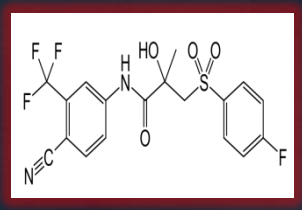
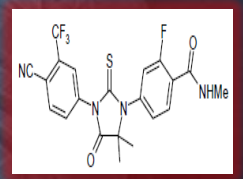
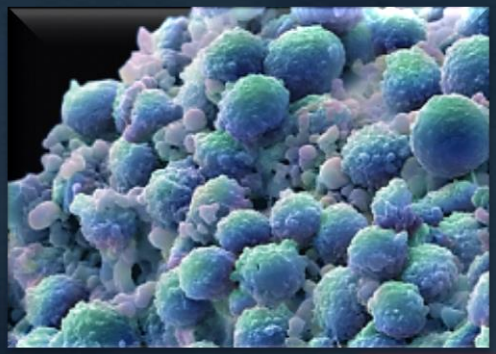
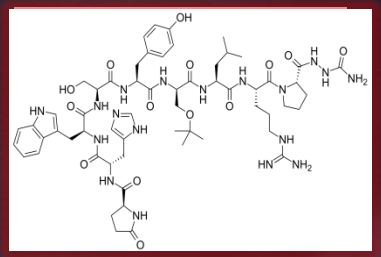
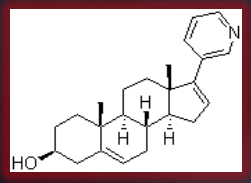
First line therapy - Advanced Prostate Cancer
Agonist or Antagonist?

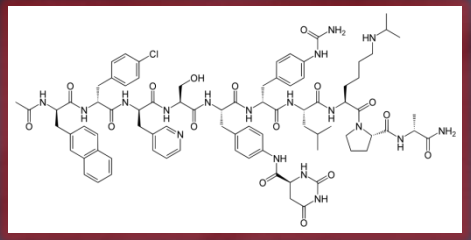








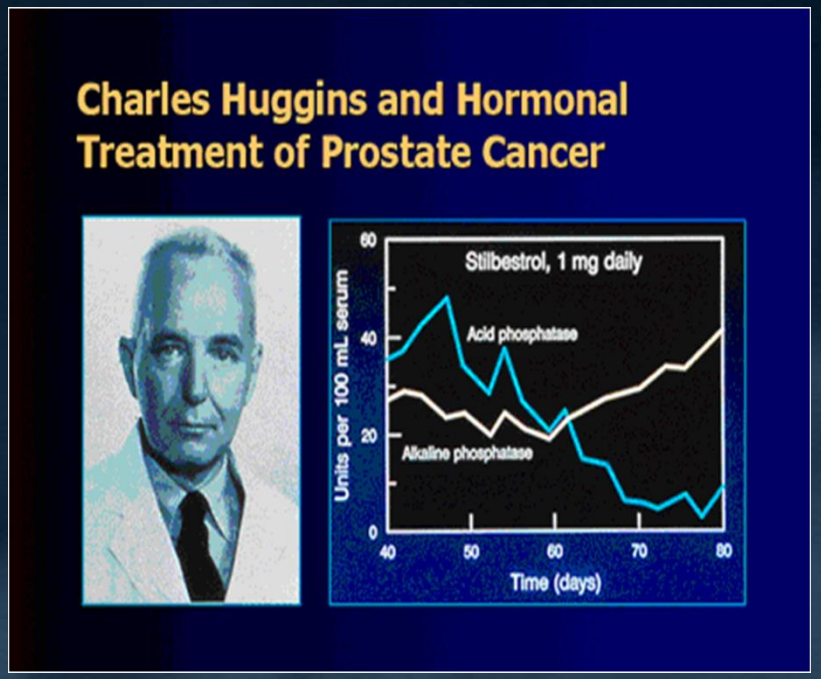




Evolution of Androgen Deprivation Therapy (ADT) and its role in prostate cancer

- The pioneering work of Huggins and Hodges, demonstrated that orchidectomy & oestrogen resulted in significant clinical improvement in men with advanced prostate cancer (PCa) [Huggins and Hodges,1941]

- Androgen deprivation therapy (ADT) has been the mainstay for management of advanced/metastatic prostate cancer.



Hormonal therapy
Treatment options

ADT:

- Surgical castration (orchidectomy)
- Luteinising Hormone Releasing Hormone (LHRH/GnRH) agonists (Stimulators!):
  - Zoladex (Goserelin)
  - Decapeptyl (Triptorelin)
  - Prostap (leuprorelin acetate)
- Gonadotrophin Releasing Hormone (LHRH/GnRH) antagonists (Blockers!)
  - Firmagon (Degarelix)

