A Novel one month long acting injection (LAI) technology for prolonged release of leuprorelin

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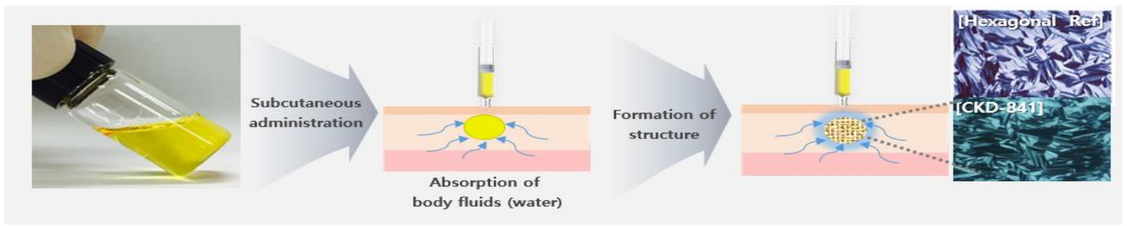
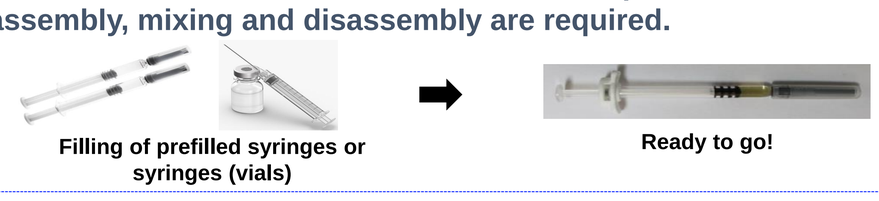
Introduction

CKD-841 is a one-month long-acting subcutaneous leuprolide depot based on CKD's proprietary DDS technology, LIQUISTAL®. It is under development for the treatment of precocious puberty, prostate cancer, premenopausal breast cancer, uterine fibroids and endometriosis.



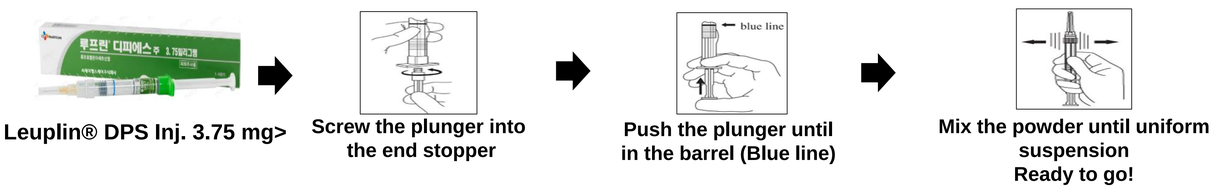
Competitive landscape

- **High convenience of administration as no additional processes such as special syringe assembly, mixing and disassembly are required.**

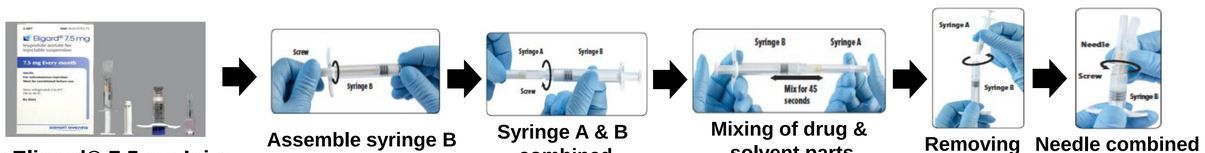


Filling of prefilled syringes or syringes (vials) → Ready to go!

- **PLGA particle products require the operation of the device during administration.**
  (Ex, Leuplin® DPS Inj. Is a dual chamber pre-filled syringe and Eligard® Inj. Is a two pre-filled syringe.)
- **It can be inconvenient to use.**



< Leuplin® DPS Inj. 3.75 mg> → Screw the plunger into the end stopper → Push the plunger until in the barrel (Blue line) → Mix the powder until uniform suspension Ready to go!



< Eligard® 7.5 mg Inj. > → Assemble syringe B → Syringe A & B combined → Mixing of drug & solvent parts → Removing Syringe B → Needle combined Ready to go!

