The Role of LHRH Antagonists in the Management of both Prostate Cancer and BPH

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Professor of Urology

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LHRH antagonists: Do they have a future?
LHRH antagonists are not new

• Already developed by Schally in the late sixties

• Not available for clinical use until the mid nineties

• Initial clinical application for gynaecological conditions (IVF, endometriosis)

• Clinical research in initially in Prostate cancer and later in BPH

Different Mechanism of Action

• LHRH superagonists
  • Binds to receptor, stimulates receptor, then down regulates receptor

• GnRH antagonist
  • Binds to receptor and immediately shuts it off
**LHRH Antagonists**

### Mode of Action

- Competitive receptor binding
- Immediate suppression of LH & FSH
- Dose dependent suppression
- Suppression to castration level

### Advantages of Antagonists

- No flare
- Fast onset of action
- Intermittent therapy may be possible
- Diminished risk of side-effects in non-oncology indications (osteoporosis, loss of libido, hot flashes etc.)

LHRH-antagonists are a novel therapeutic class overcoming the side-effects associated with agonists

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**LHRH antagonists formulations**

- Cetrorelix
- Abarelix
- Ozarelix
- Degarelix
- Others
LHRH Antagonists in Prostate Cancer
**Abarelix Depot**

**Clinical Studies**

149-97-04  Phase II

149-98-02  A Phase III, Multi-Center, Open-Label, Randomized Study of Abarelix-Depot vs. Leuprolide-Depot 1-Month in Patients with Prostate Cancer Who Are Candidates for Initial Hormonal Therapy

149-98-03  A Phase III, Multi-Center, Open-Label, Randomized Study of Abarelix-Depot vs. Leuprolide-Depot 1-Month Plus Daily Bicalutamide in Patients with Prostate Cancer Who Are Candidates for Initial Hormonal Therapy

149-98-04  A Multi-Center Study of Abarelix-Depot in Patients with Prostate Cancer in whom GnRH Agonists are Contraindicated

149-99-01  Bioavailability, Pharmacokinetic, and Pharmacodynamic Study

149-99-03  Phase III, Additional Patient Exposure

149-99-04  Rollover

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**Testosterone Levels**

*Study 149-98-02 Patients Through Day 29*

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**Leuprolide Depot**

**Abarelix Depot**
**Testosterone Levels**

*Study 149-98-03 Patients Through Day 29*

### Leuprolide Depot + Bicalutamide

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Testosterone Levels (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>500</td>
</tr>
<tr>
<td>1</td>
<td>400</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

### Abarelix Depot

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Testosterone Levels (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>600</td>
</tr>
<tr>
<td>1</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>400</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

---

**Protocol Specified Primary Endpoint #2 Castration on Day 8**

<table>
<thead>
<tr>
<th></th>
<th>Comparator Castrate</th>
<th>Abarelix Depot Castrate</th>
<th>p-value$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>149-98-02 (vs. L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>0%</td>
<td>24%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 4</td>
<td>0%</td>
<td>57%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 8</td>
<td>0%</td>
<td>72%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 15</td>
<td>10%</td>
<td>75%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>149-98-03 (vs. L+C)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>0%</td>
<td>25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 4</td>
<td>0%</td>
<td>54%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 8</td>
<td>0%</td>
<td>68%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 15</td>
<td>21%</td>
<td>72%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^1$Fisher’s exact test
Testosterone Levels
Study 149-98-02 Patients Through Day 85

Leuprolide Depot

Study Day
T Level (ng/dL)

Abarelix Depot

Study Day
T Level (ng/dL)

Testosterone Levels
Study 149-98-03 Patients Through Day 85

Leuprolide Depot + Bicalutamide

Study Day
T Level (ng/dL)

Abarelix Depot

Study Day
T Level (ng/dL)
### Achievement and Maintenance of Castration

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Abarelix Depot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>149-98-02 (vs. L)</td>
<td>89</td>
</tr>
<tr>
<td>149-98-03 (vs. L+C)</td>
<td>83</td>
</tr>
</tbody>
</table>

**A&M** = Achieved and maintained castration  
Δ = Difference, abarelix depot minus comparator  
1Lower bound of a 2-sided 95% confidence interval