Antiandrogens

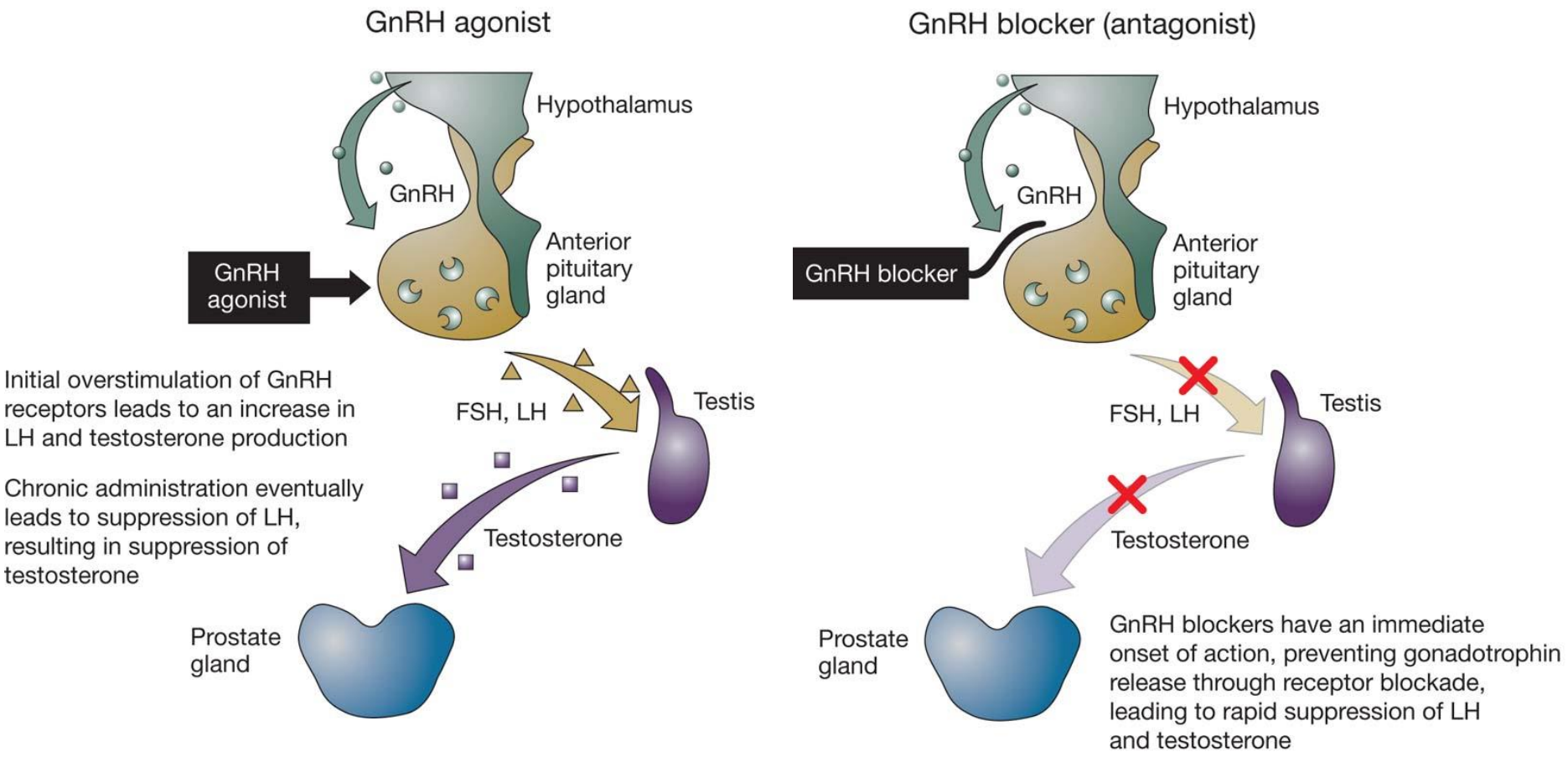
- Combined androgen blockade (CAB)
  LHRH agonists + Antiandrogens

Oestrogen treatment - diethylstilboestrol.

Androgen Biosynthesis Inhibitors – Abiraterone

Androgen receptor antagonist - Enzalutamide

A new class of agents
GnRH receptor agonists and blockers



Brawer M. Rev Urol 2001; 3(Suppl 3): S1–S9

FSH, follicle-stimulating hormone; LH, luteinising hormone; GnRH, gonadotrophin-releasing hormone

Disadvantages of GnRH/LHRH agonists

- Initial stimulation of the anterior pituitary; leading to an initial burst of LH release and subsequent testosterone flare in all patients.

  - Approximately 4–10% of patients, those with high-volume and symptomatic bone metastases, are at risk of clinical flare of symptoms[1,2]
  - increased bone pain, spinal cord compression, ureteral obstruction, urethral obstruction

- Delays the achievement of castrate testosterone levels for about 2–4 weeks[3]
- Require the use of an antiandrogen – blocks the signalling activity via the androgen receptor
- LHRH agonists may also cause testosterone microsurges after each dose administration (around 6%) of patients – impact on disease control[4]

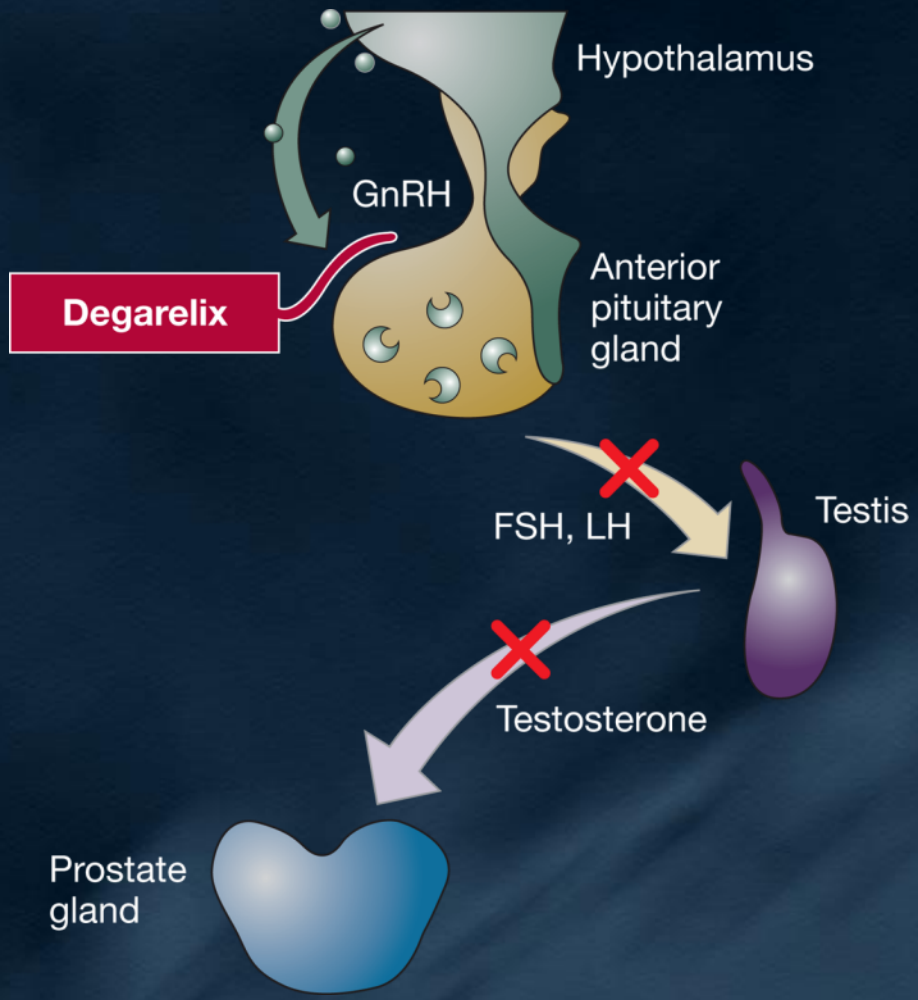
1.Thompson IM . Rev Urol. 2001;3 Suppl 3:S10–S14. 2. van Poppel H. *Urology.* 2008;71(6):1001–1006. 3 Schröder F. BJU Int. 2012;109 Suppl 6:1–12. 4.Klotz L et al. BJU Int 2008;102:1531-8

