

**Europa Uomo Board Meeting  
March 19, 2011**

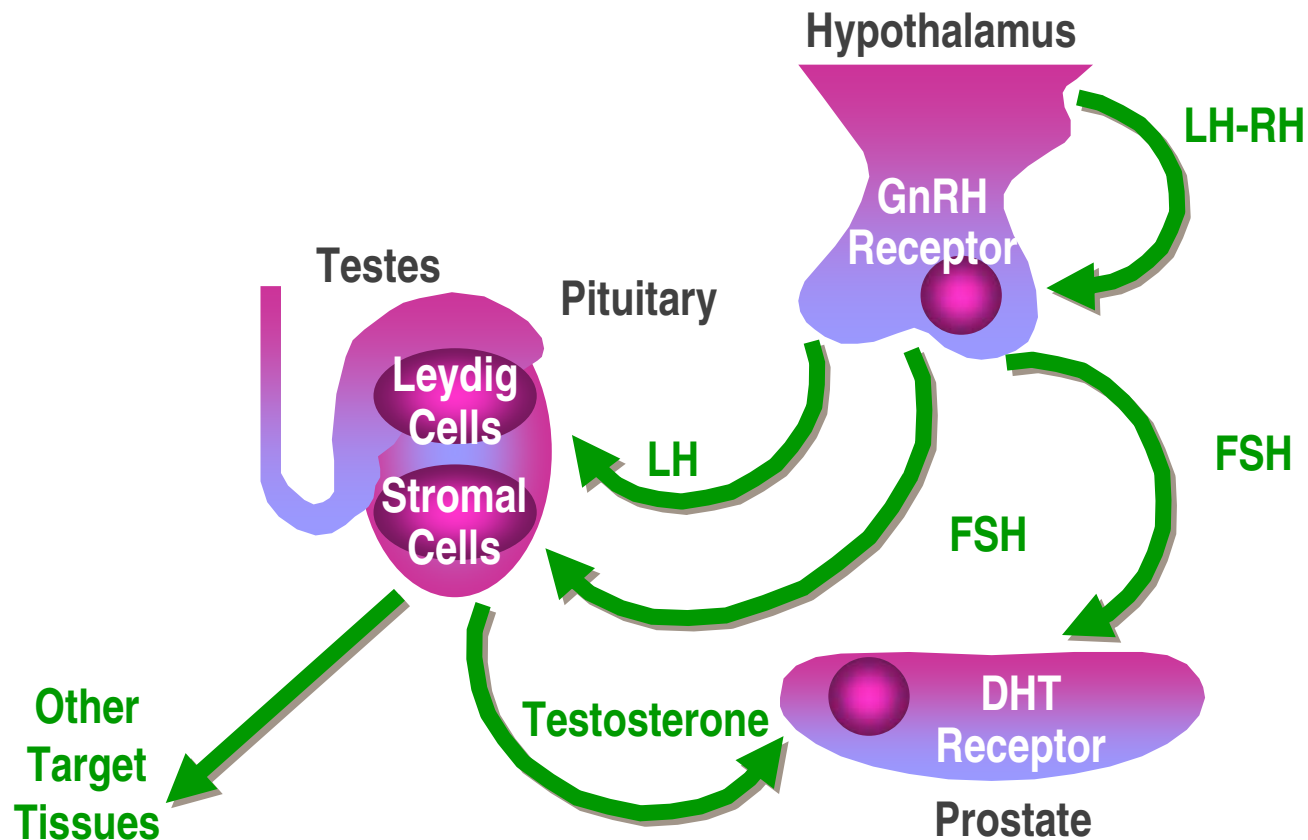
**Vantas: A once-yearly LH-RH agonist**



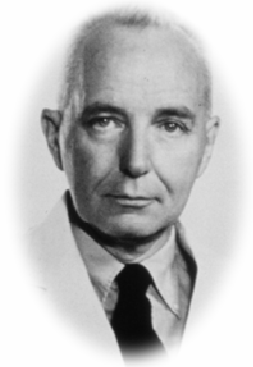
**Dr Neal Shore**  
**Carolina Urologic Research Center/Atlantic Urology Clinics,**  
**South Carolina, USA**

# Hormonal influences on prostate cancer

- Androgens, mainly testosterone, stimulate the growth, function and proliferation of prostate cells