### Maintenance of Castration Once Achieved

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Abarelix Depot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>149-98-02 (vs. L)</td>
<td>85</td>
</tr>
<tr>
<td>149-98-03 (vs. L+C)</td>
<td>76</td>
</tr>
</tbody>
</table>

**M/A** = Maintenance of castration once achieved  
Δ = Difference, abarelix depot minus comparator  
1Lower bound of a 2-sided 95% confidence interval
Abarelix Depot Efficacy Summary
Studies 149-98-02 and 149-98-03

- Abarelix depot is superior to leuprolide depot or leuprolide depot + bicalutamide for the avoidance of testosterone surge
- Abarelix depot is superior to leuprolide depot or leuprolide depot + bicalutamide for achieving medical castration by day 8
- Rates of achievement and maintenance of castration on or after day 29 are >90%
- Abarelix depot is a rapid acting monotherapy without testosterone surge.

Potential Allergic Symptoms – All Relationships
Study 149-98-02 and 149-98-03

<table>
<thead>
<tr>
<th></th>
<th>Leuprolide Depot (N=89)</th>
<th>Leuprolide Depot plus Bicalutamide (N=83)</th>
<th>Abarelix Depot (N=348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash¹</td>
<td>9%</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Eczema</td>
<td>1%</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1%</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

¹Rash, erythematous rash, maculopapular rash
Abarelax Depot

Conclusions I

• Abarelax depot influences multiple hormones that may be important in prostate cancer biology, including testosterone, dihydro-testosterone, and FSH

• Abarelax depot can safely be used in all patients, including advanced patients in whom LHRH superagonists are contraindicated because of testosterone surge

• Abarelax depot represents an important medical alternative for the treatment of prostate cancer

Abarelax Depot

Conclusions II

• Results of two randomized, prospective, multi-institutional, sponsor-blinded Phase III studies demonstrate:
  – Superiority of abarelax to L or L/C in avoiding testosterone surge
  – Superiority of abarelax to L or L/C in more rapidly causing medical castration by the first week of treatment
  – Equivalence in maintaining medical castration

• Excellent safety profile
Abarelix Depot

Conclusions III

• Abarelix depot represents a completely unique hormonal therapy for patients with prostate cancer

• Abarelix depot is a rapid acting monotherapy without testosterone surge.

Abarelix Depot Safety Summary

• Abarelix depot was as well tolerated as leuprolide depot and leuprolide plus bicalutamide

• Clinically notable elevations in transaminases and allergic reactions were transient and reversible with abarelix depot, leuprolide depot and leuprolide depot plus bicalutamide
Degarelix dose finding study

A mixed of localized, locally advanced, metastatic
Median PSA 27.

CS12: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics (N=187)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>72 (52–93)</td>
</tr>
<tr>
<td>Testosterone (ng/mL) (range)</td>
<td>4.13 (0.82–10.2)</td>
</tr>
<tr>
<td>PSA (ng/mL) (interquartile range)</td>
<td>27.6 (11.9–55.0)</td>
</tr>
<tr>
<td>Prostate cancer stage</td>
<td>N (%)</td>
</tr>
<tr>
<td>Localised</td>
<td>41 (22%)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>60 (32%)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>36 (19%)</td>
</tr>
<tr>
<td>Not classifiable</td>
<td>50 (27%)</td>
</tr>
<tr>
<td>Histology (Gleason Grade)</td>
<td>N (%)</td>
</tr>
<tr>
<td>2–4: well differentiated</td>
<td>36 (19%)</td>
</tr>
<tr>
<td>5–6: moderately differentiated</td>
<td>76 (41%)</td>
</tr>
<tr>
<td>7–10: poorly differentiated</td>
<td>73 (39%)</td>
</tr>
</tbody>
</table>
CS12: patients with testosterone ≤0.5 ng/mL from Day 0 to 28

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Day</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>240</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>95</td>
</tr>
<tr>
<td>200</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>86</td>
</tr>
</tbody>
</table>
### Patients with testosterone ≤0.5 ng/mL long term

<table>
<thead>
<tr>
<th>Dose (mg) (Conc. 40 mg/ml)</th>
<th>One Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
</tr>
<tr>
<td>80</td>
<td>44/48</td>
</tr>
<tr>
<td>120</td>
<td>48/50</td>
</tr>
<tr>
<td>160</td>
<td>49/49</td>
</tr>
</tbody>
</table>