GnRH/LHRH antagonists…
Addressing agonist shortcomings?

- Direct mechanism of action (inhibition of GnRH receptors)
- Immediate fall in LH, FSH and testosterone
- No initial stimulation of GnRH receptors and consequently no testosterone surge or clinical flare
- Fast and sustained suppression of PSA

Degarelix: Direct & Logical mode of action

- Directly blocks!! GnRH receptors in the pituitary
- Immediate onset of action



Princivalle M et al. J Pharmacol Exp Ther 2007; 320: 1113-1118

GnRH/LHRH antagonists

- Direct mechanism of action (inhibition of GnRH receptors)
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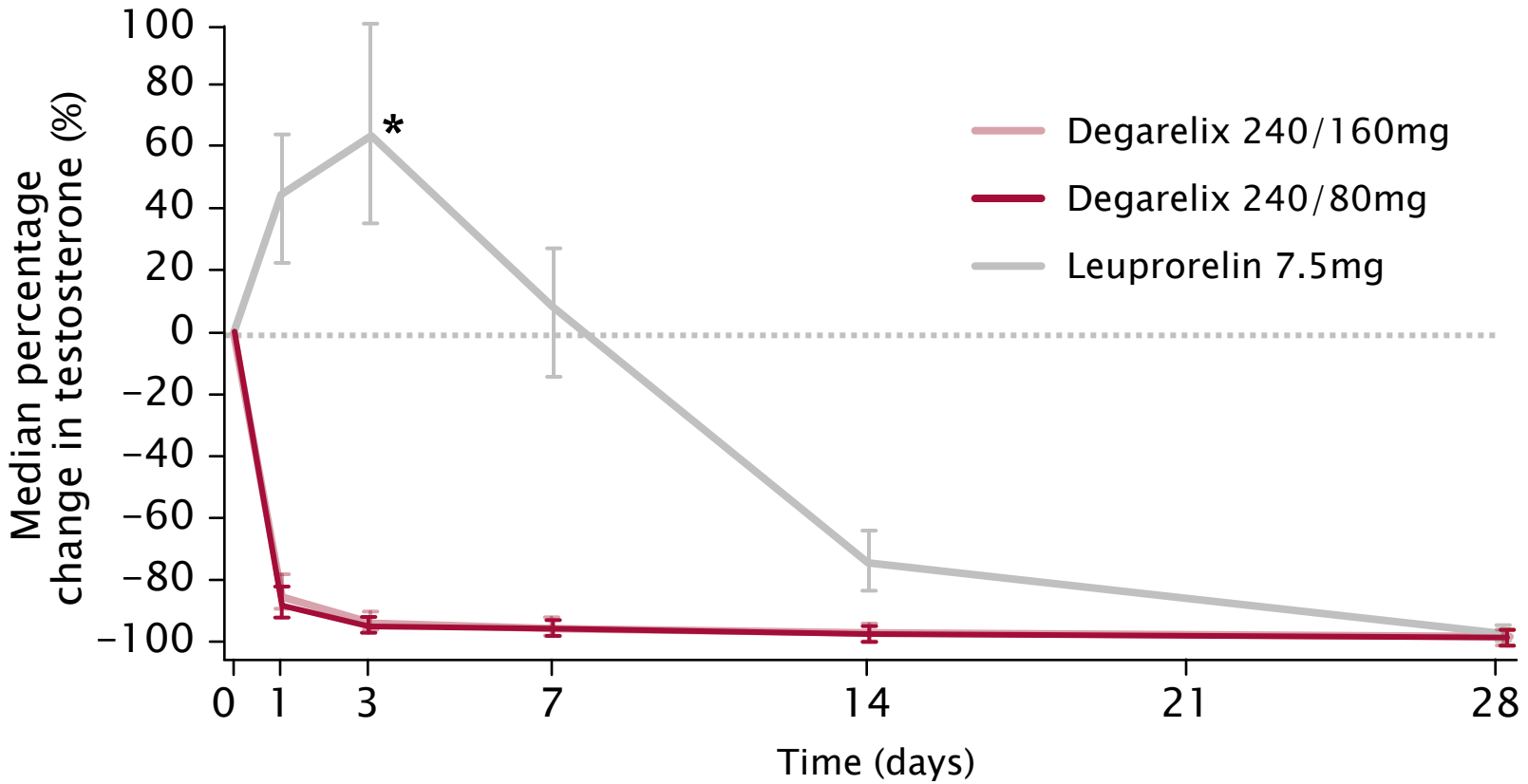
Degarelix – immediate testosterone reduct
no risk of clinical flare