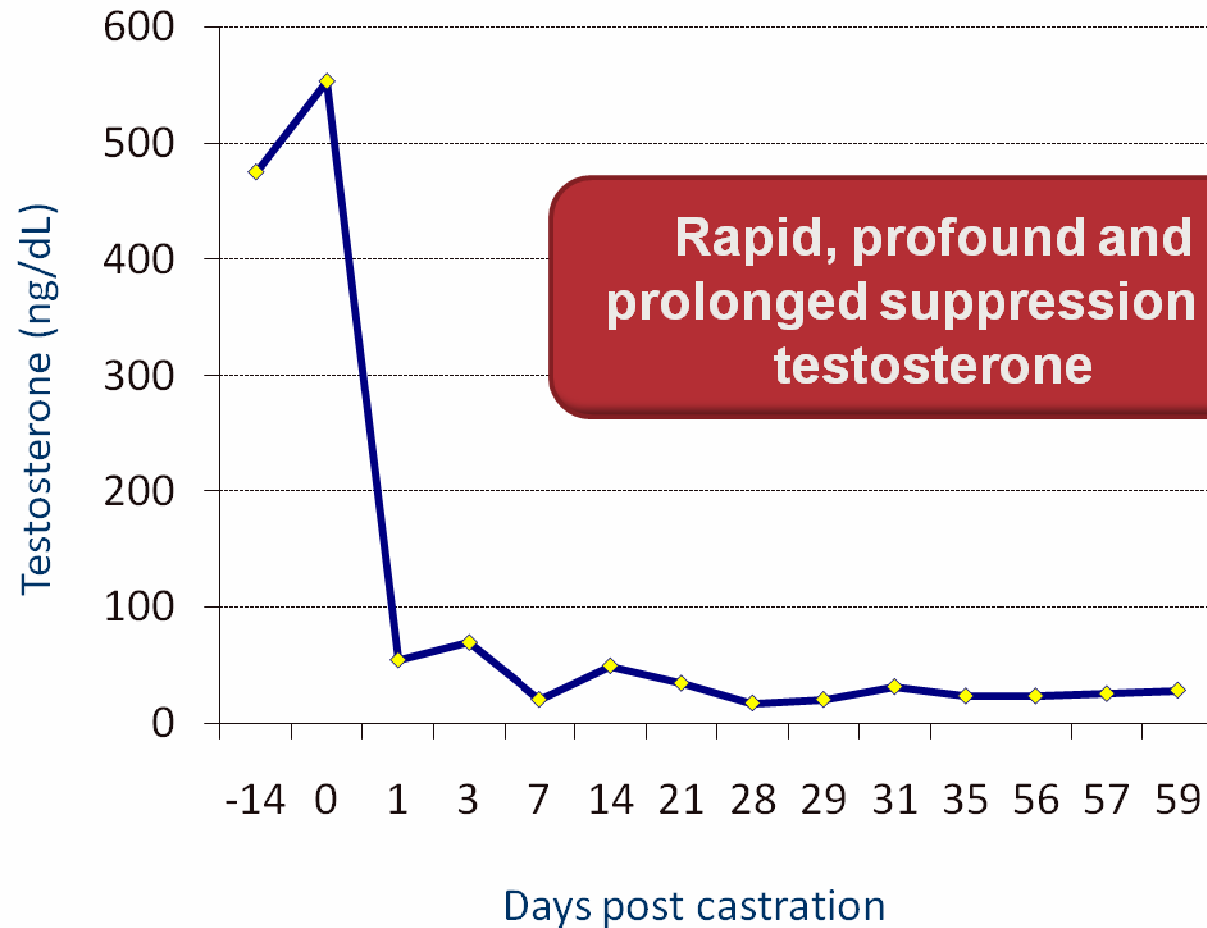


DHT: dihydrotestosterone; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; LH: luteinising hormone; LH-RH: luteinising hormone-releasing hormone



Charles HUGGINS  
1901 – 1955  
1966 Nobel Prize

II. The effect of castration on advanced carcinoma of the prostate gland  
**Huggins C. Arch Surg 1941;43:209–23**



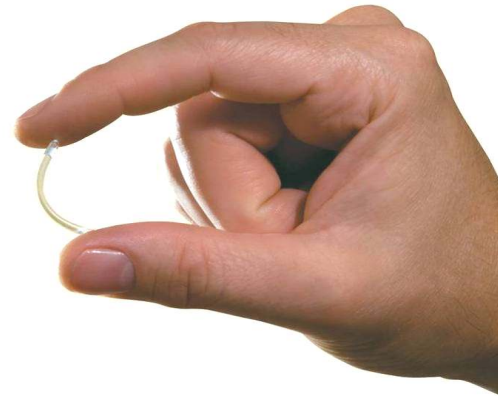
# Hormonal therapy

- **Used for the management of advanced prostate cancer for >30 years**
- **LH-RH agonists – current ‘standard of care’ for advanced prostate cancer – antagonists now also available**
- **Currently available as 1-, 2-, 3- and 6-monthly depot injections (intramuscular and subcutaneous)**
  - Leuprolide
  - Triptorelin
  - Goserelin
  - Buserelin

# Potential disadvantages of injectable therapies

- Efficacy is proportional to binding affinity and concentration
- Untimely and unpredictable reversibility
- Increased costs/inconvenience due to multiple patient visits (travel, QoL/time, emotional burden)
- Inconvenience of multiple injections per year may affect patient compliance, especially in older men
- Clinic efficiency: aging population, increasing volume of advanced prostate cancer patients, Urology manpower