* Source : Approval label (Leuplin® DPS Inj. and Eligard® Inj.)

Simple Manufacturing Process

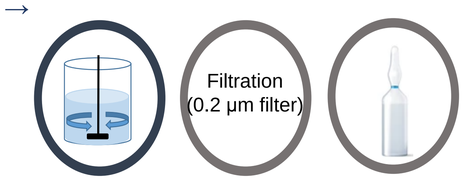
Microsphere Powder

→

STEP1 **Leuprorelin Solution PLGA Solution PVA Solution** → STEP2 **Sterilizing Filtration** → STEP3 **Homgenaizer** → STEP4 **Evaporation & Solidification** → STEP5 **Sieving** → STEP6 **Freeze drying** → Microsphere Powder

Diluent

→



STEP1 **Na-CMC + additives solution** → STEP2 **Sterilizing Filtration** → Diluent Solution

PLGA microsphere

The PLGA microsphere is largely composed of two parts (Powder and diluent) and must be manufactured separately; each process is very complex. The total manufacturing process takes at least 7 days and costs are high.

LIQUISTAL® (CKD-841)

STEP 1
Mixing and Homogenization
Leuprorelin + Liquistal® vehicle solution

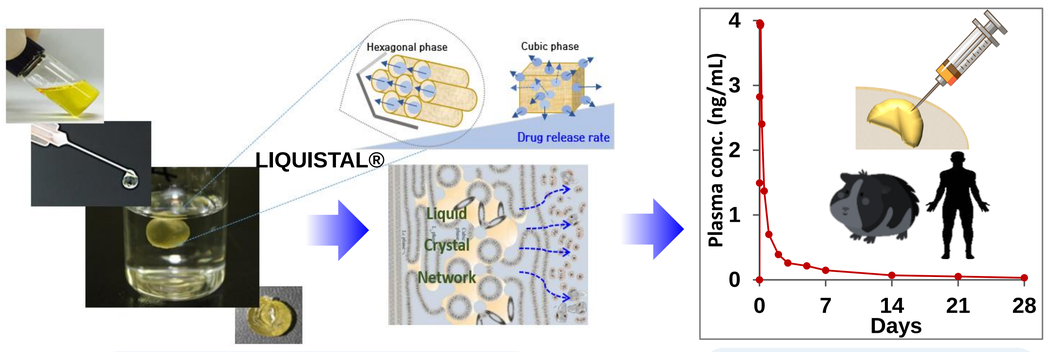
STEP 2
Filtration
(0.2 μm filter)

CKD-841 Injection

Compared to PLGA microsphere of injection, the simple dissolution and mixing process takes up to 2 days to produce, and the manufacturing cost is low.

Method

Designed a novel CKD-841 injectable formulation of the LAI of leuprorelin



Liquid crystal gel formation
after injections (Sol → Gel Transition)
(In-vitro test)

PK/PD profiles
Plasma concentrations
(In-vivo test)