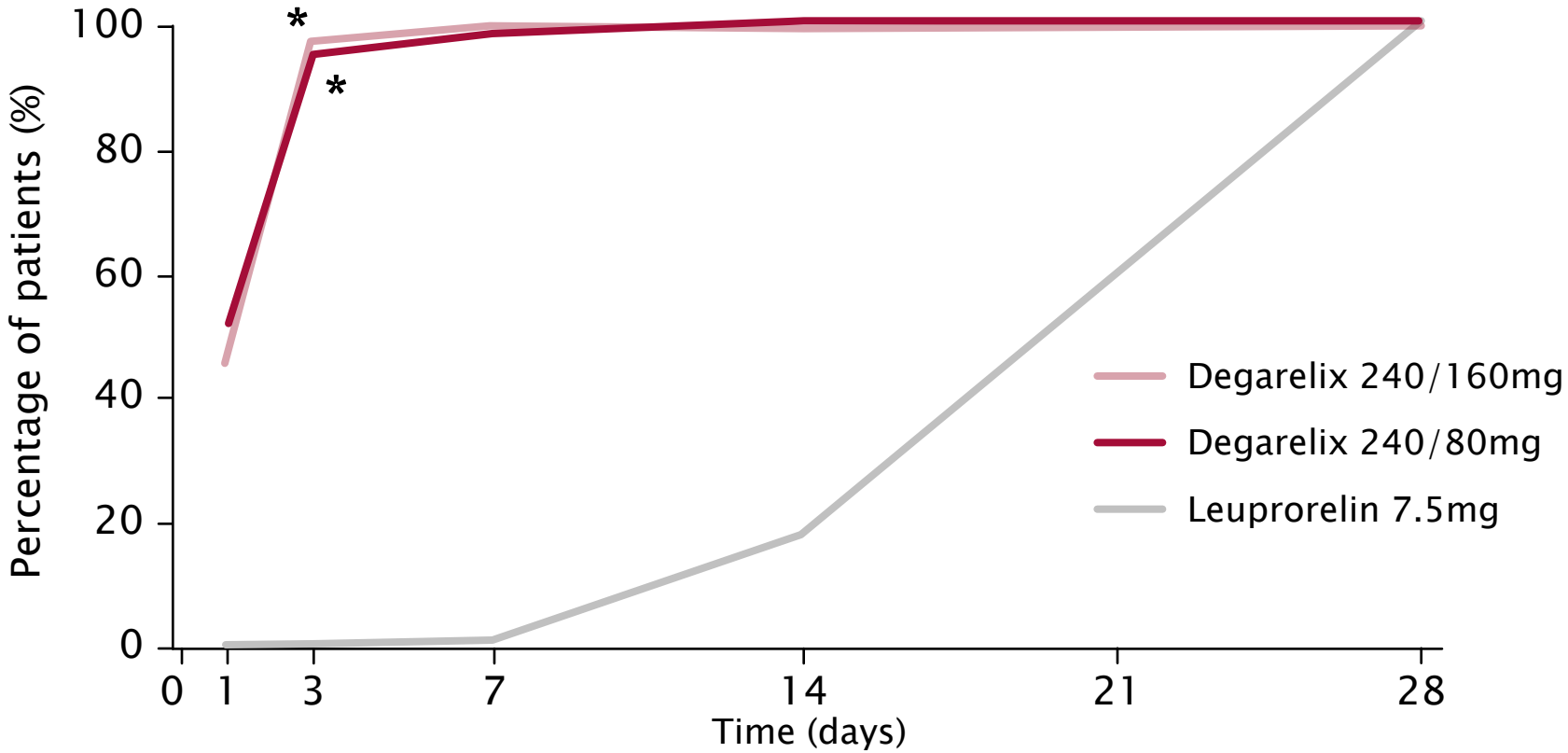
*p<0.001 degarelix (both doses) versus leuprorelin

Boccon-Gibod L et al. Poster presentation. 23rd EAU Congress, Milan, Italy, 2008

The licensed dose for degarelix is 240/80 mg
The licensed dose for leuprorelin in the UK is 3.75 mg

Degarelix
Significantly faster testosterone suppression

Percentage of patients with testosterone levels ≤0.5 ng/mL during the first month of treatment



*p<0.001 versus leuprorelin (pairwise comparisons by Fisher's exact test)

