Clinical development of a new GnRH blocker

Bo-Eric Persson MD Assoc Prof FEBU
Med Dir urology/Oncology

Uppsala
Sweden

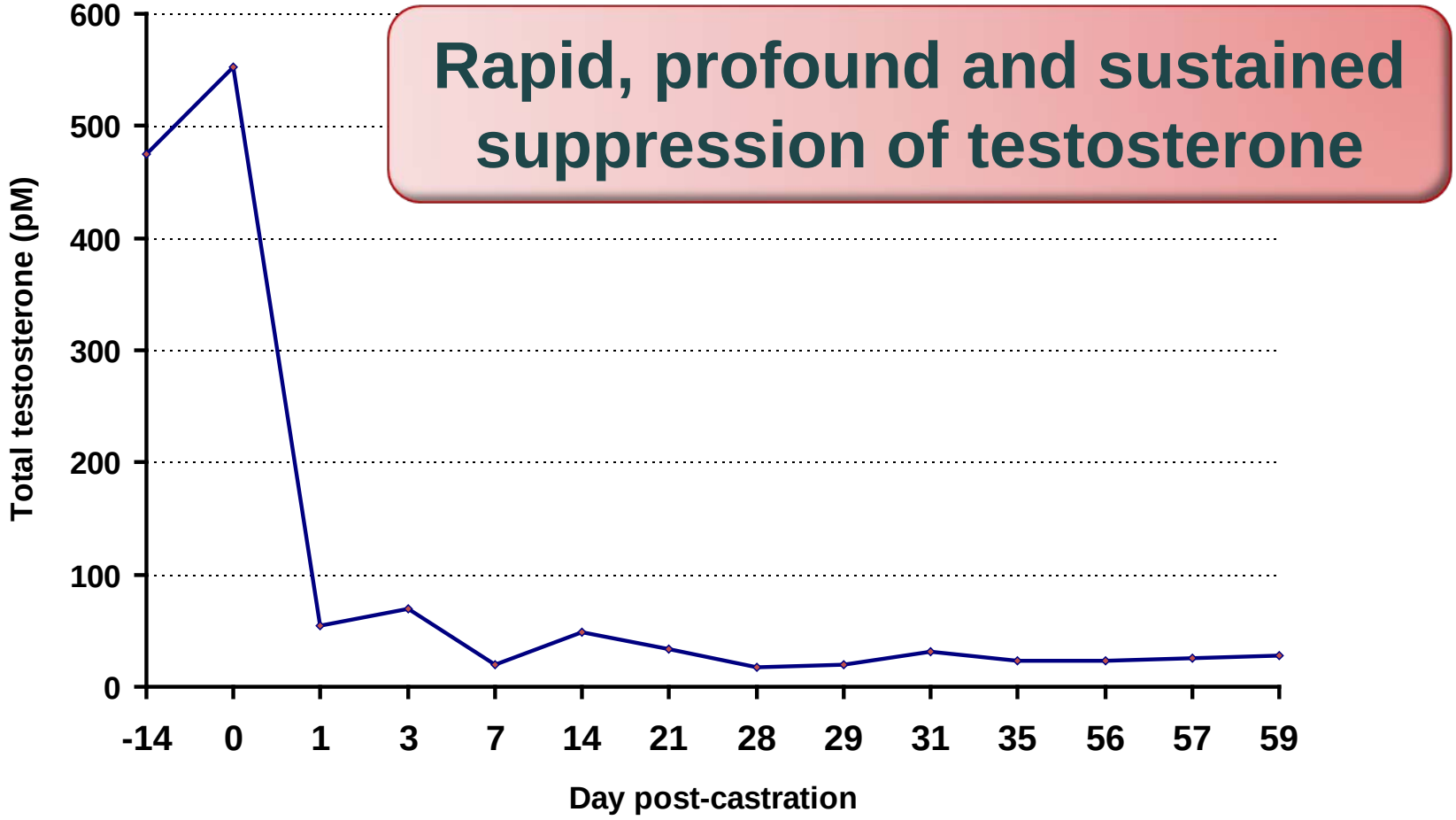
Saint-Prex
Switzerland

Presentation overview

- Need for a GnRH blocker
- Clinical development of degarelix (FIRMAGON®)
  - ➔ Phase II dose-finding conclusions
  - ➔ Phase III clinical trial (CS21)
  - ➔ Phase III extension trial (CS21a)
- Where is FIRMAGON® available?