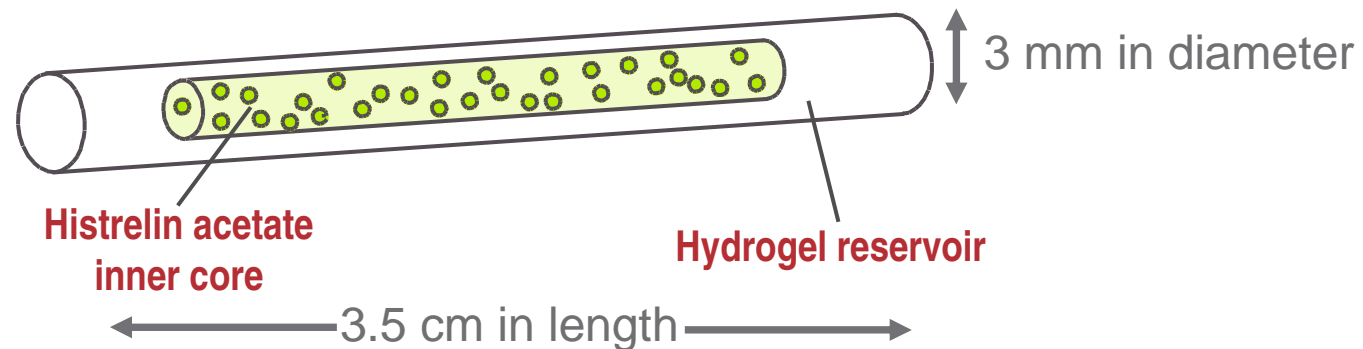
# The histrelin implant



- **Histrelin is the most potent LH-RH agonist available<sup>1</sup>**
  - 1.5 x as potent as goserelin at the LH-RH receptor
  - 10 x as potent as leuprolide
- **First long-acting LH-RH agonist (histrelin acetate) available as a once-yearly subcutaneous implant**
- **Indicated for the treatment of advanced prostate cancer**

# What is the histrelin implant?

- The cylindrical histrelin implant consists of a 50 mg histrelin acetate inner core inside a flexible, non-biodegradable, Hydrogel™ reservoir like a contact lens
- Histrelin acetate is released at a continuous rate of 50 µg/day and is effective for a minimum of 1 year<sup>1</sup>



# About the insertion technique

- The implant is inserted just below the skin
- Insertion takes only a few minutes with a local anaesthetic to ensure the process is painless
- The implant is soft and flexible, so will not interfere with daily activities once the insertion site has healed (~1 week)
- One implant is effective for at least 1 year
- The implant can be easily removed (and replaced)
- Once removed, the effects stop faster than after a depot injection

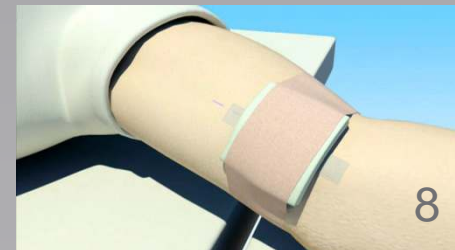
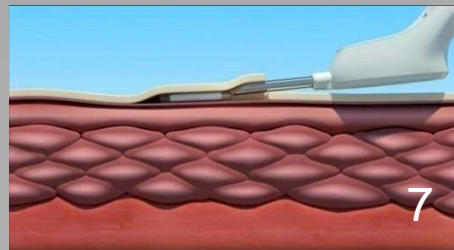
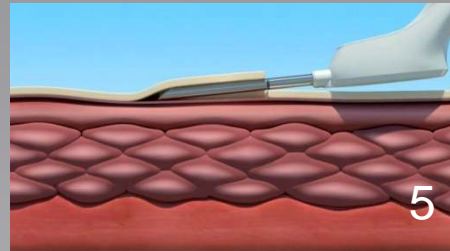
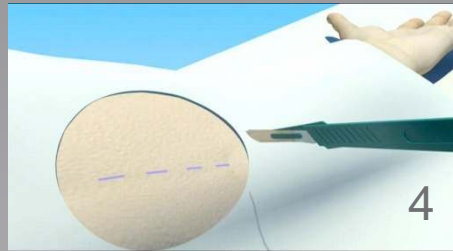
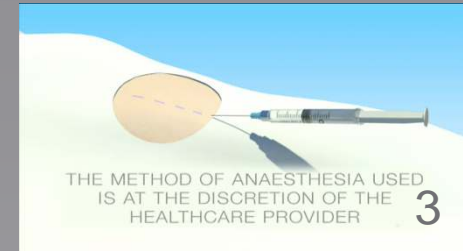
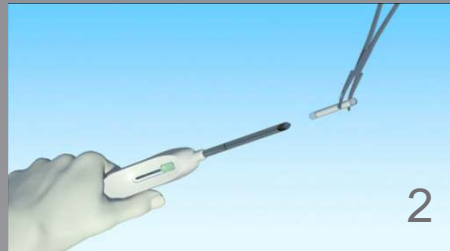
# Implant insertion



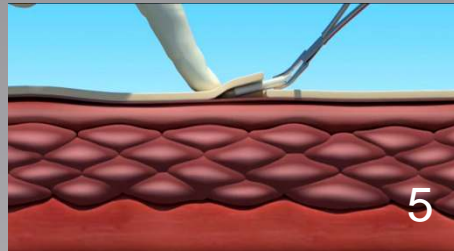
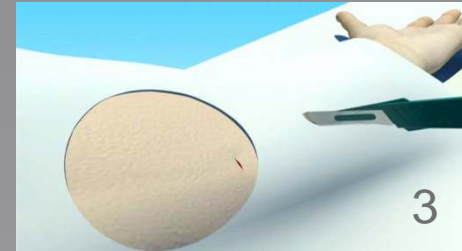
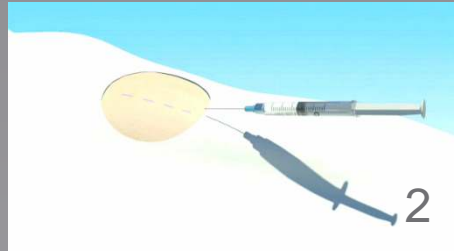
# Implant removal



# The histrelin implant is straightforward to insert



# The histrelin implant is straightforward to remove



# Phase III study: Efficacy and tolerability of the histrelin implant

## Trial Design



Open-label, multicentre US study in 138 men aged  $\geq 45$  years with advanced prostate cancer