Klotz L et al. BJU Int 2008;102:1531-8

The licensed dose for degarelix is 240/80 mg
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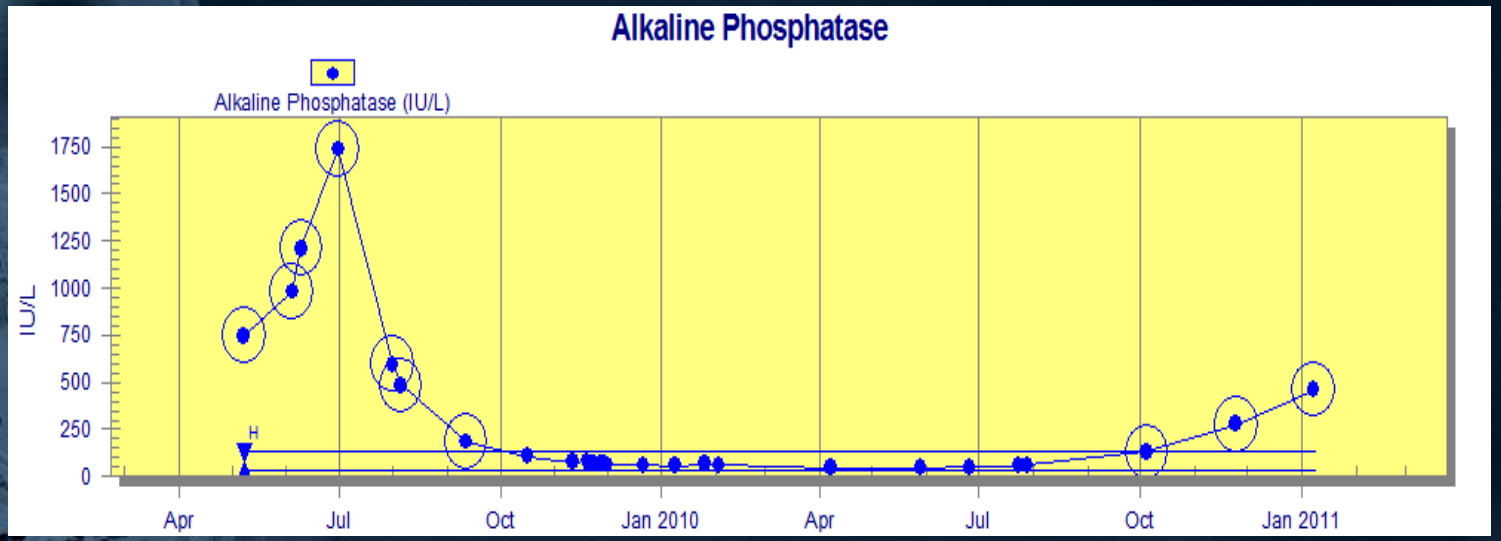
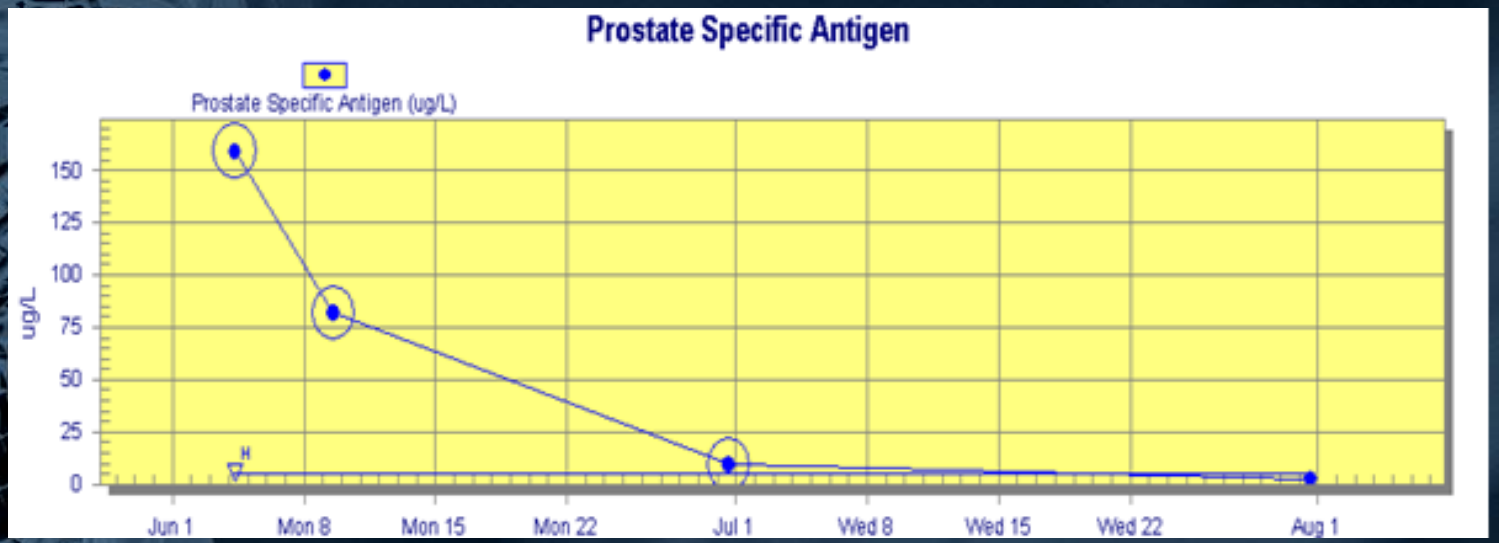
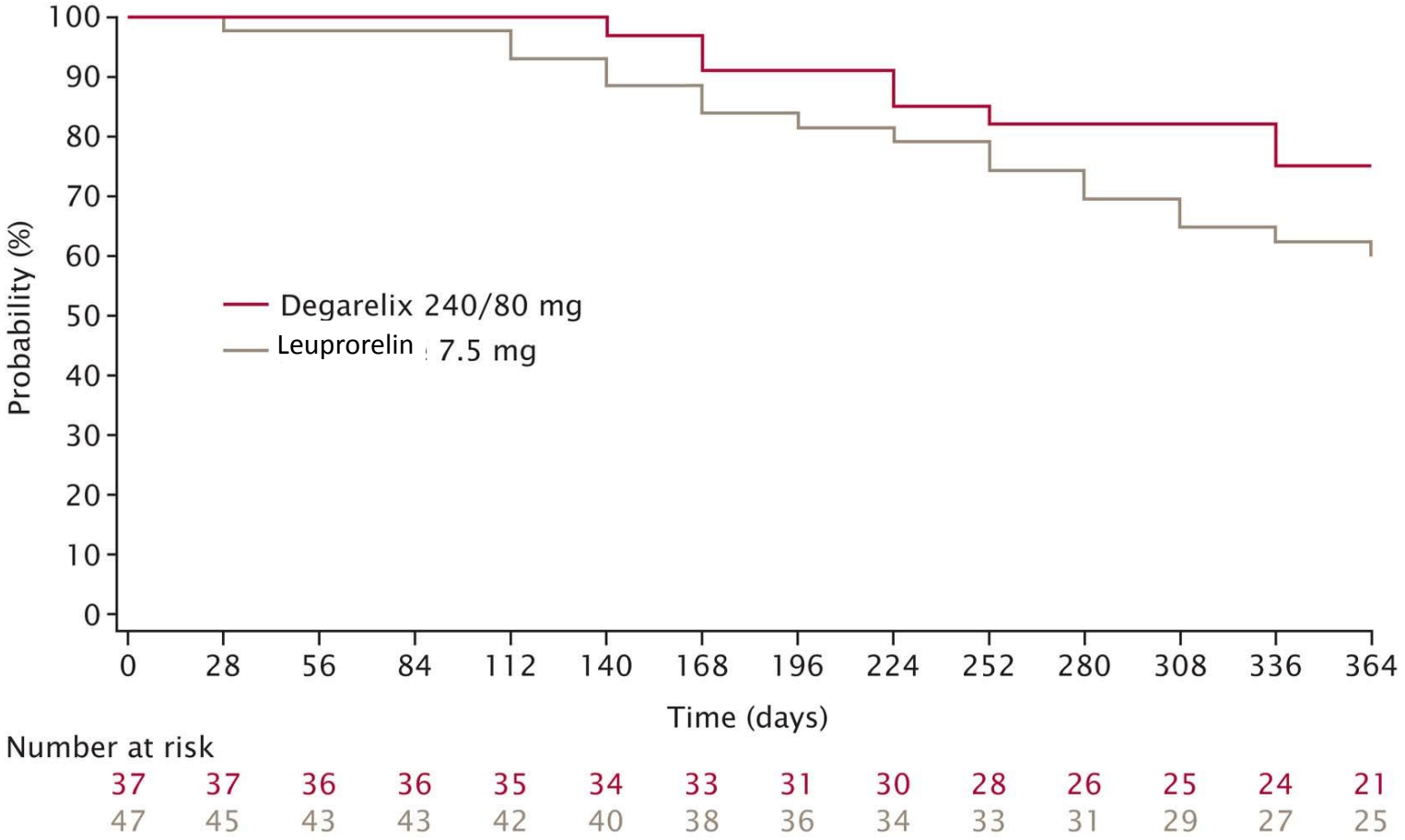
Initial PSA & Alkaline phosphatase responses with degarelix