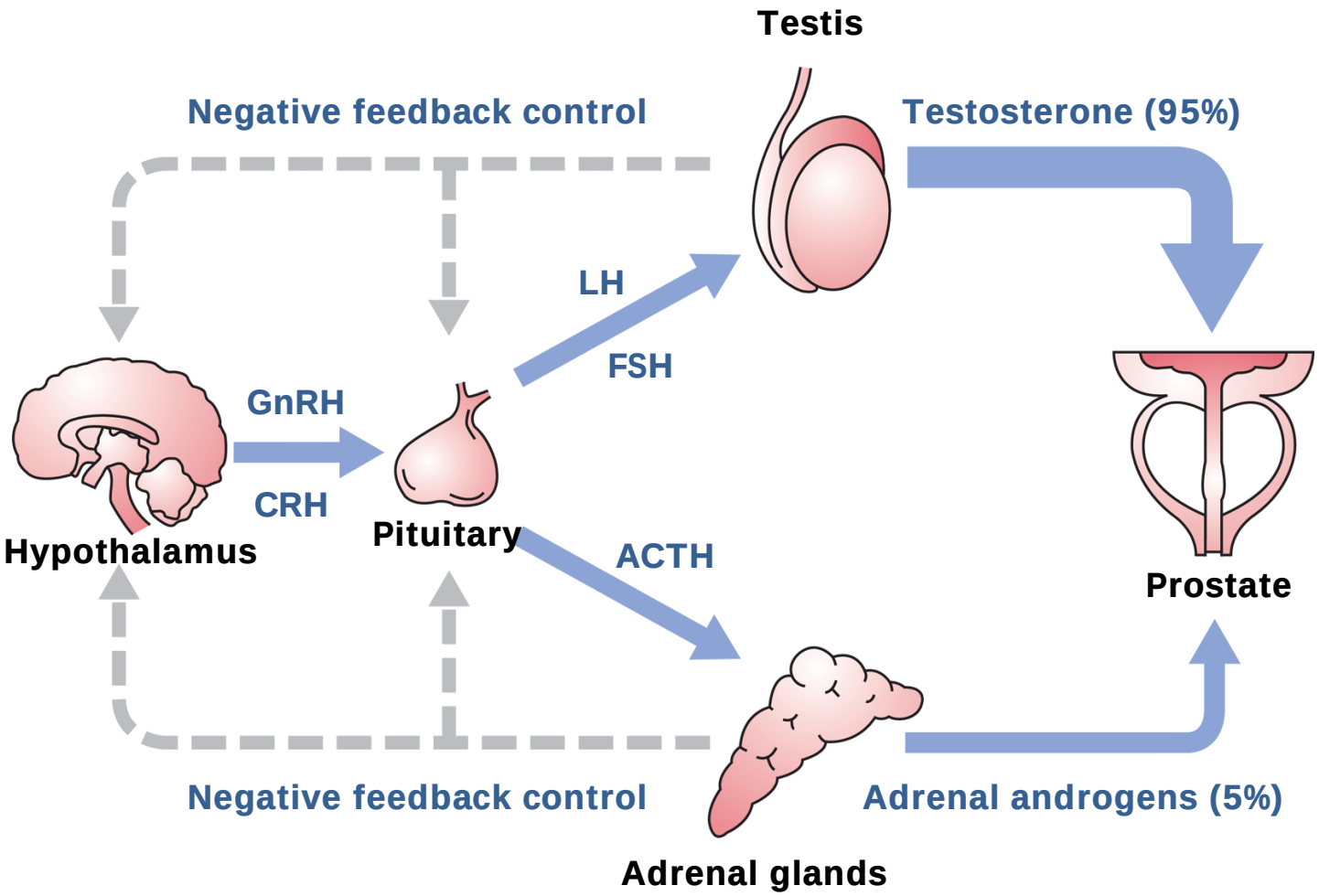
GnRH, gonadotrophin-releasing hormone

Pharmacological description of surgical castration



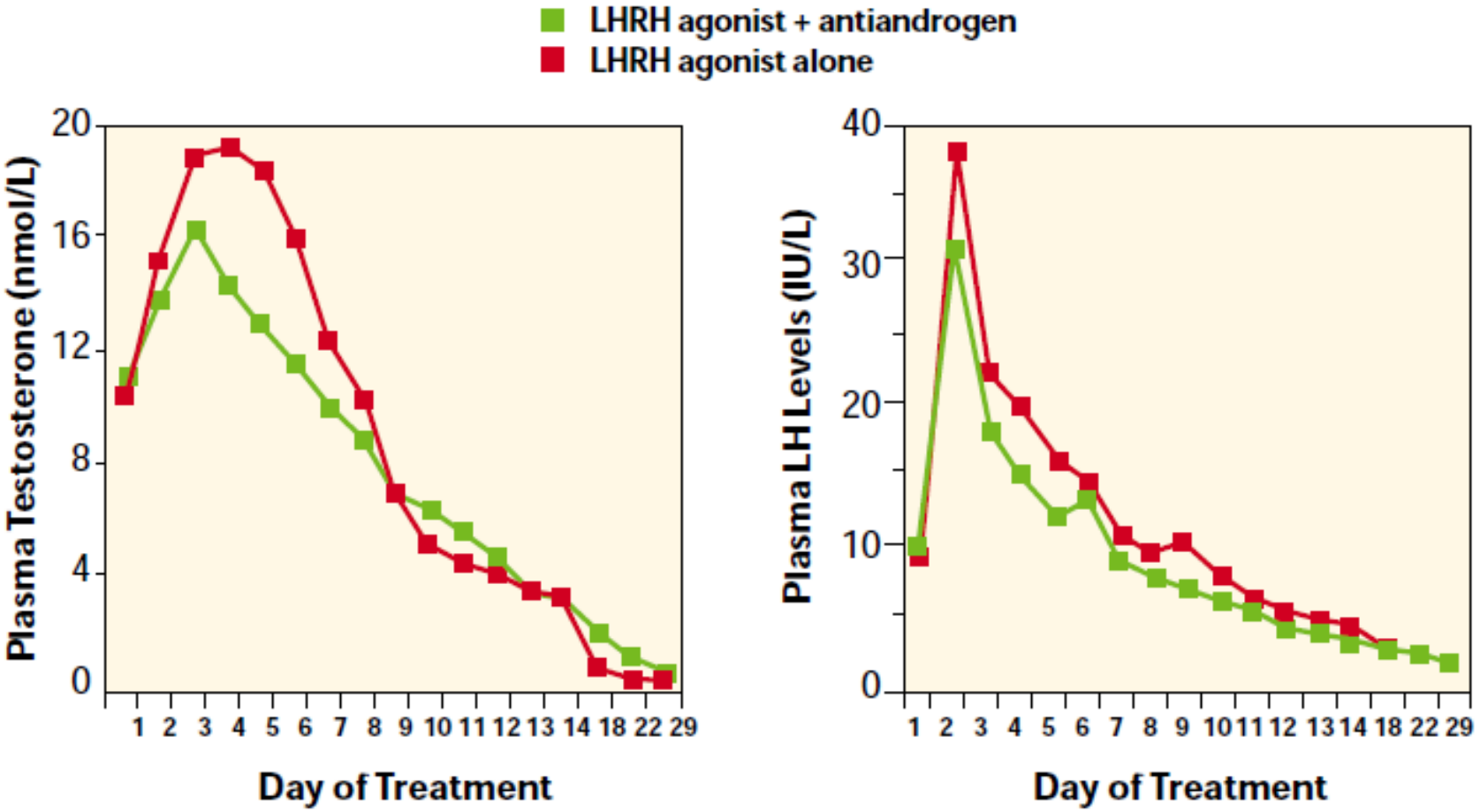
Tombal B. Eur Urol Suppl 2007;6:834–9

Hypothalamic–pituitary–gonadal axis



ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone

LH and testosterone surge

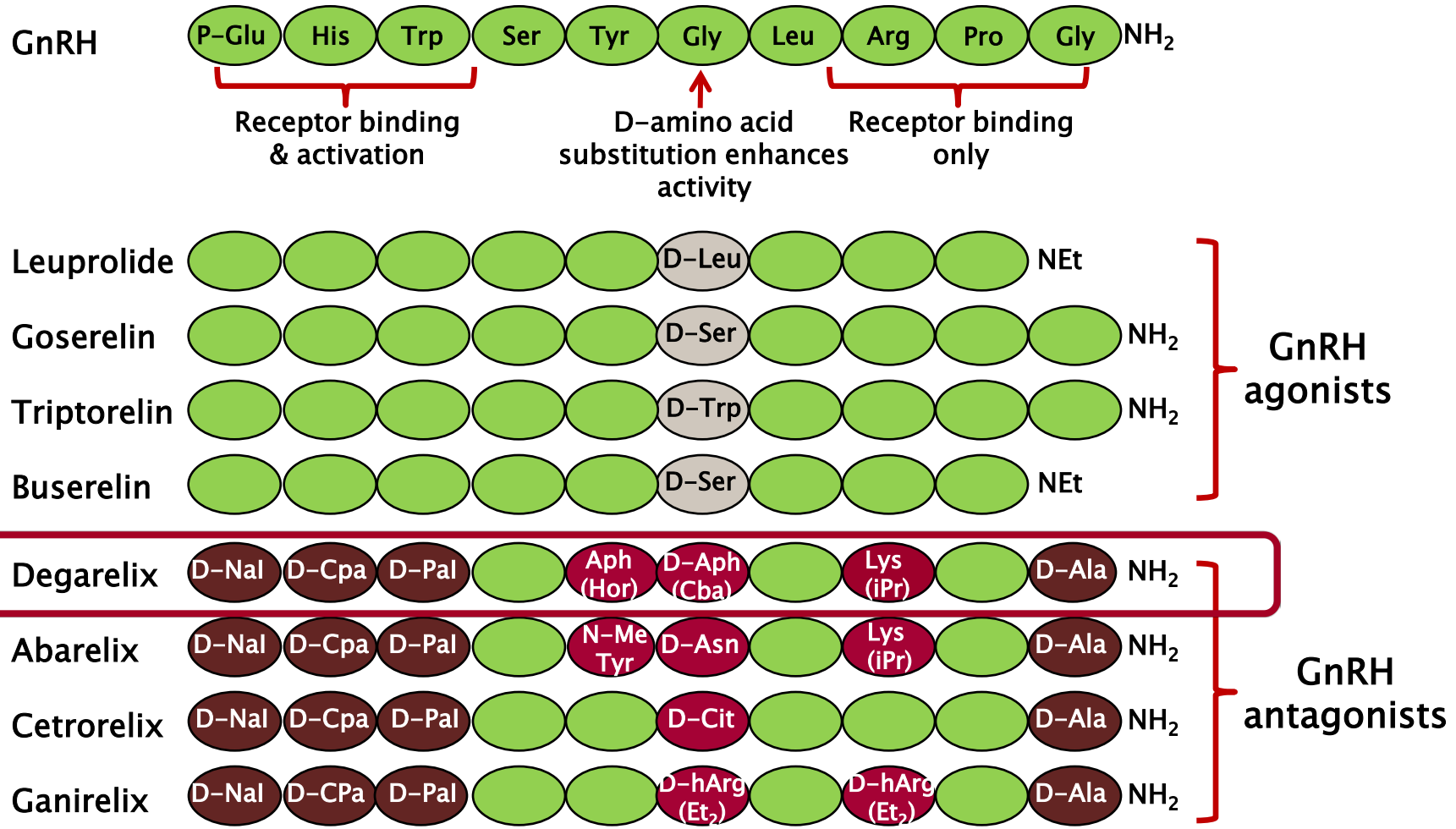


Bubley GJ. Urology 2001;58(2 suppl 1):5–9

GnRH agonists

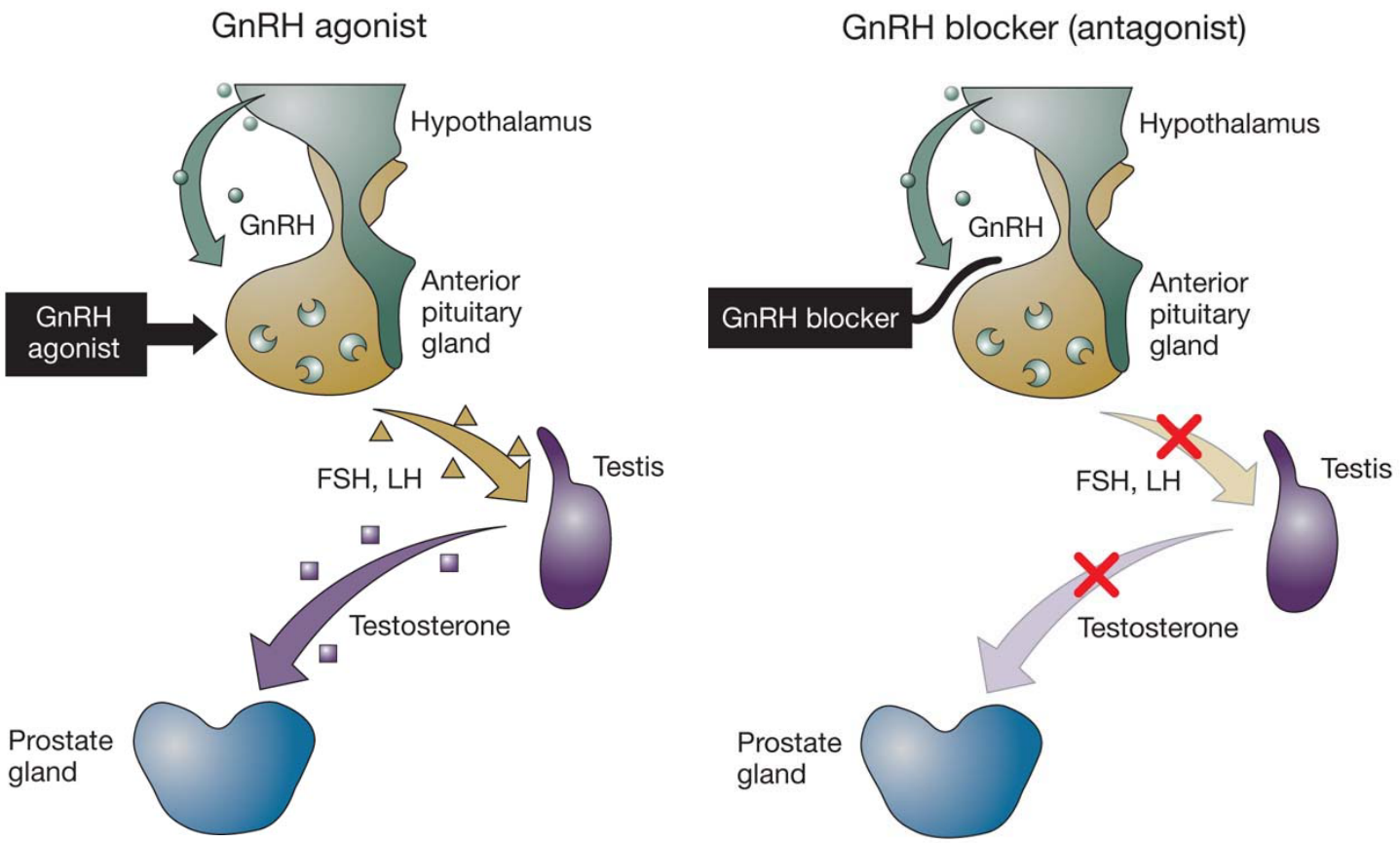
- Most widely used strategy for androgen suppression
  - ➔ Generally considered similar to surgical castration in terms of oncological results and side effects
  - ➔ Medical castration preferred by patients
- Associated with testosterone surges
- Do not achieve similar levels of castration as orchidectomy
  - ➔ Microsurges
- Often used in combination with antiandrogens

Peptide structures of GnRH agonists and antagonists



Millar et al. Endocr Rev 2004;25:235-75

GnRH receptor agonists and blockers have a different mechanism of action



FSH, follicle-stimulating hormone
LH, luteinisng hormone

Degarelix studies

Phase I

- 4 phase I studies (CS01, 05, 08, 23)
  - ➔ More than 100 healthy men

Phase II dose-finding

- UK (CS02)
  - ➔ 129 patients
- European (CS06)
  - ➔ 82 patients
- North American (CS07)
  - ➔ 172 patients
- European (CS12)
  - ➔ 187 patients
- North American (CS14)
  - ➔ 127 Patients

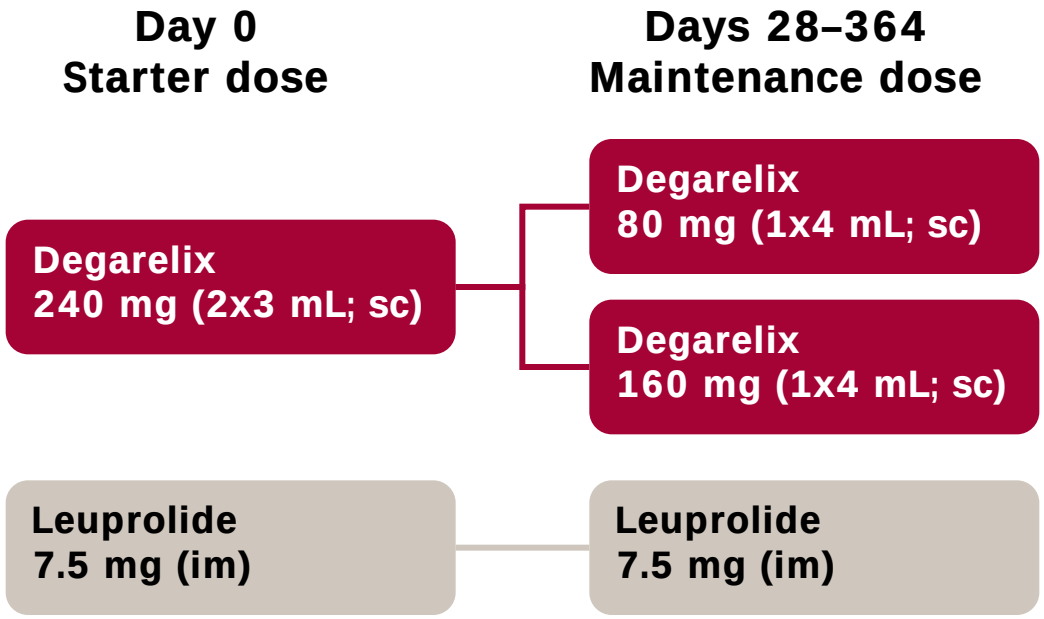
Phase III (B) / IV)