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## Outcomes



Testosterone suppression (median level 11.9 ng/dL) achieved at Week 4 and maintained for 1-year treatment period



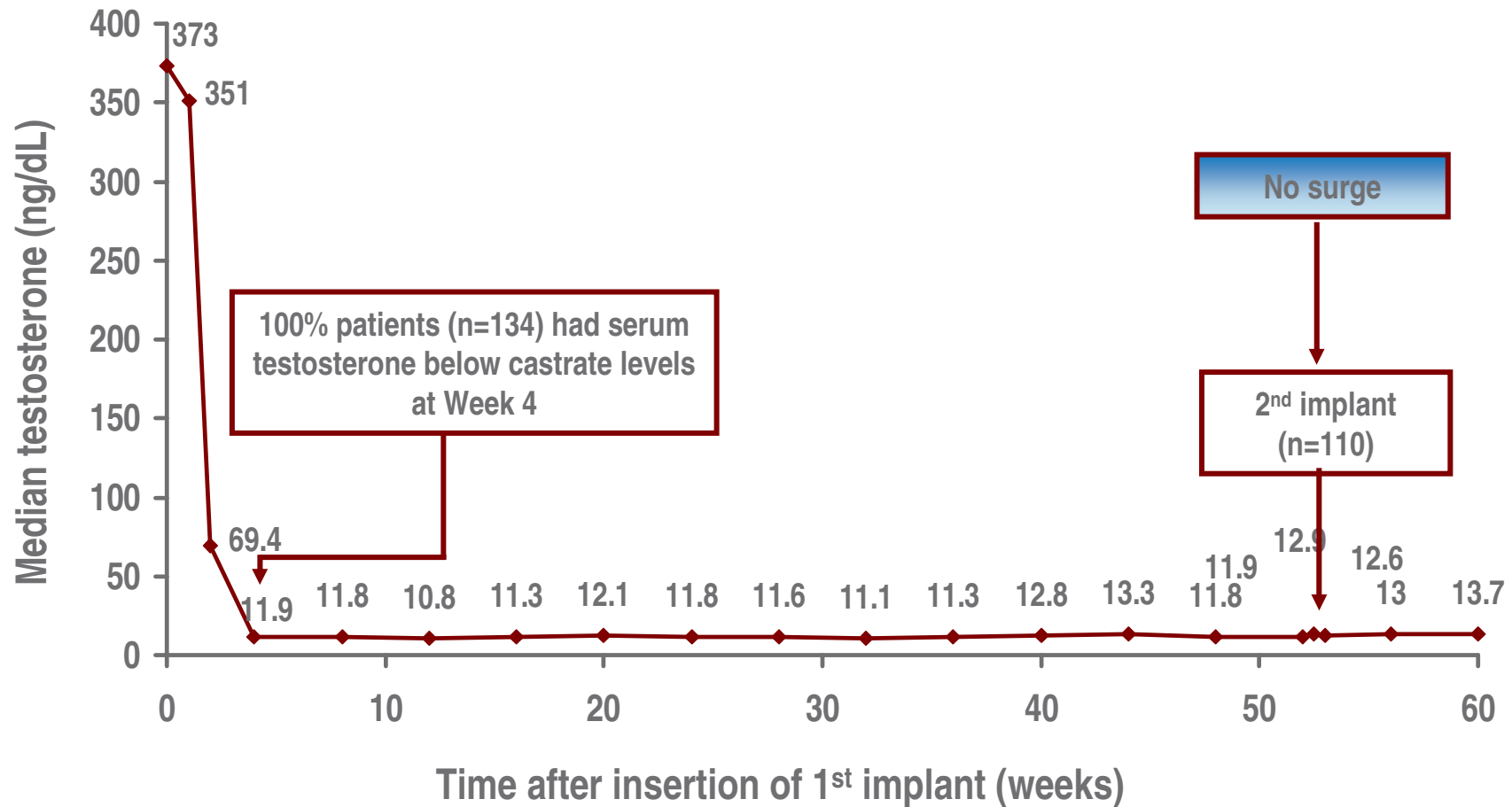
Castrate serum testosterone levels maintained following insertion of a second implant