* n = Number of patients with testosterone ≤0.5 ng/mL Days 28–364
* N = Number of ITT patients

### CS12: mean testosterone and PSA with 1 year of treatment with Degarelix
North American dose finding study:
Proportion of patients with testosterone ≤0.5 ng/mL month 1–12

- 200 mg loading dose followed by 60 or 80 mg/month

<table>
<thead>
<tr>
<th>Maintenance dose (mg)</th>
<th>% castrate</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>42/45</td>
<td>93</td>
<td>82-99%</td>
</tr>
<tr>
<td>80</td>
<td>41/42</td>
<td>98</td>
<td>87-100%</td>
</tr>
</tbody>
</table>

n = Number of patients with testosterone ≤0.5 ng/mL Days 28–364
N = Number of ITT completer patients
95% CI calculated by Clopper-Pearson method

Degarelix adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flushes</td>
<td>62 (33%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>19 (10%)</td>
</tr>
<tr>
<td>Increased weight</td>
<td>17 (9%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (6%)</td>
</tr>
</tbody>
</table>
Degarelix

North American degarelix dose finding study in prostate cancer patients (n=127, CS14)

CS14: North American Phase II study
CS14: Median testosterone and PSA

Degarelix Summary

- 92% of patients achieved testosterone ≤0.5 ng/mL within 3 days with a dose of 240 mg
- 98% and 100% of patients achieve testosterone ≤0.5 for 1 year at 80 and 160 mg/month
- No flare
- LH, FSH, T, and PSA rapidly suppressed
- No evidence of systemic allergic reactions
- 3 month depot
- Phase 3 trial (vs LHRH agonists)
**CS14: Conclusions**

- 93% of patients achieved testosterone ≤0.5 ng/mL within 3 days with a dose of 240 mg
- 98% patients maintain testosterone ≤0.5 ng/mL during 1 year with a monthly dose of 80 mg
- Fast, profound and sustained testosterone suppression without surge; similar to orchiectomy
- Fast, profound and sustained reduction of PSA
- Degarelix was well tolerated with no evidence of systemic allergic reactions

**Conclusions from Phase II studies**

- Doses were identified where degarelix suppresses and maintains testosterone <0.5 ng/mL for 1 year in up to 100% of patients
- Fast, profound and sustained suppression of LH, FSH, testosterone and PSA
- Degarelix is well tolerated
LHRH antagonists

- Clear (modest) benefit of absence of flare
- 1st generation limited by histamine release/allergic reaction
- 2nd generation: No evidence of this
- Effective T suppression
- Clinical application will depend on:
  - Convenience
  - 3 month dose
  - Cost

LHRH Antagonists in BPH
Medical Therapy of BPH

- **α blockers**
  - Terazosin
  - Doxazosin
  - Tamsulosin
  - Afluzosin SR

- **5ARIs**
  - Finasteride
  - Dutasteride

Medical Therapies Under Development for BPH

- Anticholinergics
- Metabolic targeting – lonidamine
- Botox
- GnRH/LHRH antagonists
CETRORELIX

- Decapeptide analog of LHRH
- Antagonist of LHRH
- Low histamine releasing effects

- 2 different formulations available: CET acetate and CET pamoate
- CET acetate approved for COS/IVF treatment (Cetrotide®)
- CET pamoate (depot formulation) not yet available commercially

Clinical Evidence Supporting Cetrorelix for the Treatment of BPH
CETRORELIX –
Open-Label Studies: BPH

Gonzalez-Barcena, D et al.
The Prostate, 1994
Responses to the Antagonistic Analog of LH-RH (SB-75, Cetrorelix) in Patients With Benign Prostatic Hyperplasia and Prostatic Cancer

Comaru-Schally, AM et al.
J Clin Endocrinol Metab, 1998
Efficacy and Safety of Luteinizing Hormone-Releasing Hormone Antagonist Cetrorelix in the Treatment of Symptomatic Benign Prostatic Hyperplasia

Design: Open-label study in 11 patients with symptomatic BPH
Dosage: 0.5 mg twice daily s.c. for 4 weeks
Results: At the end of therapy, all the patients show a significant decrease of the prostatic volume and improvement of symptoms. In one patient, long-term follow-up was done: Decrease of prostatic volume was observed for up to 1 year after therapy.
CETRORELIX –
Open-Label Studies: BPH