One single injection for months

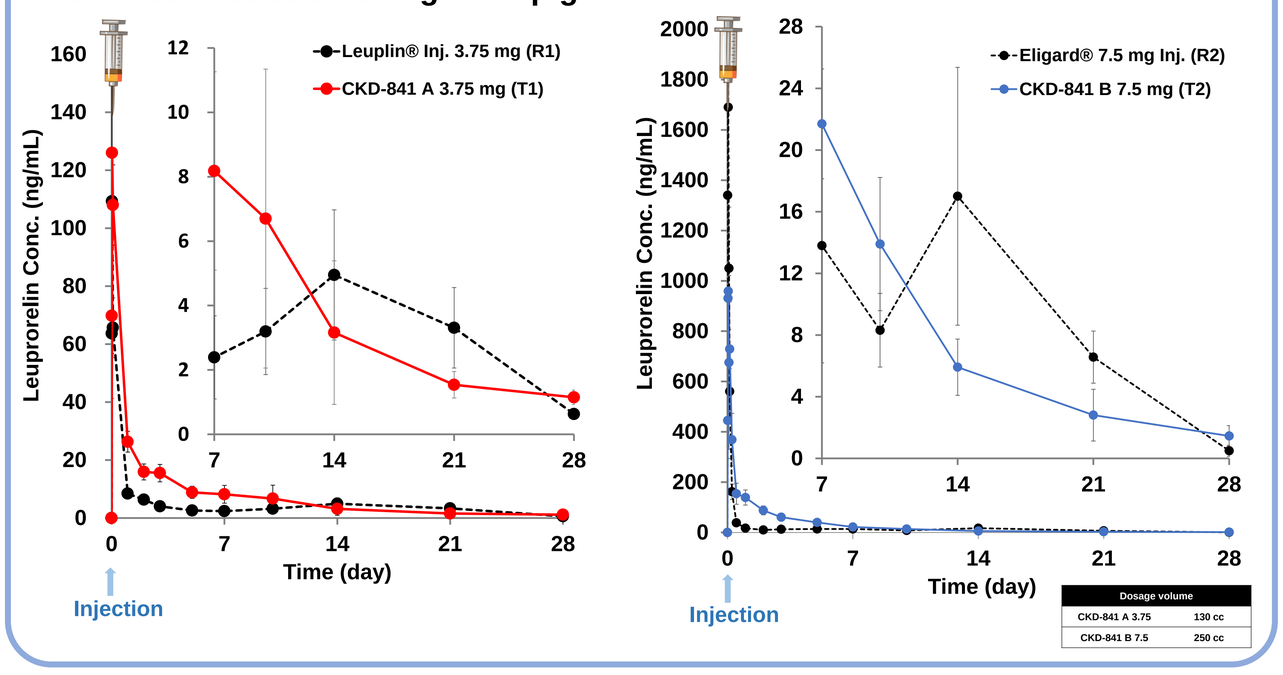
Overview of clinical trials

Study Title	▪ A randomized, open-label, parallel-design, to investigate the pharmacokinetics/pharmacodynamics and safety of CKD-841 investigational product or *Leuplin® Inj. 3.75 mg (R1) or Eligard® 7.5 mg Inj. After subcutaneous injection in healthy males.
Study Objective	▪ To assess the pharmacokinetics, pharmacodynamics and safety of Leuprorelin Acetate (CKD-841) subcutaneous injection by CKD Pharmaceutical Corp. in comparison to that of the comparator drug (*Leuplin® Inj. 3.75 mg or Eligard® 7.5 mg Inj. after subcutaneous injection) over 4 weeks in healthy male subjects.
Study Drugs	▪ Test Drug 1 : CKD-841 A 3.75 mg (CKD Pharmaceutical Corp.,) ▪ Test Drug 2 : CKD-841 B 7.5 mg (CKD Pharmaceutical Corp.,) ▪ Comparator Drug 1 : *Leuplin® Inj. 3.75 mg (Takeda Pharmaceutical Co., Ltd.,) ▪ Comparator Drug 2 : Eligard® 7.5 mg Inj. (HANALL BIOPHARMA Co., Ltd.,)
Study Subjects	▪ Healthy males ≥19 and ≤40 years of age at screening.
Study Design	PK/PD Sampling points
	0, 0.33, 0.67, 1, 2, 3, 6, 12, 24h (1day), 2d, 3d, 5d, 7d, 14d, 21d, 28d, 35d, 42d

▪ This study was performed in compliance with Good Clinical Practice (GCP)