- Long-term safety / tolerability (CS21) [CS21A]
- Agonist failures (CS27)
- Symptomatic disease (CS28)
- Intermittent therapy (CS29)
- Neoadjuvant therapy (CS30)
- Prostate size (CS31)
- 3-monthly dosing (CS35)
- Comparative intermittent study (CS37)

Conclusions of phase II dose-finding studies

- Degarelix has an immediate onset of action
- Degarelix induces a fast, profound and sustained testosterone and PSA suppression
- Degarelix is well tolerated
- Suitable degarelix doses identified for further study
  - ➔ 240 mg is the most effective initiation dose
  - ➔ 80 mg and 160 mg are effective maintenance doses

CS21: degarelix phase III pivotal study



- 610 patients
- Monthly dosing
- Antiandrogen flare protection at investigator discretion

Primary end point: suppression of testosterone to ≤0.5 ng/mL from Day 28 through to Day 364

CS21: baseline demographics and disease characteristics

	Degarelix 240➔80 mg	Degarelix 240➔160 mg	Leuprolide 7.5 mg
Number of patients (ITT)	207	202	201
Age (years)	71.6	72.1	72.5
Weight (kg)	79.8	78.7	79.4
BMI (kg/m^2)	26.7	26.6	26.9
Prostate cancer stage			
Localised (%)	33	29	31
Locally advanced (%)	31	31	26
Metastatic (%)	18	20	23
Rising PSA after radical therapy or indecisive bone scan or failed curative intent (%)	18	20	19
Gleason score			
2–4 (%)	10	11	12
5–6 (%)	33	33	32
7 (%)	30	28	31
8–10 (%)	27	28	26

BMI, body mass index

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

CS21: primary endpoint

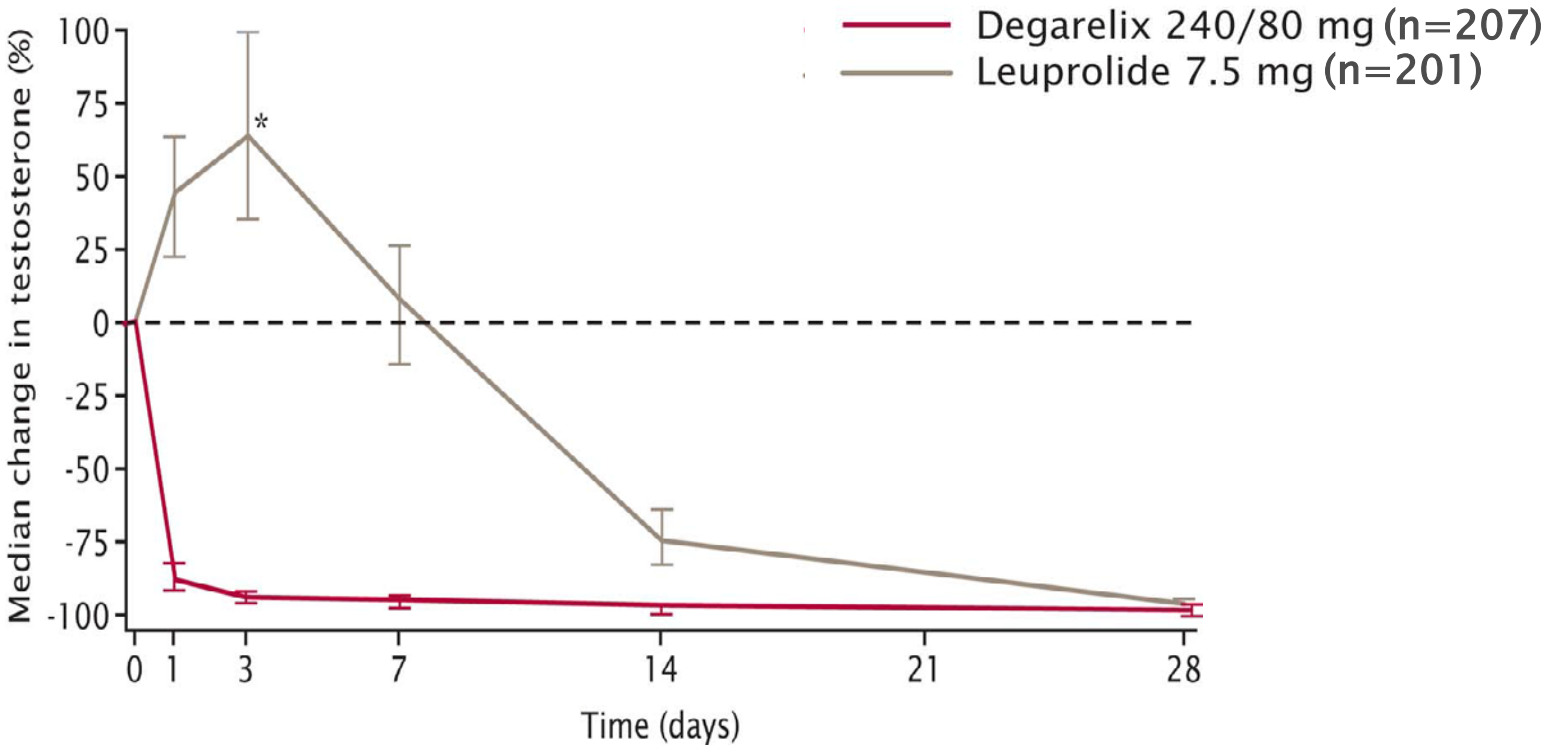
Degarelix is non-inferior to leuprolide in suppressing testosterone to ≤0.5 ng/mL for 1 year

	Degarelix 240➔80 mg	Degarelix 240➔160 mg	Leuprolide 7.5 mg
Patients with treatment response	202	199	194
Response rate, (% [95% CI])	97.2 (93.5, 98.8)	98.3 (94.8, 99.4)	96.4 (92.5, 98.2)
Difference to leuprolide (%)	0.9 (−3.2 to 5.0)	1.9 (−1.8 to 5.7)	–