- Design: Open-label study in 13 patients with moderate to severe symptomatic BPH
- Dosage: 5 mg twice daily s.c. for 2 days + 1 mg / day s.c. for 2 months
- Results: At the end of therapy, symptom score (IPSS) and quality of life score were significantly improved (by 53% and 46%, respectively). Prostatic volume was reduced by 27%.
- All patients were followed for at least 4 months after start of therapy. Long-term follow-up was done in 7 patients for up to 6 months, in 5 patients for up to 12 months and in 3 patients for up to 18 months:
  - Symptom scores continued to improve after therapy. IPSS was reduced by 72% in the evaluable patients even 18 months after start of therapy.
  - Mean quality of life score was significantly improved during all the follow-up periods.
  - At the end of individual follow-up prostatic volume was below basal values in 10 of 13 patients. The mean prostatic volume at the end of individual follow-up was reduced by 20%.
# Cetrorelix BPH – Phase 2 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Formulation</th>
<th>Dosage Scheme</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>2980</td>
<td>Acetate</td>
<td>10 mg oid x5 + 1 mg oid x23 1 mg oid x5 + 1 mg oid x23 PLA</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 (Σ=75)</td>
</tr>
<tr>
<td>Z004</td>
<td>Acetate</td>
<td>5 mg q7d x4*</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>(gluconic acid)</td>
<td>10 mg q7d x4</td>
<td>35 (Σ=140)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg q14d x2* PLA q7d x4</td>
<td>35</td>
</tr>
<tr>
<td>3207</td>
<td>Pamoate</td>
<td>30 mg single dose*</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mg single dose PLA single dose</td>
<td>35 (Σ=105)</td>
</tr>
<tr>
<td>Z003</td>
<td>Pamoate</td>
<td>30 mg q14d x2*</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg q14d x3</td>
<td>50 (Σ=250)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mg q14d x2* PLA q14d x3</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mg q14d x2* PLA q14d x3</td>
<td>50</td>
</tr>
</tbody>
</table>

* * + double dummy Placebo injections

Acetate =215 Pm. =355 Total =570
Cetrorelix in BPH

Study 2980: “Proof of concept”

Proof of Concept Study: Study Design

- **Trial design:** Double-blind, placebo-controlled, randomized, dose ranging study
- **Tx period:** 28 days sc injection + 7 days placebo run-in
- **Follow-up:** 3 months or until return of I-PSS to 50% of max. improvement

**Investigators/Sites:**
- H. Lepor, C. Dixon - New York
- M. Auerbach - Newport
- E.D. Crawford - Denver
- P. Steidle - Fort Wayne
- J.E. Oesterling - Michigan
Proof of Concept Study: Objectives

- Does Cetrorelix relieve symptoms of BPH?
- Does Cetrorelix reduce prostate volume?
- Is castration required to achieve clinical efficacy?
- Do clinical benefits persist following cessation of therapy with Cetrorelix?
- Safety profile?

Conclusion

- Cetrorelix Proof-of-Concept Study
- Improvements in total IPSS, individual symptoms of IPSS, PFR, perception of QoL were not statistically significant due to small sample size and greater than anticipated placebo effect
- These effects observed at 4 weeks were maintained up to 3 months
- Significantly greater reduction of prostate volume compared to placebo

Peak flow rate (PFR)
Quality of life (QoL)
Cetrorelix in BPH:

Study Z004
Key Results

Study Z004
Study Design

**Inclusion criteria**
- Benign Prostatic Hyperplasia
- Voiding symptoms: I-PSS > 13
- Uroflow 5 - 13 ml/sec
- Age: 50 years or older

**Exclusion criteria**
- Urgent need for prostate surgery
- Serum PSA > 10 ng/ml or above age related range
- Residual urine volume of > 350 ml
- Previous or current treatment with sexual hormone drugs, alpha blockers, 5 α-reductase inhibitors or steroids
  (to be discontinued 6 weeks and 6 months for hormone-treatment and 5 α-reductase inhibitors, respectively, prior to start of the screening run-in period)
Study Z004
Study Design: Endpoints

**Main target parameter**
- International Prostate Symptom Score: I-PSS

**Secondary parameters**
- uroflow
- residual urinary volume
- prostate size
- quality of life
- circulating testosterone