Results and Conclusions

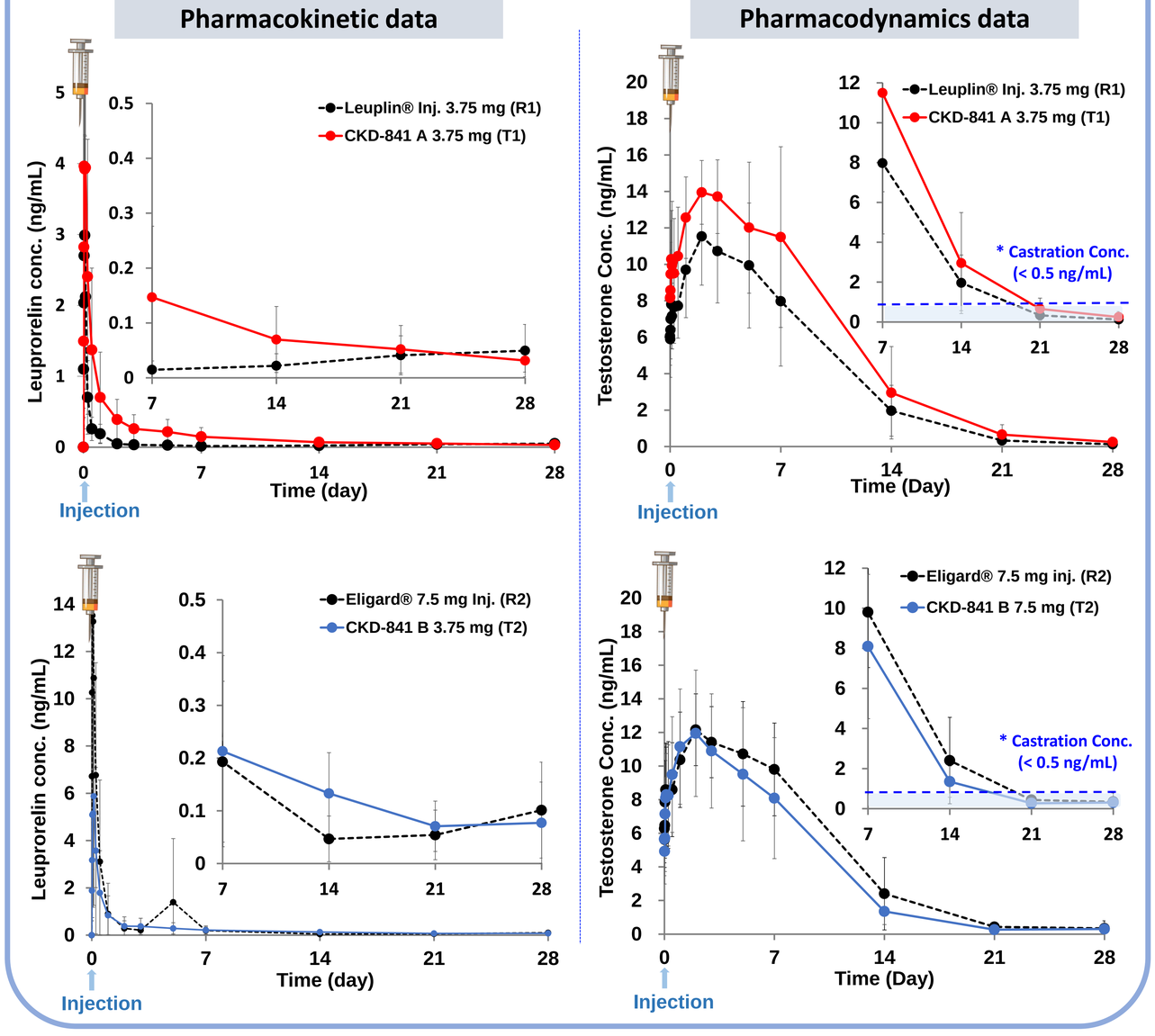
Pharmacokinetics data in guinea pig



PK & PD data In human

[Dosage volume]
• CKD 841 A (0.13 mL) VS Leuplin A (1.00 mL)
• CKD 841 B (0.25 mL) VS Eligard B (0.36 mL)

Pharmacokinetic data | **Pharmacodynamics data**



Conclusions

We developed a novel formulation based on LAI injection that could release leuprorelin for one month after single injection. The clinical trial results confirmed similar results in PK/PD data. Liquistal® technology (CKD-841) is a convenient new formulation. Plasma concentrations of leuprorelin maintained similar for one month after a single injection of CKD-841 test products and commercial products (Leuplin® Inj. 3.75 mg (R1), Eligard® 7.5 mg Inj. (R2)) in guinea pigs and humans.

Highlight

- Small volume compared to commercial products.(Leuplin® Inj. 3.75 mg (R1), Eligard® 7.5 mg inj. (R2)) ; May lead to Improved patient compliance.
- Compared to commercial products, it is convenient for administration.
- Low cost manufacturing process and simple dissolving process

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