekh, Ph.D.**	**Dosage Form**	**Polymeric Implant (removable)**
		Dosing Regimen	**Once a year**
Date of Submission	**12/12/2003**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCPB Review	**08/31/2004**	**Sponsor**	**Valera Pharmaceuticals Inc.**
PDUFA Due Date	**10/12/2004**	**Priority Classification**	**3S**
Division Due Date	**09/21/2004**		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	500 µg aqueous solution (S.C.) bolus dose for characterization of histrelin ADME. The implant itself was not tested in healthy volunteers.
multiple dose:				
Patients-				
single dose:	X	2	2	
multiple dose:	X	2	2	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	1	1	
Phase 3:	X	1	1	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:	X	1	1	
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted] Effect of renal/hepatic impairment and race
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1		Drug release
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**5**	**5**	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Dose response, pharmacokinetics in renal & hepatic impairment, in vitro dissolution specifications, IVIVC**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandhya Apparaju
10/7/04 02:42:23 PM
BIOPHARMACEUTICS

Ameeta Parekh
10/7/04 02:55:47 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-732	*Brand Name*	VANTAS
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	Histrelin Acetate
Medical Division	DRUDP (HFD 580)	*Drug Class*	GnRH agonist
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	Prostate Cancer
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	Subdermal implants
Date of Submission	12/12/2003	*Dosing Regimen*	Once a year implant
Estimated Due Date of OCPB Review	8/31/2001	*Route of Administration*	Subdermal
PDUFA Due Date	10/12/2001	*Sponsor*	Valera Pharmaceuticals Inc.
Division Due Date	9/12/2001	*Priority Classification*	3S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	6		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:				
pediatrics:				
geriatrics:				
body wt.				
renal impairment:	X			
hepatic impairment:	X			

PD:				
Phase 2:	X			
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X			
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above	1) Please confirm that the formulation used in the Phase 3 clinical evaluation is the same as the formulation intended to be marketed 2) If possible, please provide electronic study summaries/reports for all the clinical pharmacology and biopharmaceutics related studies.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dhruba Chatterjee
1/20/04 01:54:29 PM
BIOPHARMACEUTICS
Filable - 2 comments to sponsor.

Ameeta Parekh
2/2/04 02:46:41 PM
BIOPHARMACEUTICS