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

CS21: faster testosterone suppression with degarelix

Degarelix has an immediate onset of action



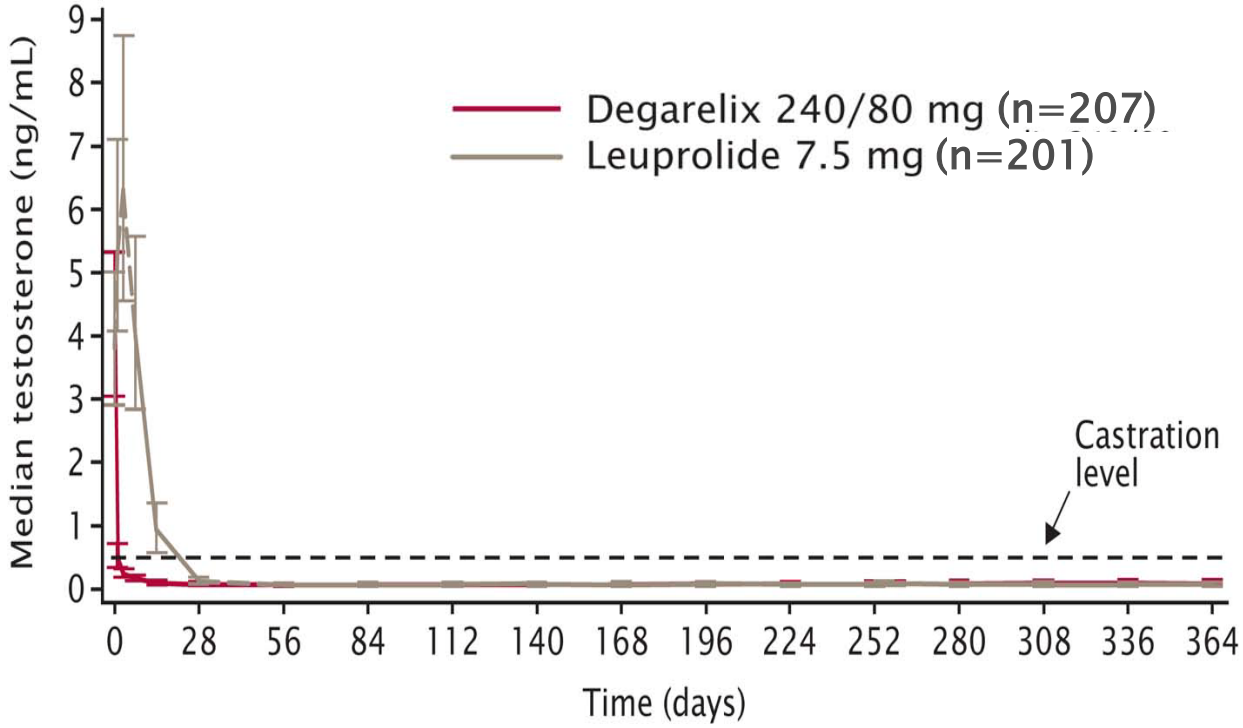
*P<0.001 degarelix vs leuprolide

Data are median changes ± standard error

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

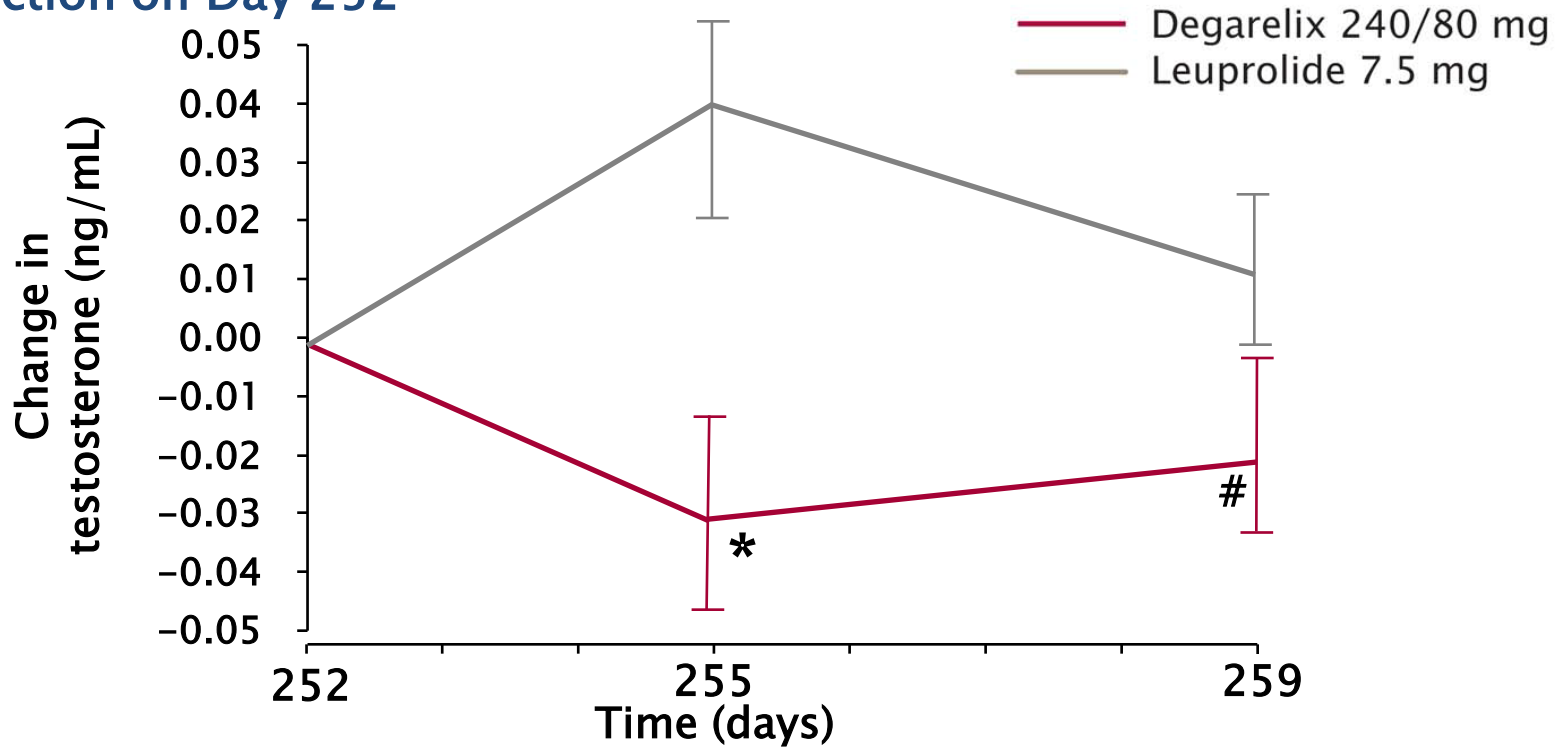
CS21: sustained testosterone suppression

Degarelix sustains testosterone suppression as effectively as leuprolide over 1 year



CS21: leuprolide microsurges

Mean testosterone levels significantly increased following leuprolide injection on Day 252

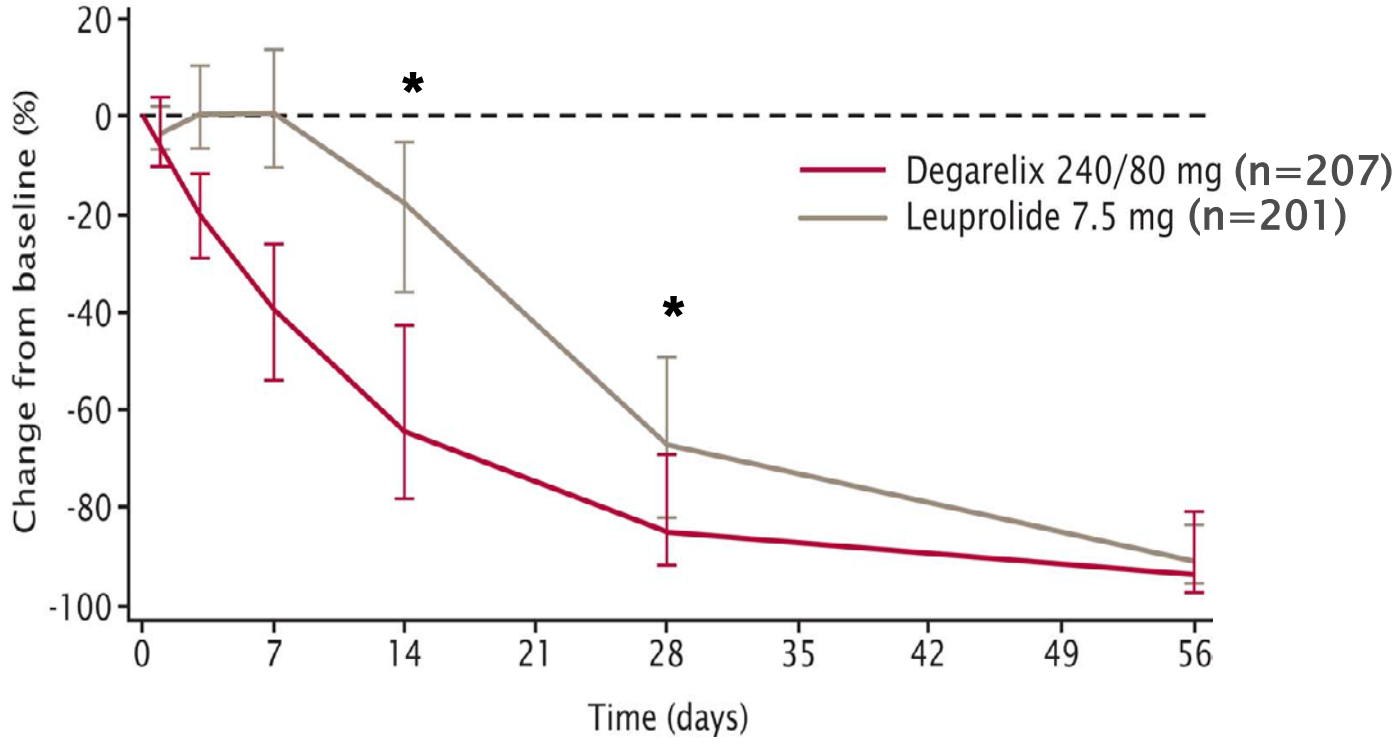


*P<0.0001 vs leuprolide; #p=0.0015 vs leuprolide

Data are means ± 95% CI

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

CS21: PSA reduction is faster with degarelix



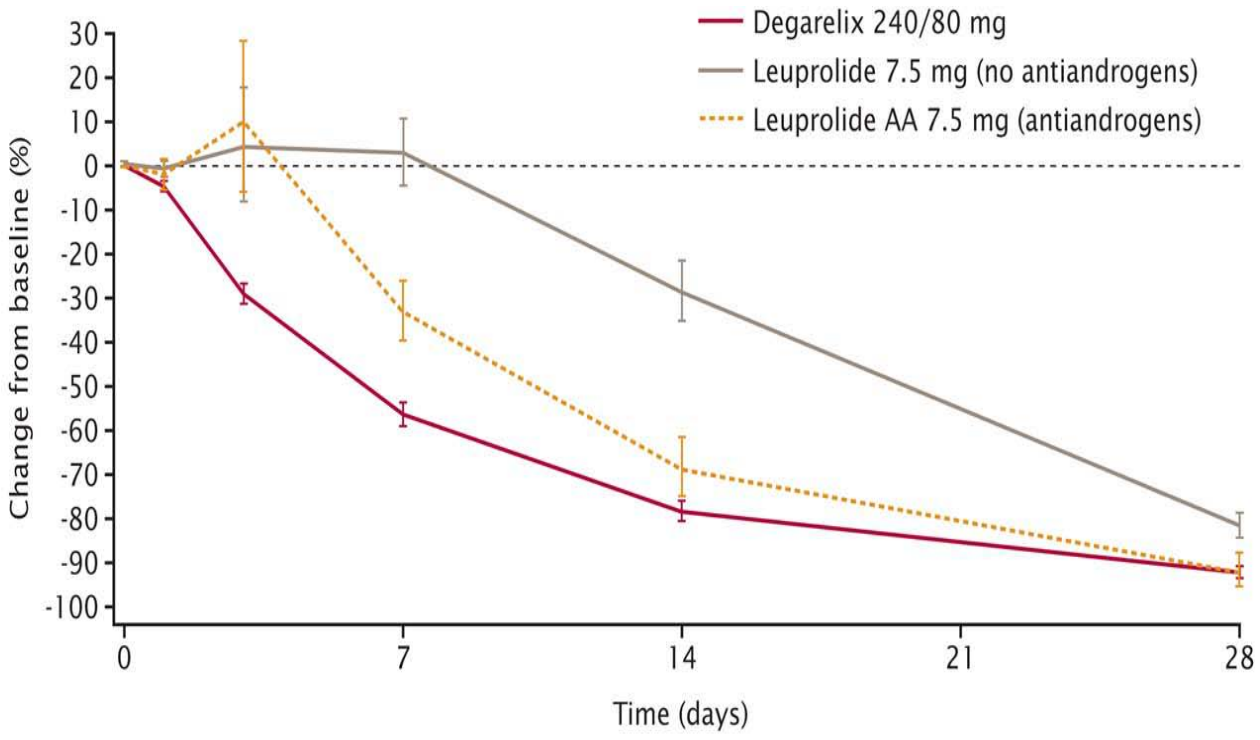
*P<0.001 vs leuprolide (Wilcoxon pairwise comparisons)
11% of leuprolide patients received bicalutamide as flare protection

Data are medians ± interquartile range

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

PSA over 28 days (metastatic patients)

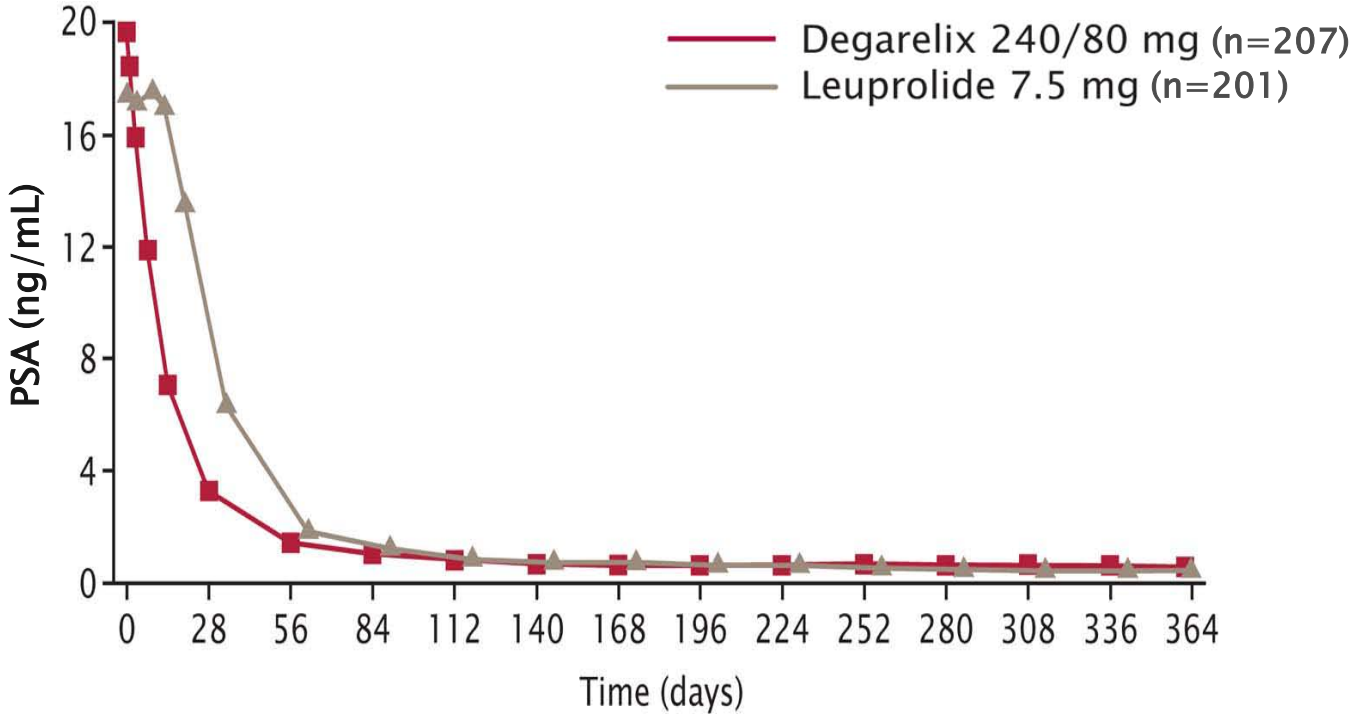
Log-transformed mean (SE)