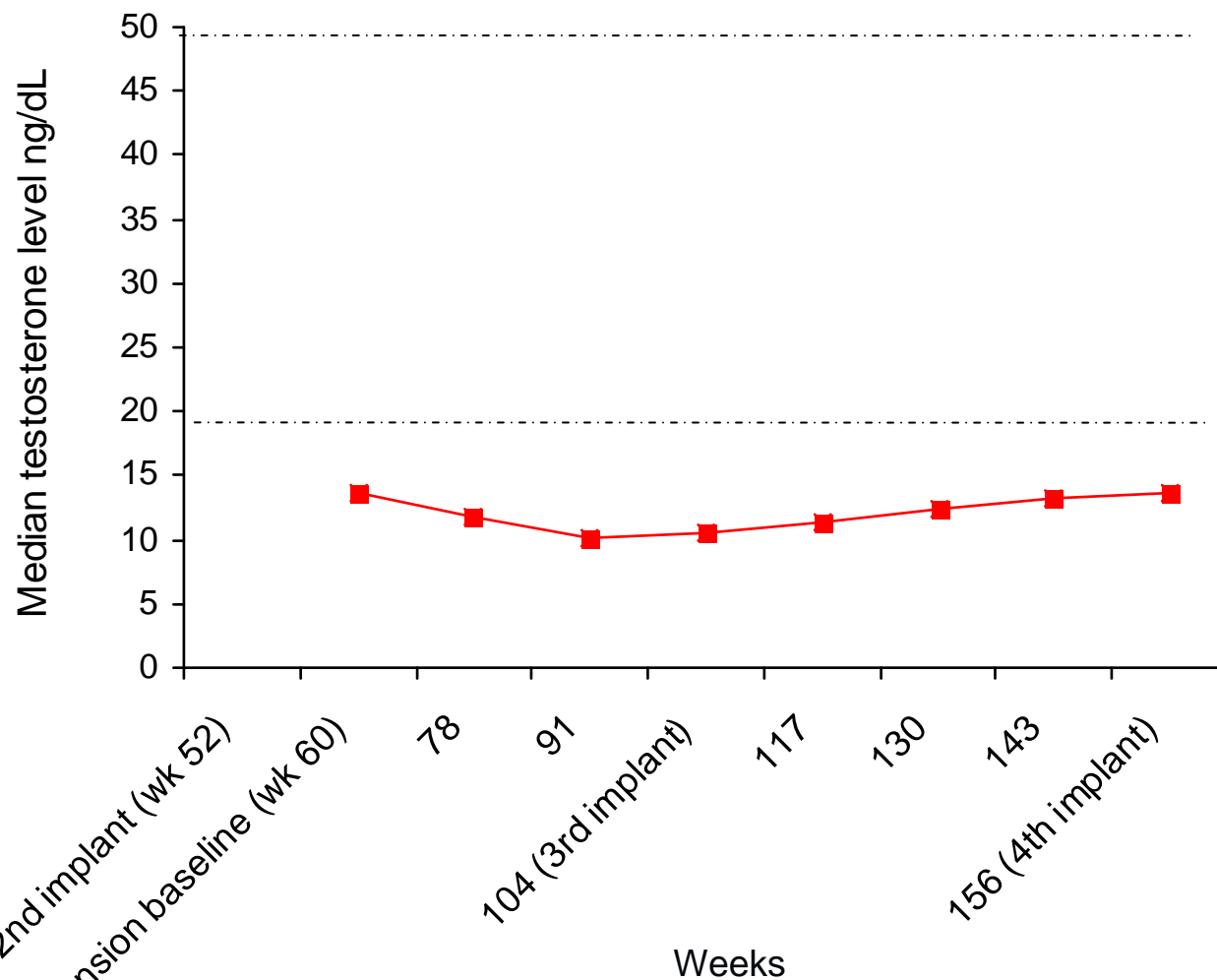
Based on this study, FDA approval for Vantas was received in 2004

# The histrelin implant suppressed testosterone by Week 4

Effective for 1-year treatment period in >99% of patients



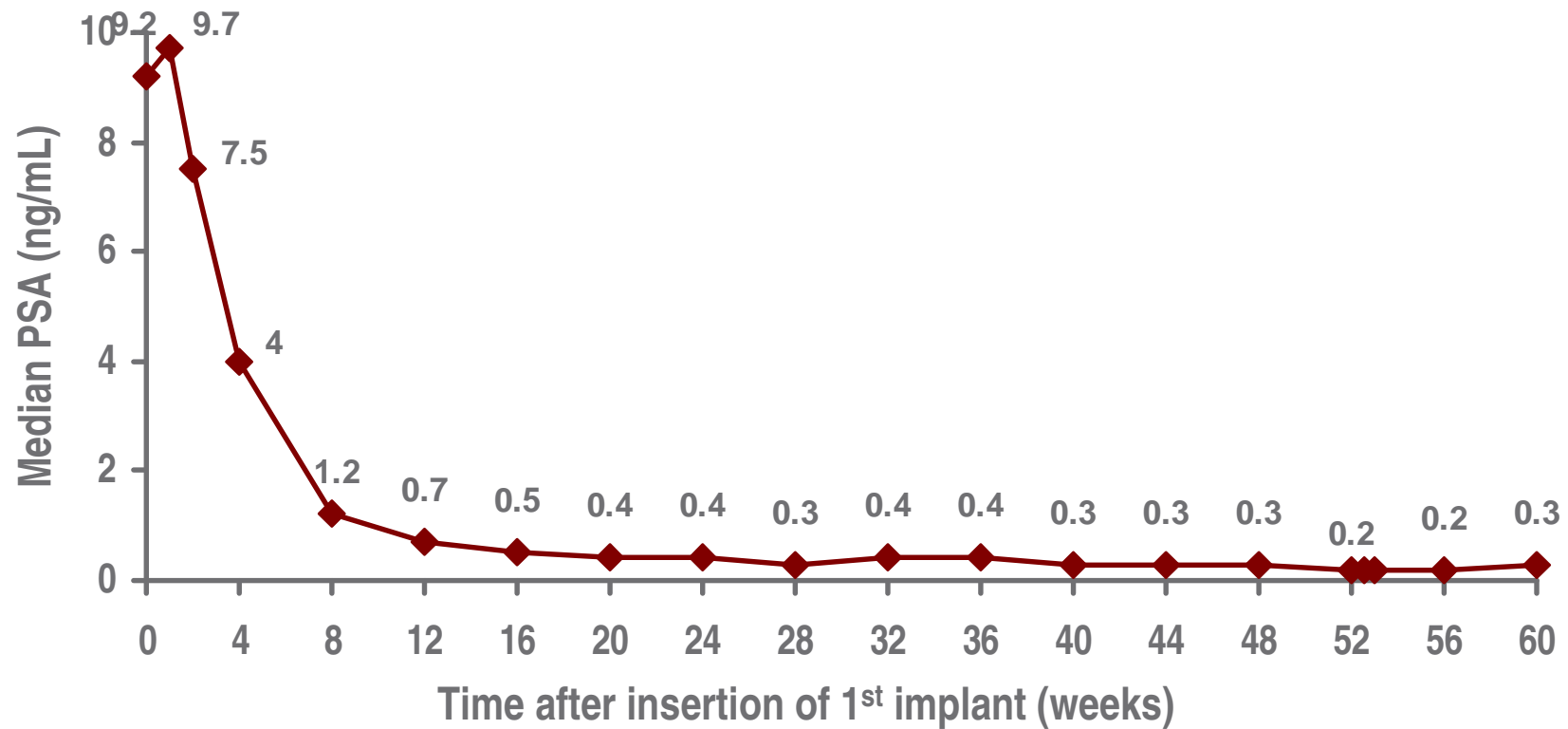
# Replacing implants maintains testosterone suppression during long-term treatment