PSA failure in patients with metastatic disease at baseline



Tombal B et al. Eur Urol 2010;57:836–842.

The licensed dose for degarelix is 240/80 mg
The licensed dose for leuprorelin in the UK is 3.75 mg

Adverse events

	Degarelix 240➔160 mg	Degarelix 240➔80 mg	Degarelix pooled	Leuprorelin 7.5 mg
Any AE	**83%**	**79%**	**81%**	**78%**
Injection site AEs	44%	35%	40%	<1%***
Hot flush	26%	26%	26%	21%
Weight increased	11%	9%	10%	12%
Back pain	6%	6%	6%	8%
Arthralgia	3%	5%	4%	9%*
Hypertension	7%	6%	6%	4%
Fatigue	6%	3%	5%	6%
Urinary tract infection	1%	5%	3%	9%**
Nausea	5%	4%	5%	4%
Constipation	3%	5%	4%	5%
Hypercholesterolaemia	6%	3%	5%	2%
Chills	3%	5%	4%	0%**

*$p<0.05$, **$p<0.01$, and ***$p<0.001$ versus degarelix pooled

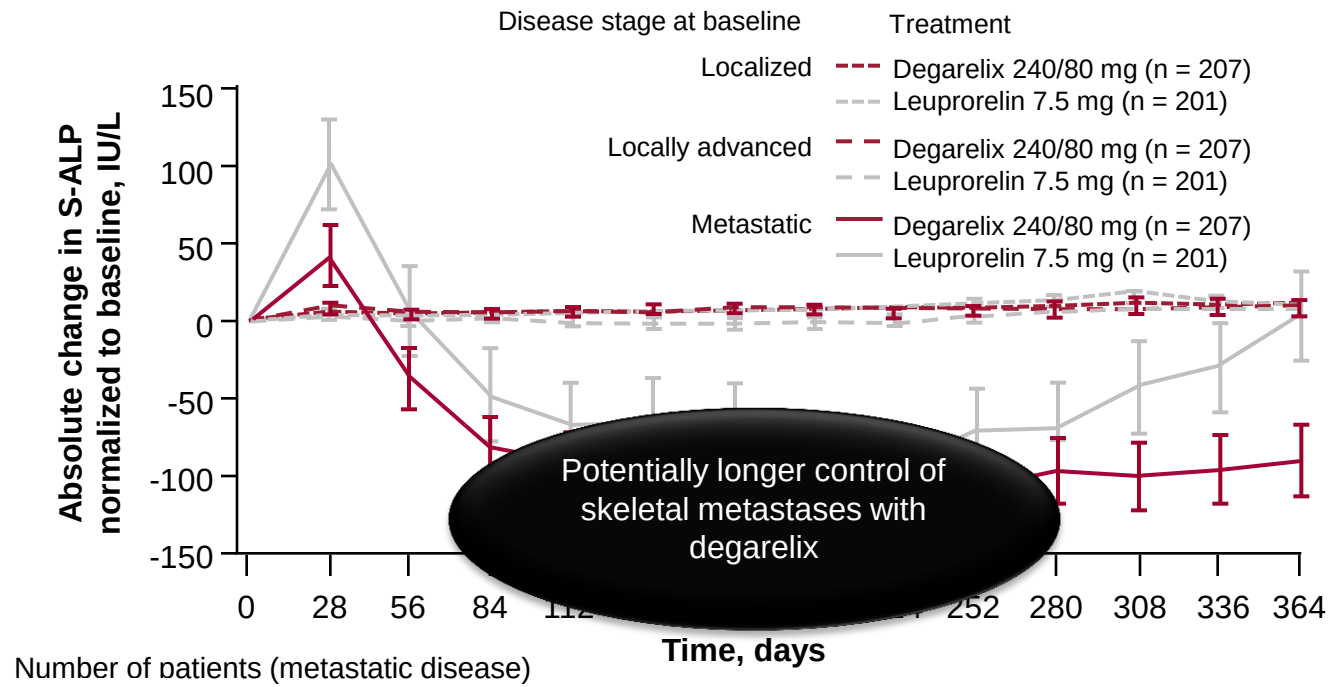
The licensed dose for degarelix is 240/80 mg
The licensed dose for leuprorelin in the UK is 3.75 mg

Injection site reactions

	Degarelix 240➔80 mg	
	Injections, n	Injection-site reactions, n (%)
Starter dose	**207**	**66 (32)**
Maintenance dose(s)	**2244**	**82 (4)**

Site reactions : Higher with the initial injection v maintenance dose

Faster and More Profound S-ALP Control With Degarelix in Metastatic Disease



Degarelix has a faster and more profound effect on the suppression of S-ALP levels in the subgroup of patients with metastatic disease (day 364; 96 *vs.* 179 IU/L; *P* = 0.014)

S–ALP, serum alkaline phosphatase

Data are means ± standard error; *P* = 0.014 for overall S-ALP suppression *vs.* leuprorelin

Schröder F, et al. BJU Int. Jul 2010;106(2):182-187.