Degarelix	37	37	37	37	36	37
Leuprolide	38	38	38	38	38	37
Leuprolide AA	9	9	9	9	9	8

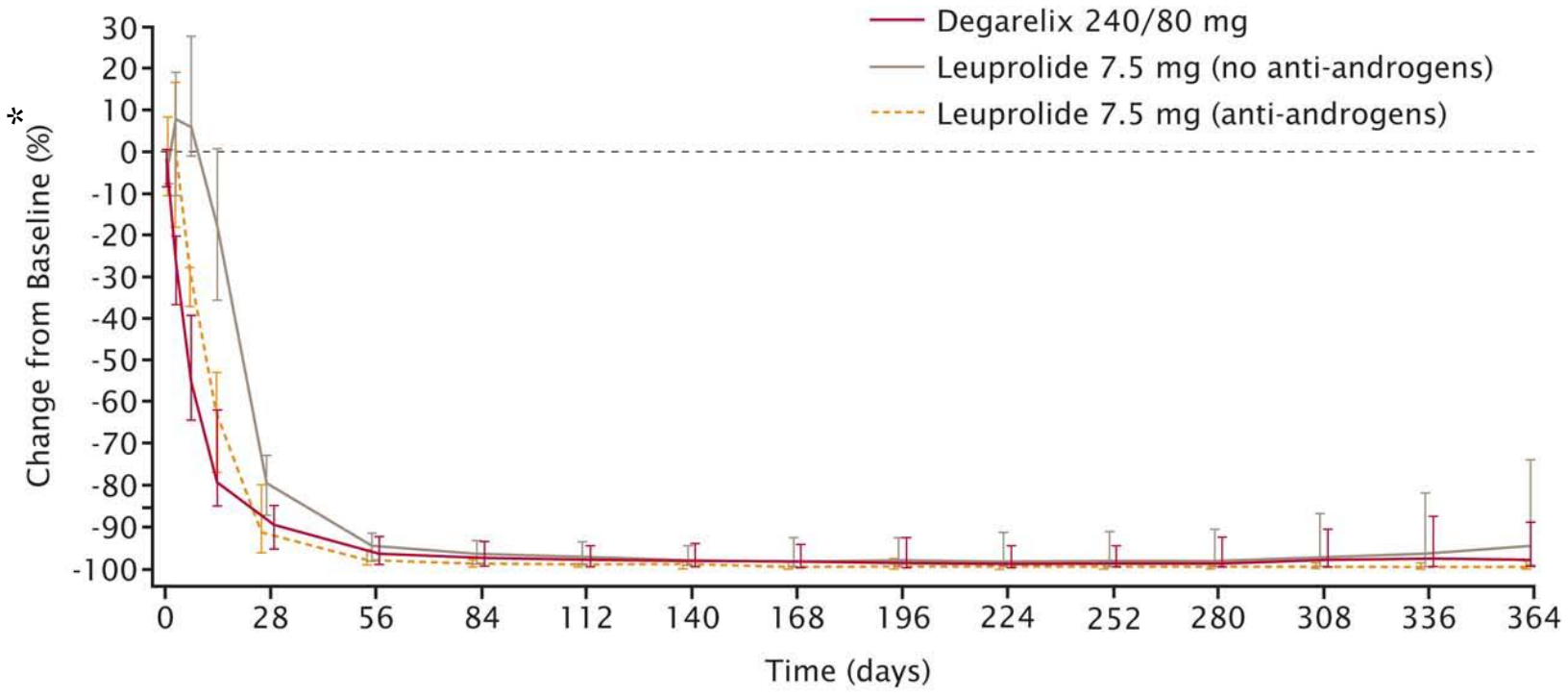
Data on file

CS21: sustained reduction in PSA



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

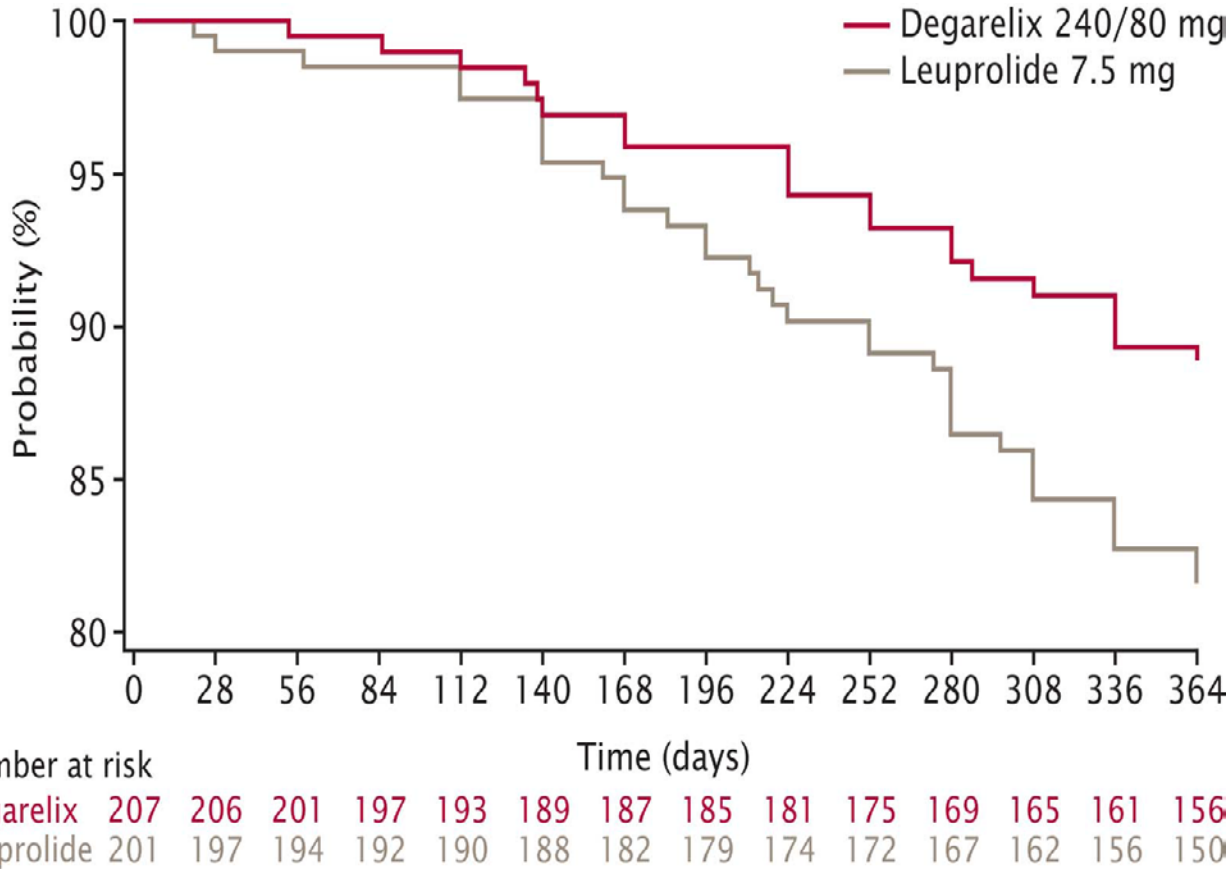
CS21: PSA control in metastatic patients



Degarelix	37	37	36	36	35	33	34	34	31	31	29	28	26	26
Leuprolide	38	37	36	35	35	35	34	35	33	33	33	33	33	32
Leuprolide AA	9	8	8	8	8	8	7	7	7	7	7	7	7	7

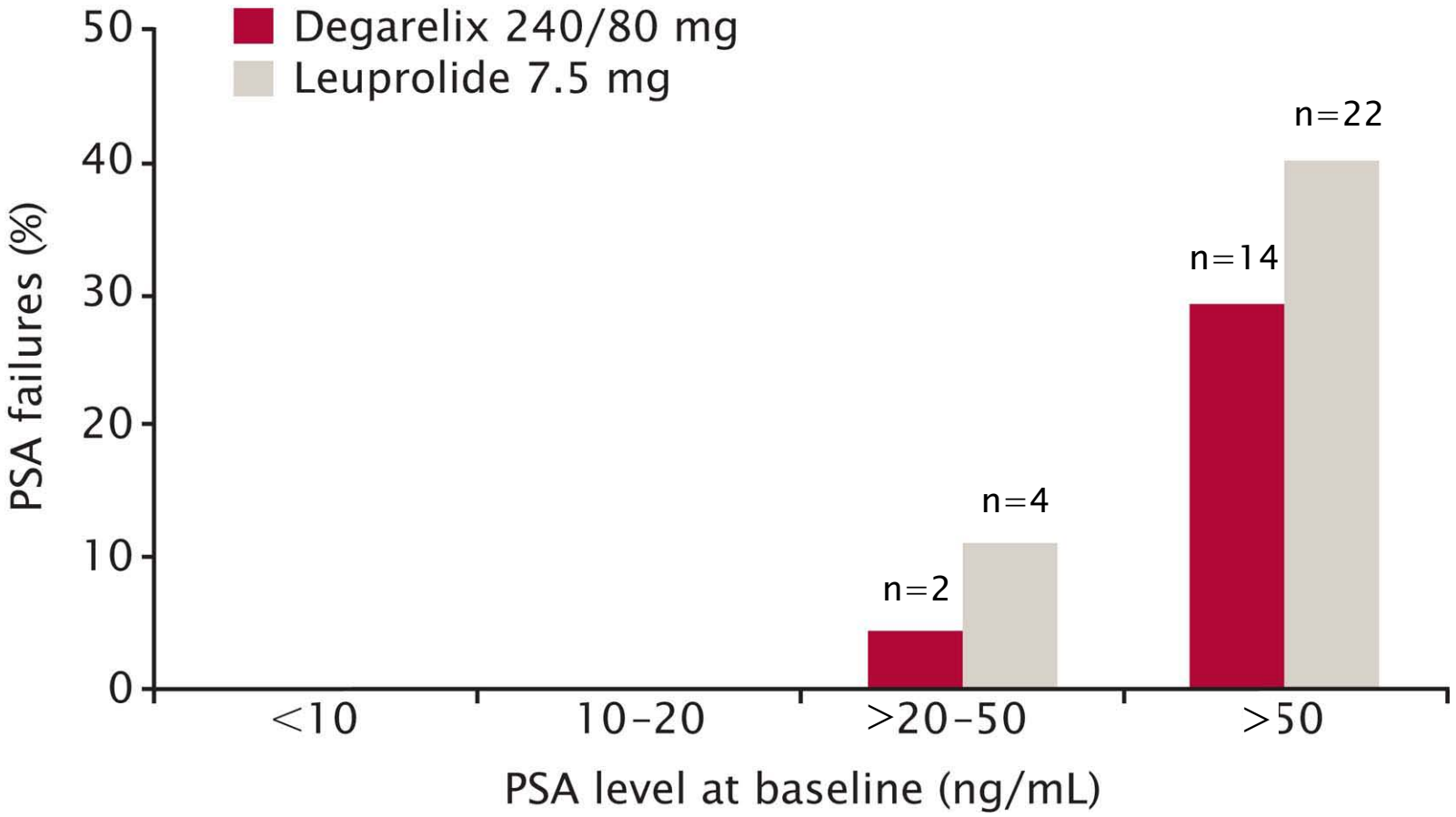
*Median (quartiles) percentage change from baseline