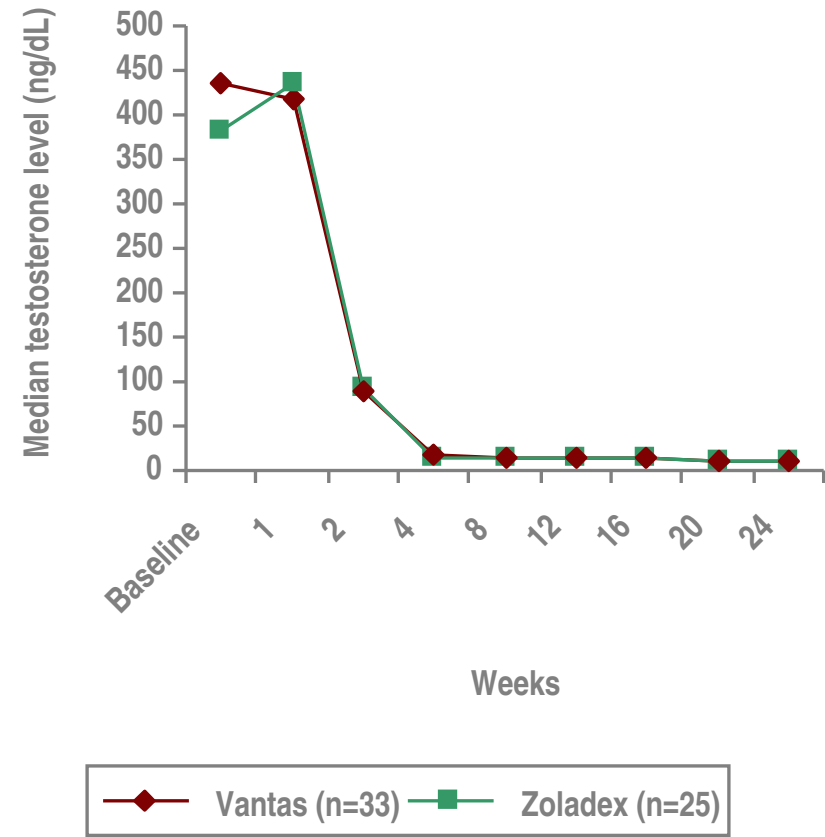
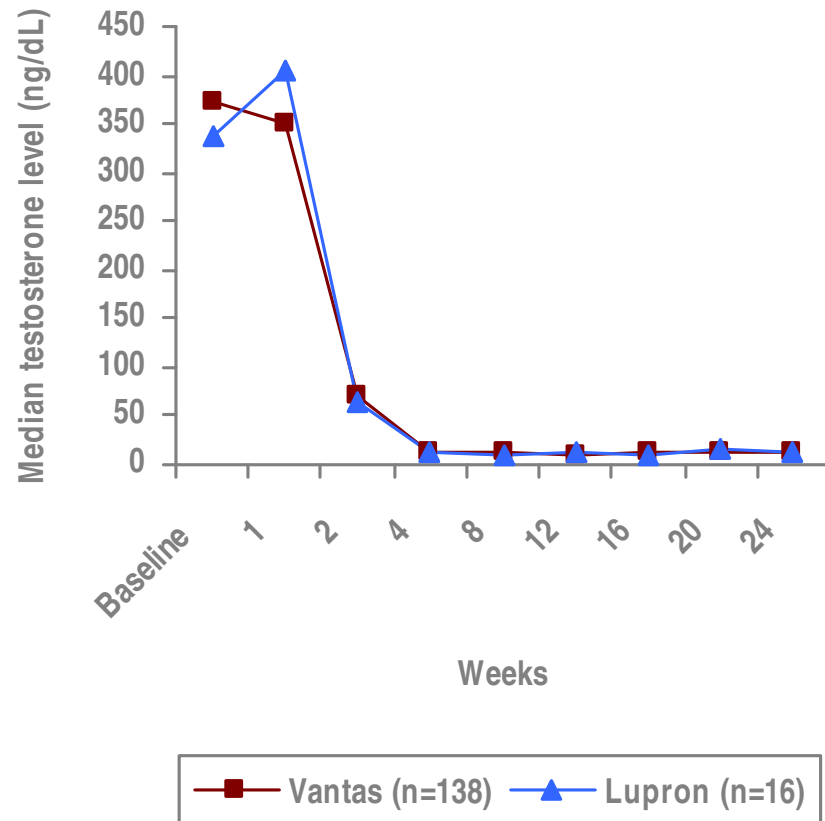
Data on file