Study Z004
Study Design: Safety

**Safety Parameters**
- Sexual function (IIEF-5)
- Serious adverse events / Adverse events
- Clinical laboratory parameters
- Vital parameters
Study Z004
Study Design: Dosage Regimens

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Dose (total)</th>
<th>Cetorelix (acetate) (5 mg/2 ml)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in (each patient)</td>
<td>placebo</td>
<td>2 x 2 ml: D1 + D7 + D14 + D21</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>placebo</td>
<td>2 x 2 ml: D1 + D7 + D14 + D21</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>CET 20 mg</td>
<td>5 mg: D1, D7, D14, D21</td>
<td>1 x 2 ml: D1 + D7 + D14 + D21</td>
</tr>
<tr>
<td>Group 3</td>
<td>CET 40 mg</td>
<td>10 mg: D1, D7, D14, D21</td>
<td>2 x 2 ml: D1 + D7 + D14 + D21</td>
</tr>
<tr>
<td>Group 4</td>
<td>CET 20 mg</td>
<td>10 mg: D1, D14</td>
<td>2 x 2 ml: D1 + D14</td>
</tr>
</tbody>
</table>

Study Z004
Study Design

- Number of patients: 140
- Patients were divided equally over the 4 treatment groups: 35 patients per group
**Z004 - Key Results**  
**IPSS Score: Primary Endpoint**

- Statistically significant difference from baseline and from placebo (ANOVA)
  - Wk12: Primary study endpoint
- Apparent dose relationship in early response
- More rapid onset of effect at highest dosage
- Long-lasting effect at all dosages

---

**Rate of patients with > 30% or > 40% IPSS decrease was significantly higher at all time points and all dosages over placebo (P<0.0001)**
**Z004 - Key Results**

**Urinary Flow: Secondary Endpoint**

- **Uroflow max (mean)**
  - 0 4 8 12 16 20
  - Week [ng/ml]
  - PLA
  - 4x5 mg
  - 2x10 mg
  - 4x10 mg

- **Statistic. signif. improvement in maximum uroflow at all time points**
  - Week 2: p<0.05
  - All other: p<0.003

- **Rapid onset of effect at all dosages**

- **Long-lasting effects at all dosages**

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**Z004 - Key Results**

**Mean Uroflow: Secondary Endpoint**

- **Uroflow mean (mean)**
  - 0 4 8 12 16 20
  - Week [ng/ml]
  - PLA
  - 4x5 mg
  - 2x10 mg
  - 4x10 mg

- **Statistic. signific. improvement in mean uroflow at all time points, (e.g. for 4x10mg: p<0.0005)**

- **Rapid onset of effect**

- **Long-lasting effect**

---
Z004 - Key Results
Prostate Size: Secondary Endpoint

- Mean % Change from baseline at Week 4 (t-test):
  - PLA: -3% NS
  - 4x5: -5% NS
  - 2x10: -8% p<0.05
  - 4x10: -8% p<0.05
- Persisting effects in 10 mg dosage groups

Z004 - Key Results
Testosterone Levels: Secondary Endpoint

- Dose dependent, reversible suppression of testosterone concentrations
- Biweekly intervals for 10 mg dose are longer than needed for maintaining testosterone suppression in a steady state
- Nevertheless this dosage induced therapeutic response
Z004 - Key Results
Erectile Dysfunctions (IIEF-5)

IIEF-5 Grading of ED
- 12-16: mild-moderate
- 8-11: moderate
- 5-7: severe

- Fluctuations within same severity grade "moderate"
- No statistically significant differences according to ANOVA

Cetrorelix Pamoate in BPH:
Study Z003
Key Results
Z003 - Cetrorelix pamoate in BPH

Study design: Dosage

Total number of patients: 250
The patients were equally divided over 5 treatment groups: 50/group