CS21: PSA progression-free survival
(time to PSA failure / death: ITT population)



P<0.05 (Log-Rank)

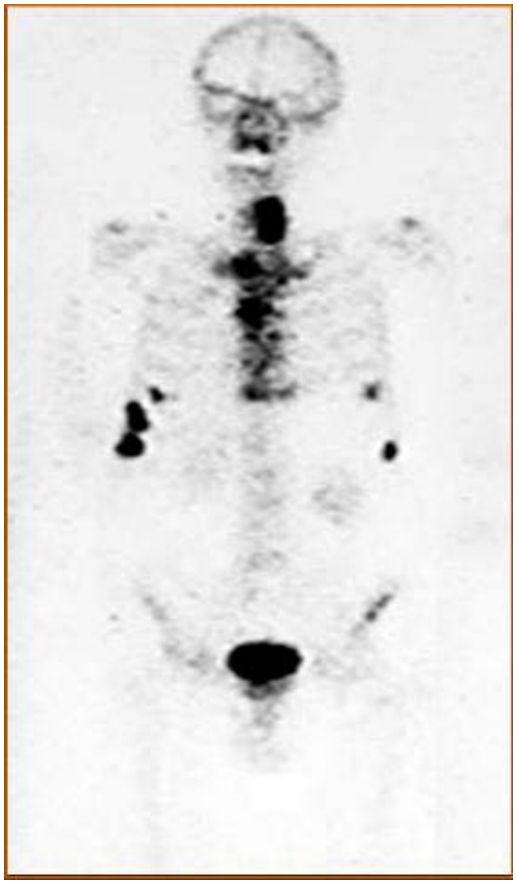
Degarelix: Fewer PSA failures vs leuprolide if baseline PSA >20 ng/mL



Tombal B et al. Eur Urol 2010;57:836–42

Rationale for the S-ALP analyses

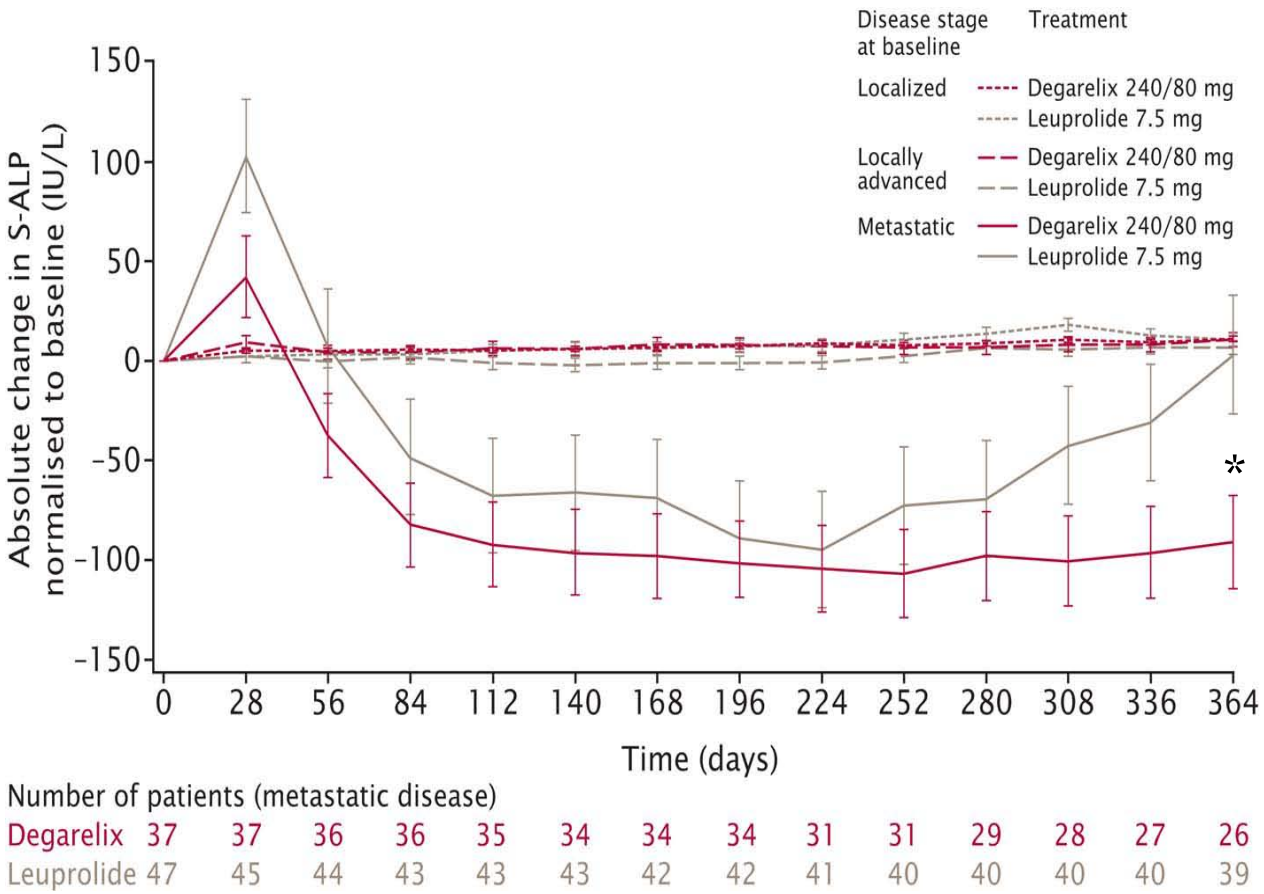
- S-ALP is a bone formation marker that can be used in the diagnosis and follow-up of bone metastases
- Elevated S-ALP is associated with progression of bone metastases[1] and reduced overall survival[2]



S-ALP, serum alkaline phosphatase

1. Lein M et al. Eur Urol 2007;52:1381-7
2. Johansen JS et al. Clin Cancer Res 2007;13:3244-9

S-ALP: baseline disease stage



*P=0.0137

Data are means ± standard error

Schröder FH et al. BJU Int 2010;106:182–7

CS21: adverse events

	Patients reporting adverse events (%)			
	Degarelix 240➔80 mg	Degarelix 240➔160 mg	Degarelix pooled	Leuprolide 7.5 mg
Any adverse event	**79**	**83**	**81**	**78**
Injection-site adverse events	35	44	40	<1***
Hot flushes	26	26	26	21
Increased weight	9	11	10	12
Back pain	6	6	6	8
Arthralgia	5	3	4	9*
Hypertension	6	7	6	4
Fatigue	3	6	5	6
Urinary tract infection	5	1	3	9**
Nausea	4	5	5	4
Constipation	5	3	4	5
Hypercholesterolaemia	3	6	5	2
Chills	5	3	4	0**