# Suppression of serum PSA parallels that of testosterone

Median PSA had fallen by 23% from baseline at Week 2, 57% at Week 4, 95% at Week 16 and 98% at Week 52

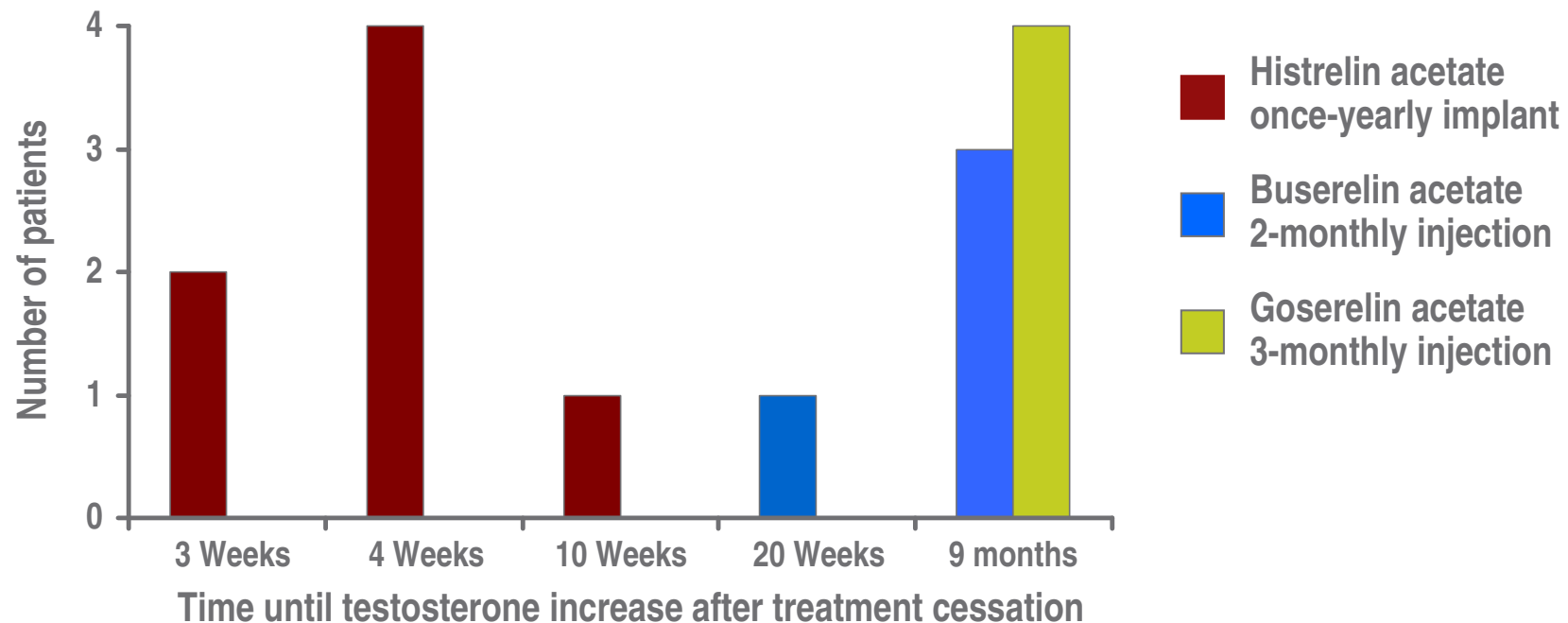


# Minimal initial testosterone surge with histrelin implant vs. leuprolide or goserelin



# Testosterone suppression is reversed after removal of the histrelin implant

Testosterone levels recover more quickly after treatment cessation with the histrelin implant compared with depot LH-RH agonists



# The histrelin implant has a favourable tolerability profile

- The adverse events (AEs) profile of the histrelin implant is similar to that of other LH-RH agonists
- The most common AE observed during treatment was hot flushes,<sup>1</sup> which are a common side-effect of hormonal therapy<sup>2</sup>
  - Hot flushes were mild in 53 (38.4%) patients, moderate in 34 (24.6%) patients, and severe in 3 (2.2%) patients<sup>1</sup>
- Insertion site reactions and implant expulsions rarely occur with the current insertion device
- The histrelin implant was well tolerated

1. Schlegel PN on behalf of the Histrelin Study Group. J Urol 2006;175:1353–8

2. Damber JE, Aus G. Lancet 2008;371:1710–21

# Histrelin: US experience

- **The Vantas histrelin implant has been available in the USA since 2004**
- **More than 65,000 implants have been administered in the USA**
- **Has been shown to be cost-effective compared to other LH-RH agonists**

# Summary

- **The histrelin implant is a new depot LH-RH agonist for the treatment of advanced prostate cancer**
  - Efficacy in line with modern expectations / very low testosterone level
  - Minimal flare and rapid onset of action
  - **Rapid recovery**
- **Patient convenience and quality of life**
  - Decreased clinic visits
  - Patient comfort
  - Flexibility