The licensed dose for degarelix is 240/80 mg
The licensed dose for leuprorelin in the UK is 3.75 mg

ADT and risk of cardiovascular disease

Numerous adverse events are associated with ADT including an increase in cardiovascular events

- LHRH agonists linked to increased CV morbidity compared to orchiectomy[1]
- Men with history of CVD most at risk[2,3]

1. Taylor LG, et al. Cancer 2009;115:2388-99
2. Nanda AN, et al. JAMA 2009;302:866-73
3. Hedlund PO, et al. Scand J Urol Nephrol 2011;45:346–53

Androgen deprivation therapy with a GnRH releasing hormone antagonist, degarelix, lowers the risk of CV events or death when compared to LHRH agonists

Albertsen P et al. Poster AUA 2013

This study is a retrospective analysis of 6 clinical trials, some of which include unlicensed preparations, dosages and indications for degarelix. In the UK, degarelix is licensed as a 1-month preparation with a starting dose of 240mg followed by a maintenance dose of 80mg monthly

Materials and Methods

- This analysis was prompted by the concerns raised by the FDA in 2010 concerning CV side effects associated with ADT.
- Data were pooled from 6 prospective, randomized trials (n=2328) comparing degarelix and LHRH agonists.
- 1686 patients received treatment for one year and 642 patients received treatment for 3-7 months.
- The treatment groups were balanced for common baseline and CV characteristics.
  - Baseline incidence of CV disease was approximately 30% in both treatment groups.

Albertsen P et al. Eur Urol 2013

Conclusions

- Over one year of treatment, when patients with a history of CVD at baseline were treated with degarelix, they had:
  - A significantly lower probability of a CV event or death than those treated with a LHRH agonist.
- Men in need of ADT, especially those with a history of CVD, may have a significantly lower risk of CVD sequelae with the GnRH antagonist, degarelix, compared with a LHRH agonist.

Albertsen P et al. Eur Urol 2013
Albertsen P et al. Poster 781. AUA 2013

NICE & degarelix

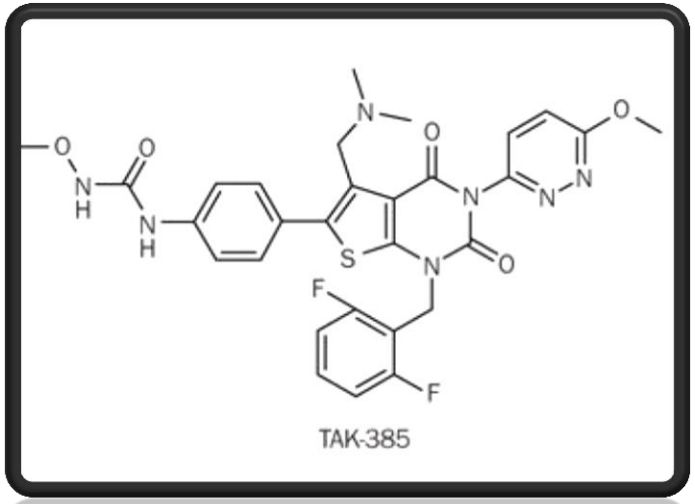
Draft guidance issues not recommending degarelix depot - to treat advanced, hormone dependent prostate cancer

- "The draft NICE guidance says it is not a cost-effective drug compared with the currently available standard treatment - LHRH agonists - and there is also no way of identifying the people who would benefit the most from it"
- "The independent Appraisal Committee had previously made a provisional positive recommendation for degarelix to treat people who already present with signs and symptoms of spinal cord compression, but clinical experts said that using the treatment at this stage would not be appropriate.
- "Based on the evidence and inputs from the experts, it concluded that it was not possible to identify the people who may develop spinal cord compression beyond those people with spinal metastases.

The committee could therefore not recommend the drug.

5th June 2015


NEWS
What's
NEW?


TAK-385

Oral GnRH antagonist

Phase 2 trial of TAK-385 (first interim analysis)

- Men aged ≥18yrs with histologically confirmed prostate cancer, baseline T >150ng/dL and prostate-specific antigen (PSA) >2ng/mL, who were candidates for first-line androgen deprivation therapy.

Randomized to receive:

- Oral TAK-385, 80 or 120mg, once daily (QD) (50 men)
- Or leuprorelin (LPR) 22.5mg subcutaneously every 12 wks (Q12W),for 48 wks.

Primary endpoint:

- Effective castration rate of TAK-385 (T <50ng/dL) from wk 5–24.

Secondary endpoints:

- Safety, pharmacokinetics (PK), and PSA kinetics.
- Plasma PK, T, and PSA measurements were collected on days 1, 4, 8, 15 and 29, and then every 4–12 wks.

Shore N, Bailen J, Pieczonka C, et al: TAK-385, an oral GnRH antagonist: Efficacy and safety results from a randomized phase 2 trial in prostate cancer patients. 2015 European Cancer Congress.Abstract 2502. Presented September 26, 2015.

Results

Phase 2 trial of TAK-385 : Estimated Study Completion March 2016

Primary endpoint:

- TAK-385 achieved consistent testosterone suppression rapidly, with a reduction to castrate levels seen by day 7 (95% v 29% LPR grp) that was sustained out to 6 months.