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Dose (total)</th>
<th>Cetrorelix (pamoate) 30 mg/2ml</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in (each patient)</td>
<td>placebo</td>
<td>D-28 + D-14</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>placebo</td>
<td>D1 + D14 + D28: 4 ml</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>CET 60 mg</td>
<td>D1: 30 mg D14: 30 mg</td>
<td>D1 + D14 + 2 ml D28: 4 ml</td>
</tr>
<tr>
<td>Group 3</td>
<td>CET 90 mg</td>
<td>D1: 30 mg D14: 30 mg D28: 30 mg</td>
<td>D1 + D14 + D28: 2 ml</td>
</tr>
<tr>
<td>Group 4</td>
<td>CET 90 mg</td>
<td>D1: 60 mg D14: 30 mg</td>
<td>D14: 2 ml D28: 4 ml</td>
</tr>
<tr>
<td>Group 5</td>
<td>CET 120 mg</td>
<td>D1: 60 mg D14: 60 mg</td>
<td>D28: 2 ml</td>
</tr>
</tbody>
</table>

Z003 - Key results

IPSS - Primary Endpoint

- Statistically significant difference from baseline and from placebo (ANOVA: P<0.001)
- Wk12: Primary study endpoint
- Dose relationship in response
- More rapid onset of effect after 60 mg initial doses
- Long-lasting effect at all dosages
**Z003 - Key results**  
**IPSS - Primary Endpoint**

Rate of patients with at least 3 point improvement in IPSS was significantly higher for all time points at the 3 higher dosages compared to placebo ($P<0.001$)

**Z003 - Key results**  
**Mean Uroflow max - Secondary Endpoint**

- Significant improvement in maximum uroflow at all time points  
  Week 2: $p=0.02$  
  Others: $p<0.003$  
- Rapid onset of effect, particularly at higher dosages  
- Long-lasting effects at the 3 higher dosages
**Z003 - Key results**

**Mean Uroflow - Secondary Endpoint**

- For regimens starting with 60 mg significant (p<0.02) improvement at all time points compared to baseline
- Rapid onset of effect
- Long-lasting effect

**Testosterone levels - Secondary Endpoint**

- Dose dependent suppression up to Week 7 of testosterone concentrations
- No dosage regimen caused castrating testosterone levels
Z003 - Key results
Erectile Functions - IIEF5

IIEF-5 Grading of ED
12-16: mild-moderate
8-11: moderate
5-7: severe

• Fluctuations within same severity grade "moderate"
• No statistically significant differences according to ANOVA

Z003 - Key results
Prostate size - Secondary Endpoint
Z003 - Key results
Cetrorelix Plasma Levels - PK data (Means)

- Dose dependent plasma concentrations
- Dosage groups with identical starting doses show identical profiles of plasma concentrations
- Sustained release (SR) characteristics of Cetrorelix pamoate ensures persisting drug concentrations over 12+ weeks
- $T_{1/2} = 535-922$ hr

Cetrorelix in BPH
Summary and Conclusions

**Tolerability**
- No local application site reactions
- No systemic side effects
- No effect on Erectile Function for all dosages
- Only very few flushing (~1%)
Cetrorelix in BPH
Summary and Conclusions

Efficacy
- Rapid onset and long duration of improvement after short treatment episodes with Cetrorelix:
  - Symptom Relief: Decrease in I-PSS
  - Improvement of Objective Signs: Increase in Maximum and mean Uroflow
- Slight or temporary reduction in prostate size
- Efficacy after non-castrating suppression of testosterone

Proof of Concept
Both, cetrorelix acetate and pamoate are suitable formulations for long-term management of BPH with intermittent dosing regimens
Cetrorelix Pamoate in BPH: Phase III Program

AEZS-102 / BPH Overview - Phase III studies

- **D20762-Z033** - Phase III in USA/Canada (extended for EU)
  - 600 patients (500 from North America; 100 from Europe: Germany+Bulgaria)
  - One year double-blind placebo-controlled phase with 9-months open-label extension
  - Dosage regimen: 52mg + 26mg given two weeks apart and repeated each 6 months

- **AEZS-102-036** - Phase III in EU

- **AEZS-102-041** - Safety open-label study
  - 500 patients from North America and Europe
  - Treatment with 52mg + 26mg at week 0+2 and then follow-up for 6 months

Additional study (scheduled for 2008)
- **AEZS-102-043** - Cardiologic safety study: “Thorough QTc”
AEZS-102 / BPH Z033 - Phase III study

- Study Design nearly identical to Study AEZS-102-036

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Treatment course 1</th>
<th>Treatment course 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 2*</td>
</tr>
<tr>
<td>A (n = 156)</td>
<td>52 mg CET (26 mg CET x 2)</td>
<td>26 mg CET (26 mg CET x 1)</td>
</tr>
<tr>
<td>B (n = 156)</td>
<td>52 mg CET (26 mg CET x 2)</td>
<td>26 mg CET (26 mg CET x 1)</td>
</tr>
<tr>
<td>C (n = 156)</td>
<td>Placebo (PLA x 2)</td>
<td>Placebo (PLA x 1)</td>
</tr>
</tbody>
</table>

*To be given 14 ± 2 days after the preceding dose.