# Which patients would be eligible to have a histrelin implant?

- Patients initiating ADT: anticipating 12 months' therapy
- PSA relapse after localised therapy
- Intermediate- / high-risk patients receiving external beam radiation therapy
- Lymph node-positive, post-radical prostatectomy
- Metastatic disease: asymptomatic, symptomatic, castrate-resistant prostate cancer
- Chronic injection therapy
- Intermittent ADT vs continuous ADT
- Neoadjuvant, prostate gland volume reduction

# Case history 1



- **72-year old, retired teacher**
  - Radical prostatectomy aged 68, lymph node +ve
  - Extensive grade 8 malignancy
  - Post-operative PSA undetectable
  - Initial treatment – LH-RH agonist depot injections
  - Tolerated therapy with no major adverse effects
- **Switched to the once-yearly implant 3 years ago**
  - Less frequent clinic visits, less travel
  - So far, very pleased with his implant
  - PSA tested every 4 months at local doctor
  - Visits clinic once a year to replace implant

# Key points 1

- **This case demonstrates that:**
  - The once-yearly implant provides a convenient option for long-term hormonal therapy following radical prostatectomy in patients with locally advanced prostate cancer
  - It is easy to switch from depot LH-RH injections to once-yearly implant treatment
  - Patients with the once-yearly implant can still receive regular check-ups at a convenient centre

# Case history 2



- **61-year old, small business owner**
  - PSA 22 ng/mL
  - Rectal examination consistent with T3 cancer
  - Prostate biopsy – Gleason score 7 in 6 out of 12 cores
  - Bone and CT scans negative for metastatic disease
- **Treatment choice**
  - Conformal radiation therapy plus 3 years of hormonal therapy with implant
  - During implant treatment he experienced some AEs, including hot flushes

# Key points 2

- **This case:**
  - Supports the use of the implant as an adjuvant to radiation therapy in men who require long-term hormonal therapy (as recommended in EAU guidelines<sup>1</sup>)
  - Shows that it is not always necessary to stabilise a patient on a short-term LH-RH agonist prior to treatment with the implant
  - Shows that the AEs with the once-yearly implant (e.g. hot flushes) are the same as those of other LH-RH agonists

## Case study 3



- 51-year old, **with young children**
- **Following radical prostatectomy**
  - PSA levels began to increase (0.1 to 0.4 ng/mL over 9 months)
  - Biochemical progression led to 3 weeks of prostatic bed radiation
  - PSA now 2.8 ng/mL. Bone and CT scans remain normal
- **Treatment choice – hormonal therapy with implant**
  - Based on high-risk PSA doubling time and desire for maximal life expectancy
  - Minimises travel/time commitments and impact on work
  - PSA now measured every 3 months

# Key points 3

- **This case**
  - Supports the use of long-term hormonal therapy with the once-yearly implant following biochemical progression after definitive therapy
  - Also shows that the once-yearly implant is a good option for patients who require hormonal therapy but do not want to be tied to fixed follow-up appointments

# Case history 4



- **73-year old, plays golf 2–3 times/week**
  - Presented with anaemia and PSA level 3.1 ng/mL
  - Hard, immobile prostate gland but no voiding symptoms
  - Bone scan revealed multiple rib and skeletal lesions, but completely free of any bone pain
- **Chose once-yearly implant**
  - Overseas travel plans + regular trips to visit children and grandchildren
  - Non-steroidal anti-androgen prior to implant
  - Post-insertion, PSA decreased to 1.8 ng/mL (3 months), 1.2 ng/mL (6 months)
  - He now attends 6-monthly follow-up visits and is looking forward to fulfilling his golf and travelling commitments

# Key points 4

- **This case:**
  - Shows that the once-yearly implant has a rapid effect following insertion
  - Shows that implant is a convenient option for patients with asymptomatic metastatic prostate cancer who are candidates for hormonal therapy
  - Demonstrates successful use of implant combined with short-term anti-androgen therapy in a patient at risk of AEs relating to tumour flare

# Case history 5

- **63-year old, moderately obese man with Crohn's disease**
  - PSA level 10.7 ng/mL, Gleason score 7 carcinoma
  - Rectal examination revealed unilateral lobe firmness
- **Intensity modulated radiation therapy (IMRT)**
  - Also opts for 2 years of adjuvant therapy with the implant
  - Decision based on clinical equivalence of treatment options and desire to minimise number of appointments
    - Will already be receiving daily IMRT for 9 weeks
    - Follow-ups with Urologist, Radiation Oncologist, Gastroenterologist and Internist also arranged
    - Ample opportunity for regular PSA monitoring

# Key points 5

- **European prostate cancer treatment guidelines recommend that patients undergoing radiation therapy should receive androgen suppression before, during, and after definitive treatment<sup>1</sup>**
- **This case highlights the convenience of the once-yearly implant as a long-term adjuvant to radiation therapy**

# Possible advantages of the histrelin implant vs. depot LH-RH agonists

- **Convenience for the patient and his doctor**
  - Fewer visits/injections needed each year
- **Testosterone is suppressed by 4 weeks and stays suppressed for the 1-year treatment period**
  - Reduced risk of 'acute-on-chronic' flares or surges compared with depot injections
- **Good recoverability**
  - Testosterone levels increase rapidly after implant removal
- **Favourable tolerability profile**
  - Predictable and manageable side-effects
  - No adverse effect on Quality of Life over extended treatment periods
- **Ease of removal if required or requested**