*P<0.05, **P<0.01, and ***P<0.001 vs degarelix pooled

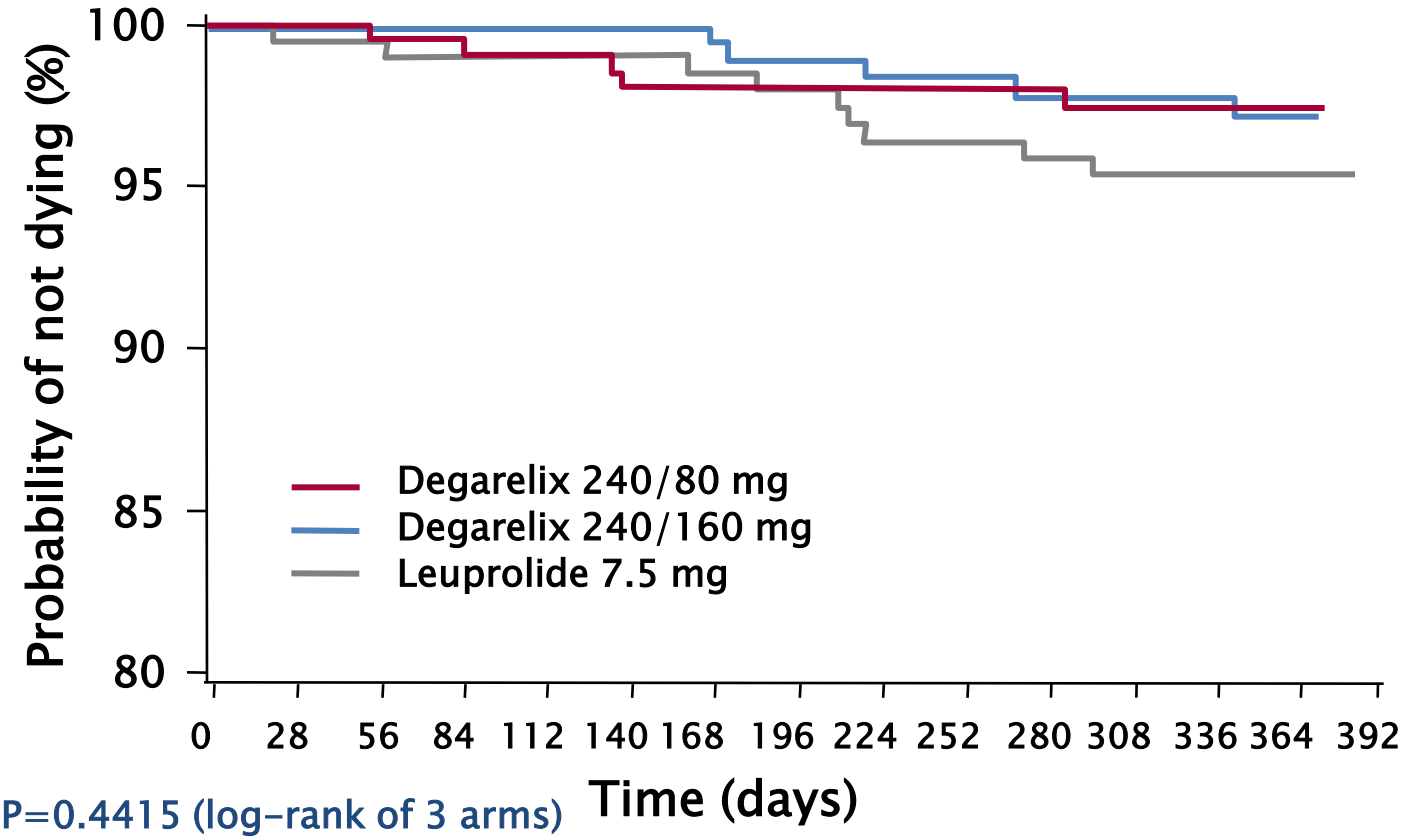
Klotz L et al. BJU Int 2008;102:1531–8

Injection-site reactions occurred predominantly with starter dose

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

CS21: survival

Probability of survival was similar in all three groups



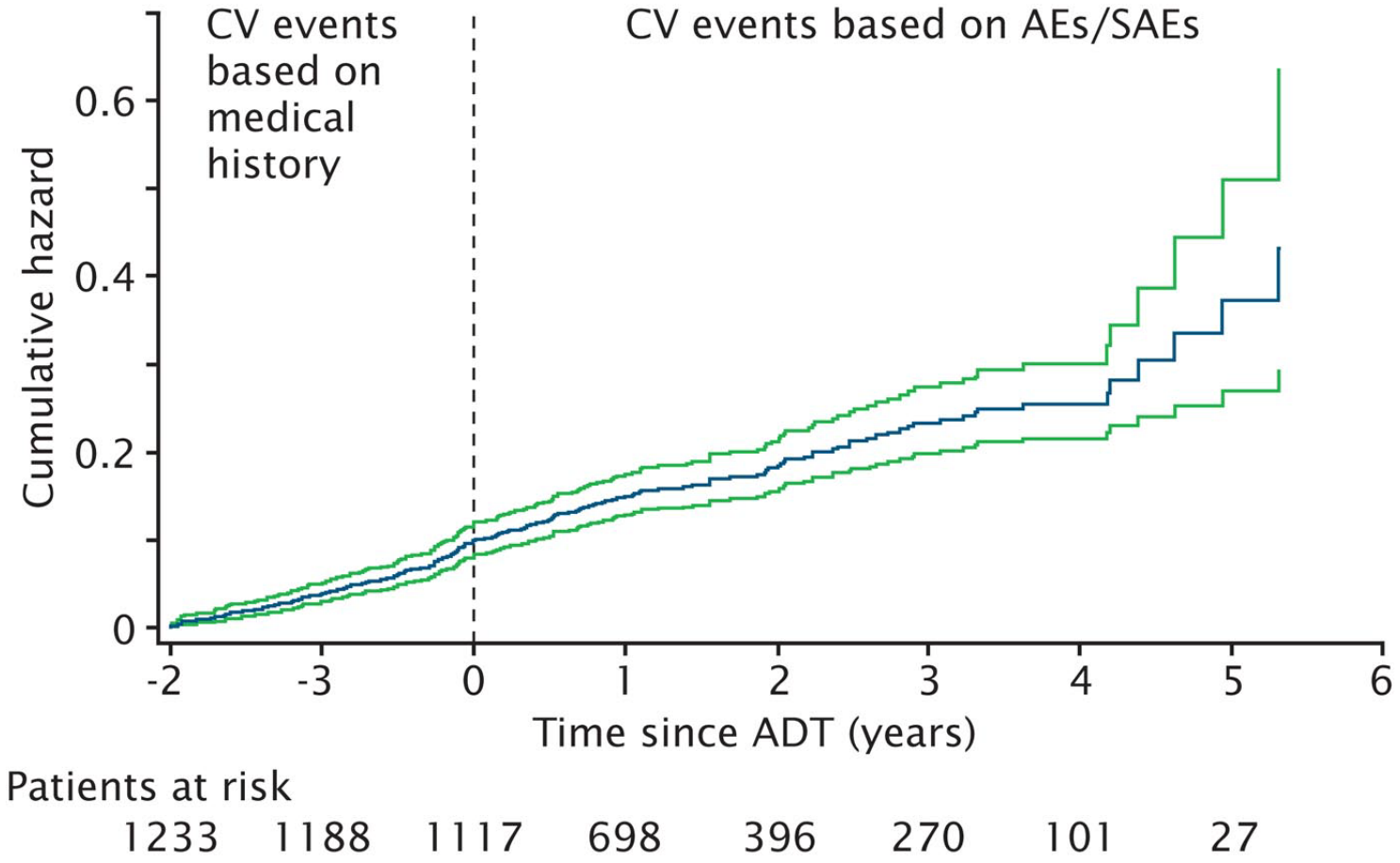
P=0.4415 (log-rank of 3 arms)

CS21: Deaths and discontinuations due to CV-related AEs

	N (%)		
	Degarelix 240/80 mg (N=207)	Degarelix 240/160 mg (N=202)	Leuprolide (N=201)
Deaths	**3 (1.5)**	**2 (<1%)**	**5 (2.5)**
Cardiac arrest	2 (1)	0	0
MI	1 (0.5)	0	1 (0.5)
Cardiac failure	0	1 (0.5)	1 (0.5)
Cardiac disorder	0	0	1 (0.5)
Cardiopulmonary failure	0	1 (0.5)	1 (0.5)
Cardiovascular disorder	0	0	1 (0.5)
Discontinuations due to cardiac disorders	**3 (1.5)**	**3 (1.5)**	**5 (2.5)**

Smith et al Urology 2010

Pooled data: Cumulative hazards of first-time CV events starting from 2 years before initiation of degarelix



Klotz et al ESMO 2010

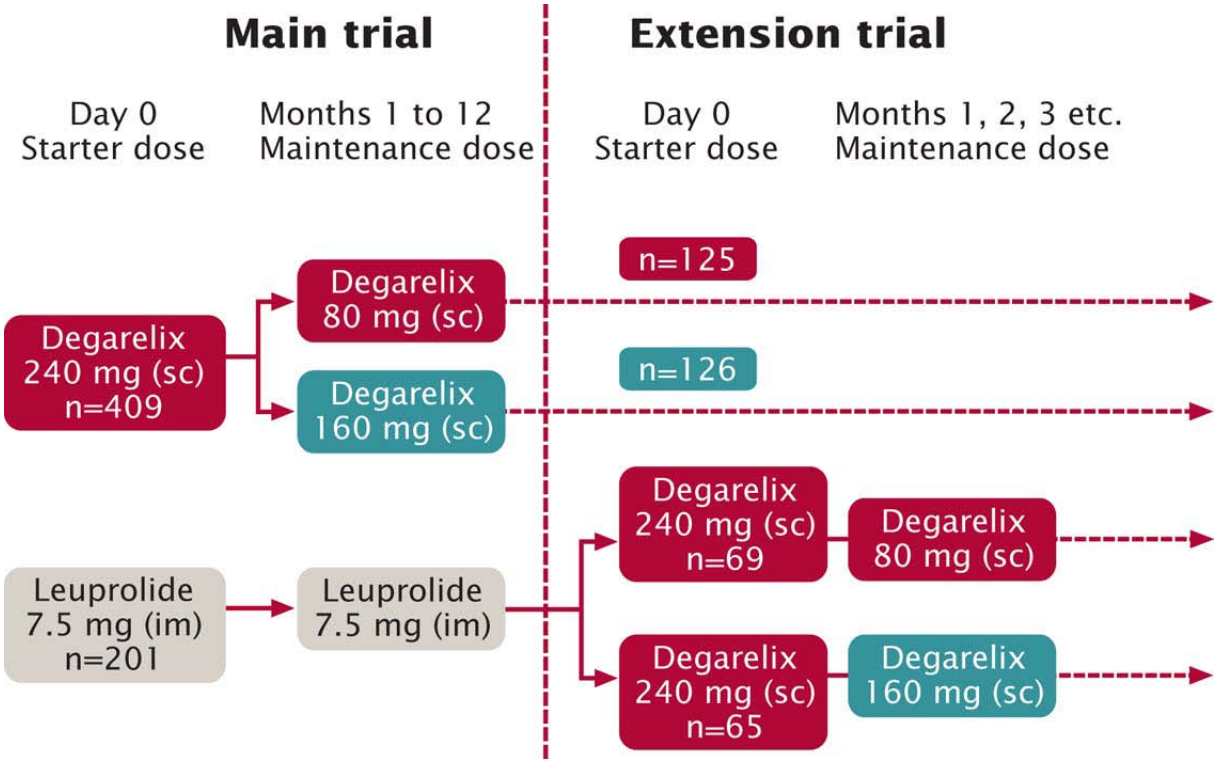
Green lines, 95% CI
No significant change in hazards after starting degarelix
Patients with a history of CV disease >2 years were excluded

CS21: conclusions

- Degarelix did not induce a testosterone surge or microsurges
- Degarelix reduced PSA levels more effectively than leuprolide
  - ➔ Degarelix reduced PSA levels more rapidly than leuprolide, irrespective of baseline disease stage
  - ➔ PSA progression-free survival was significantly longer with degarelix than with leuprolide in the ITT population
- Overall, degarelix and leuprolide had similar tolerability profiles

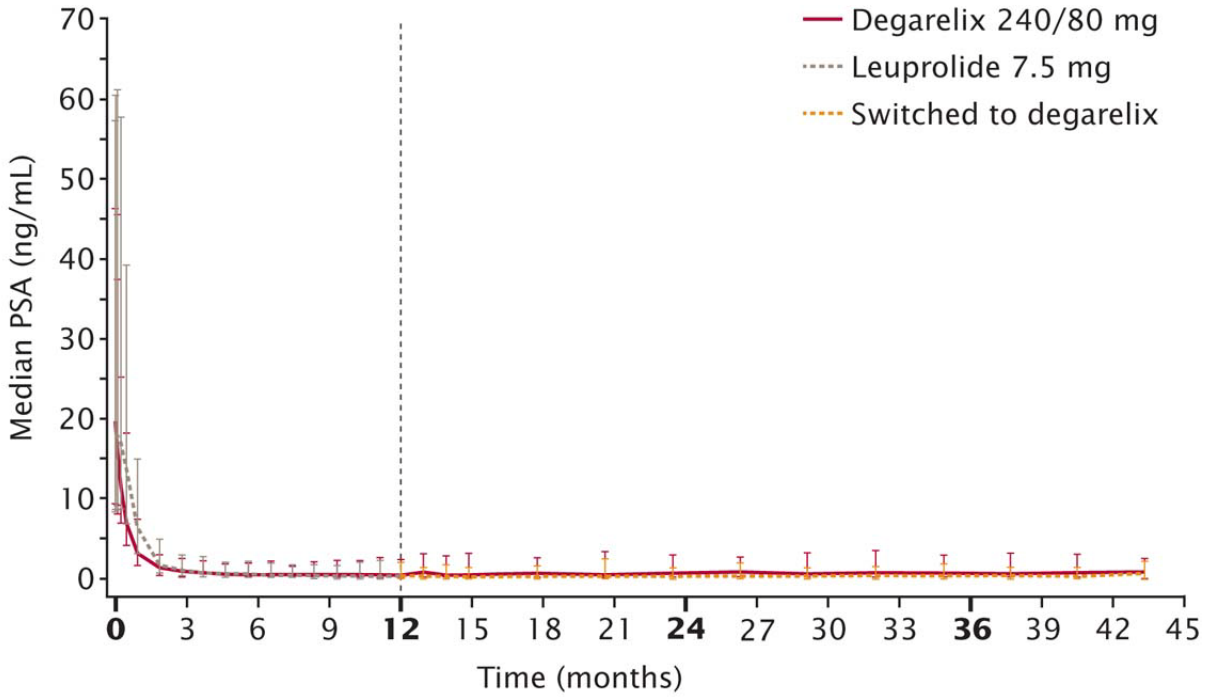
CS21a extension study: trial design

Multi-centre, open-label extension study



Crawford ED et al. J Urol 2010;183(Suppl):e262, abstr 670

CS21a extension study: median (quartiles) PSA levels for patients crossed over from leuprolide to degarelix or who continued to receive degarelix 240/80 mg