- Currently ongoing in US, Canada, Germany and Bulgaria: Already about 400 patients randomized

Use of Ozarelix, a GnRH Antagonist, in Patients with Benign Prostatic Hypertrophy
Ozarelix Background

- 4th generation LHRH antagonist
- Potential initial indications
  - Hormone-dependent prostate cancer
  - Benign prostatic hyperplasia (BPH)
  - Endometriosis
- Status
  - Phase II

MOA of Ozarelix in BPH

- Testosterone suppression
  - Ozarelix causes dose-dependent suppression
    - Can select a dose that lowers testosterone just enough
    - Maintains testosterone above castration levels
    - Agonists cannot do that
- Direct effect on growth factors
  - Inhibition of growth factors such as Insulin-like growth factors (IGF) and Epidermal growth factors (EGF) involved in:
    - Cell proliferation
    - Differentiation
    - Apoptosis
    - Inhibition of intra-tissue growth factors
Protocol Title

- Clinical Phase II trial to assess the efficacy and safety of intramuscular administration of four different dose regimens of the GnRH antagonist SPI 153 in patients with symptomatic BPH

Participating Centers

- Coordinating Investigator: Prof. Frans M.J. Debruyne, MD
- Center 1: Prof AV Bantchev; Plovdiv, Bulgaria
- Center 2: Dr. SS Karanikolov; Shumen, Bulgaria
- Center 3: Dr. M. Nikolovski; Sofia, Bulgaria
- Center 4: Prof. P. Pantchev; Sofia, Bulgaria
- Center 5: Prof. LD Petkova; Varna, Bulgaria
Design

- Randomized, double-blind, placebo-controlled, multi-center, dose ranging study
  - Placebo run in phase used to remove placebo responders

Objective

- To identify a safe, well-tolerated regimen of ozarelix that provides prolonged improvement of BPH-related signs and symptoms using the International Prostate Symptom Score (IPSS) as the primary efficacy variable
Main Selection Criteria

- At least 50 years old
- Diagnosis of BPH
- IPSS ≥ 13 (moderate to severe symptoms)
- Peak urinary flow 5-13 mL/sec

Dosing Regimens

<table>
<thead>
<tr>
<th>Placebo Run In</th>
<th>Randomized Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day –28</td>
<td>Day –14</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>5 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>10 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>15 mg</td>
</tr>
<tr>
<td>Day 1</td>
<td>Day 15</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>5 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>10 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 mg</td>
</tr>
<tr>
<td>Placebo</td>
<td>15 mg</td>
</tr>
</tbody>
</table>
Results

- 190 patients entered the placebo run in
  - Placebo responders removed prior to randomization
- 144 patients randomized to one of four dosing groups
  - Injections given IM, 2 weeks apart
- Follow-up for 6 months with no further administration of ozarelix

Results-IPSS
Results-Peak Urine Flow

Results-Testosterone
Safety-Tolerability

- Ozarelx was well tolerated
  - No change in erectile function (IIEF)
  - One case of skin rash

Summary-Conclusions

- Ozarelx led to rapid, dose-dependent improvement in symptoms of BPH
  - Improvement noted by week 4
  - 15 mg IM x 2 most effective dose
- Ozarelx led to rapid improvement in objective measure of peak urine flow
- Testosterone suppressed transiently
  - Non-castrate levels return to baseline by 4-6 weeks
Summary-Conclusions (cont.)

- Efficacy of ozarelix persisted for 6 months of observation without further dosing
  - Convenient
  - Improved compliance
- Well tolerated
  - No symptoms of androgen deficiency
  - No effect on erectile function
- Excellent safety profile

LHRH Antagonists

Are promising agents in the possible management of both Prostate Cancer and BPH

Phase II data have however been confirmed in multicenter randomized prospective clinical Phase III studies