Secondary endpoint:

- TAK-385, PSA was reduced by a median of 89% from baseline to 0.8ng/mL (0.1–118.6) after 4 wks and 97% to 0.1ng/mL (0.1–21.4) after 12 wks.
- With LPR, PSA was reduced by a median of 79% from baseline to 1.8ng/mL (0.1–16.5) after 4 wks and 92% to 0.3ng/mL (0.1–1.8) after 12 wks.

Shore N, Bailen J, Pieczonka C, et al: TAK-385, an oral GnRH antagonist: Efficacy and safety results from a randomized phase 2 trial in prostate cancer patients. 2015 European Cancer Congress.Abstract 2502. Presented September 26, 2015.

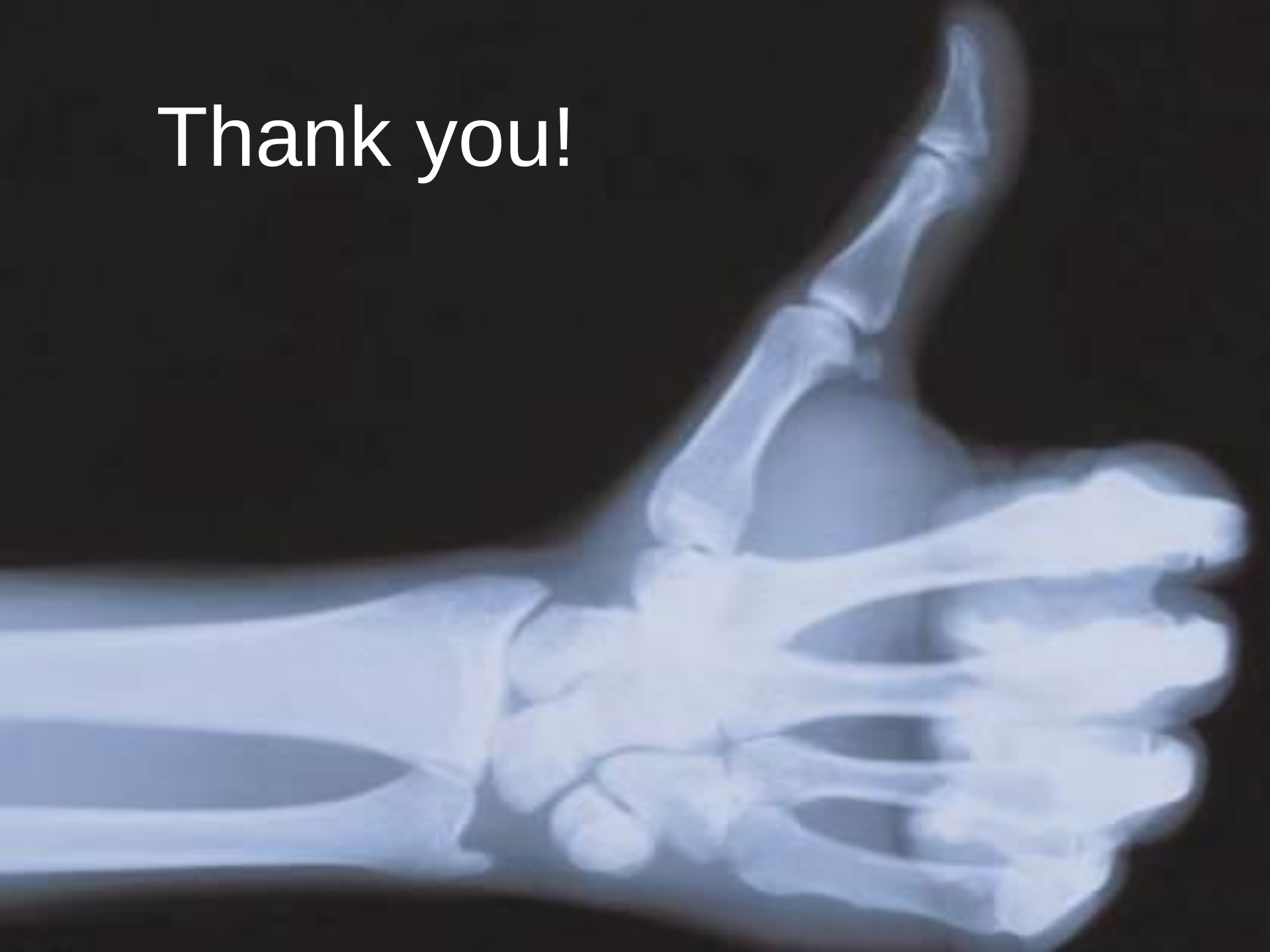
Conclusions

- The safety and efficacy profile of TAK-385 was acceptable and consistent with the mechanism of action.
- TAK-385 rapidly reduced T and maintained levels at <50ng/dL over 24 wks.
- These data support further investigation of oral TAK-385 as a therapeutic alternative to injectable GnRH androgen deprivation therapies.

Shore N, Bailen J, Pieczonka C, et al: TAK-385, an oral GnRH antagonist: Efficacy and safety results from a randomized phase 2 trial in prostate cancer patients. 2015 European Cancer Congress.Abstract 2502. Presented September 26, 2015.

Conclusions…. In the clinic

- GnRH/LHRH antagonist are certainly as effective in achieving testosterone suppression as a GnRH agonist, Thus provides an alternative first-line ADT for advanced disease.
- Their direct mechanism of action results in an immediate suppression of testosterone – symptom relief benefits to patients.
  - Metastatic patients with high tumour burden and risk of acute problems, such as urinary tract symptoms, pain or spinal cord compression
- No need for anti-androgen supplements to prevent the possibility of clinical ‘flare’.
- In patients with metastatic disease, associated with better control of the bone formation marker S-ALP than leuprolide, suggesting that it might offer prolonged control of skeletal metastases and SRE’s.
- More work is required to determine the true cardiovascular benefits – RCT.


Thank you!