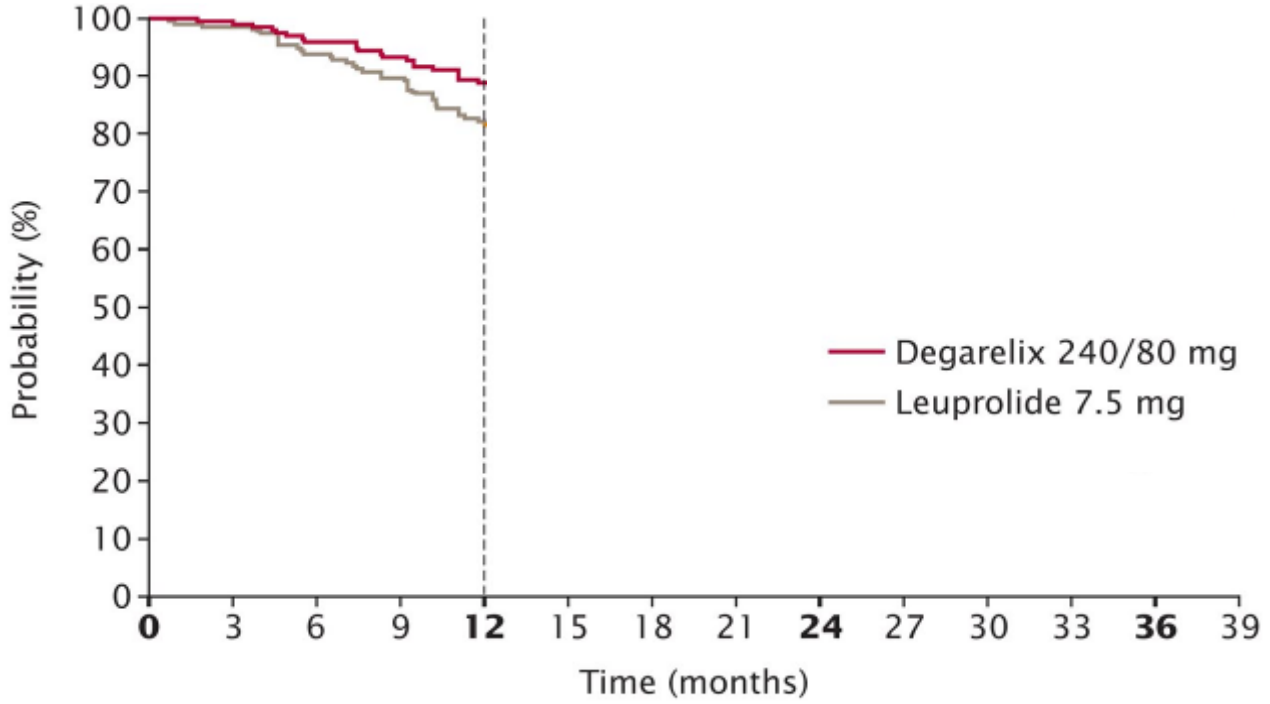


Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*532*	*616*	*700*	*784*	*868*	*952*	*1036*	*1120*	*1204*	*1288*
Number of patients at risk																
Degarelix	206	196	187	180	166	13	108	103	97	93	89	83	83	80	72	39
Leuprolide	200	192	186	183	173	123	113	105	97	92	85	80	77	74	71	31

Crawford ED et al. J Urol 2010;183(Suppl):e262, abstr 670

CS21a extension study: PSA progression-free survival for all patients crossed over from leuprolide to degarelix or who continued to receive degarelix 240/80 mg

Significantly lower hazard rate after switch to degarelix (p=0.003)

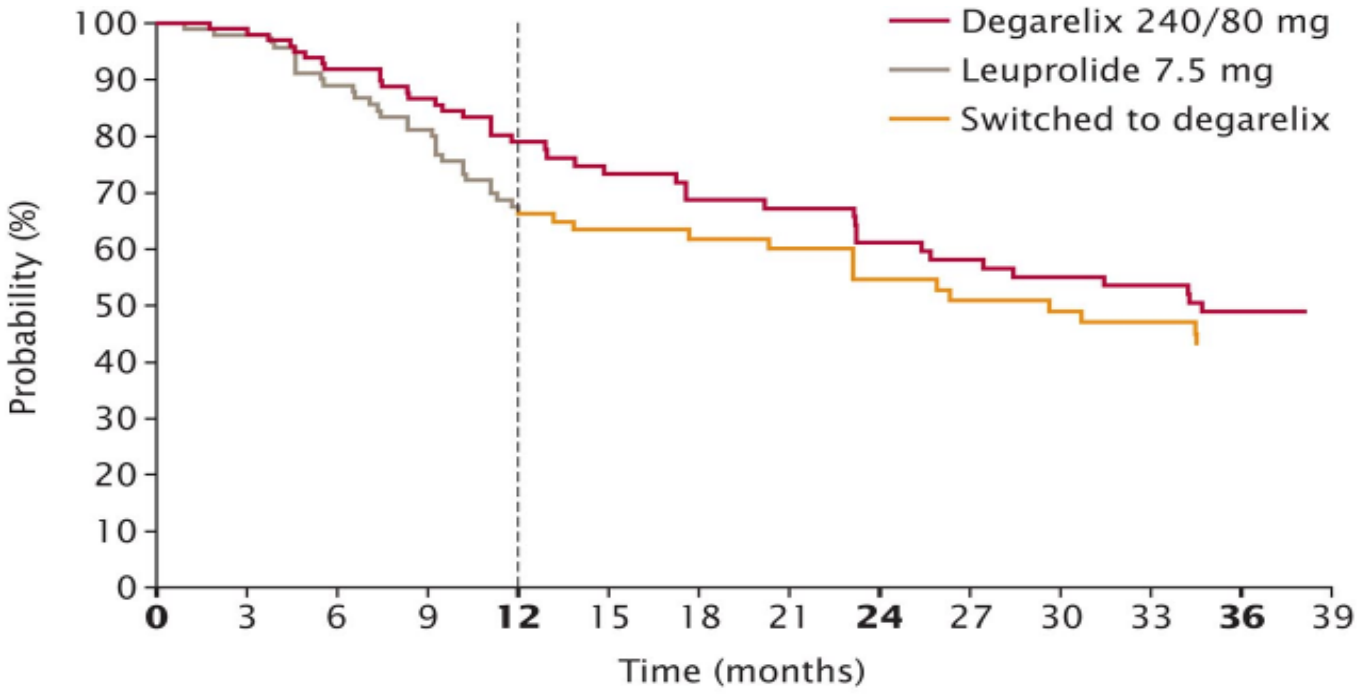


Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	207	200	187	176	162	109	101	93	91	87	83	79	75	71	67
Leuprolide	201	193	182	174	157	110	102	98	93	85	81	78	74	68	66

Crawford et al. J Urol 2010; 183(4 suppl): e262

PSA progression-free survival in patients with PSA >20 ng/mL at baseline

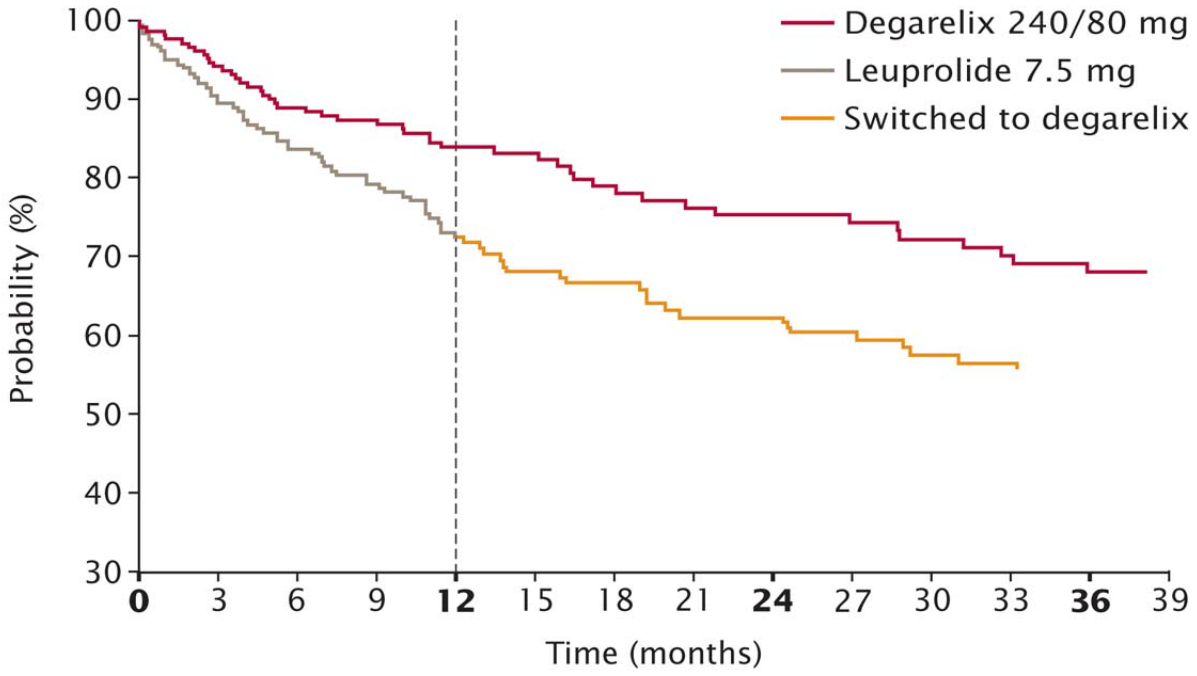
Significantly lower hazard rate after switch to degarelix (p=0.031)



Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	100	97	91	84	77	53	50	45	44	40	37	36	35	32	31
Leuprolide	93	90	81	75	63	43	40	37	35	29	27	26	23	23	21

Crawford et al. J Urol 2010; 183(4 suppl): e262

CS21a extension study: probability of freedom from musculoskeletal adverse events in all patients crossed over from leuprolide to degarelix and those continuing to receive degarelix 240/80 mg



Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	207	189	170	161	147	106	94	87	82	78	76	69	65	63	59
Leuprolide	201	177	161	149	132	94	83	76	70	65	61	58	58	58	52

Crawford ED et al. J Urol 2010;183(Suppl):e262, abstr 670

CS21a extension trial: summary

- Significantly lower risk of PSA failure or death with degarelix compared with leuprolide during the first year
- After crossover to degarelix, patients experienced a lower rate of PSA failure or death
- Patients on degarelix experienced a lower rate of musculoskeletal adverse events
- These data support the use of degarelix as first-line androgen deprivation therapy

Countries where FIRMAGON is available and reimbursed: January 2011

- Argentina
- Austria
- Belgium
- Canada
- Denmark
- France
- Germany
- Greece
- Iceland
- Ireland
- Mexico
- Netherlands
- Norway
- Portugal
- Slovakia
- Switzerland
- UK
- USA