Pharming Group NV

Transgenic Platform for Production of Recombinant Proteins

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HEALTH ■ SCIENCE ■ PRODUCTS

About Pharming

- Public biotech company *(NYSE Euronext: PHARM)* founded 1988
- Headquartered in Leiden (NL), R&D and production sites in NL and USA, approx. 75 staff
- Proprietary transgenic technology platforms for recombinant protein production
- First product (recombinant human C1 inhibitor; rhC1INH) from transgenic platform achieved EMA approval (Oct. 2010) and is marketed as Ruconest® in all countries of the EU for acute attacks of HAE.
- Received the “World Technology Award” in the category “Best Biotech Company 2010” to honour this first approved product that was derived from the platform

Pharming has strong major partners for Ruconest® / Rhucin®

SANTARUS, INC.®

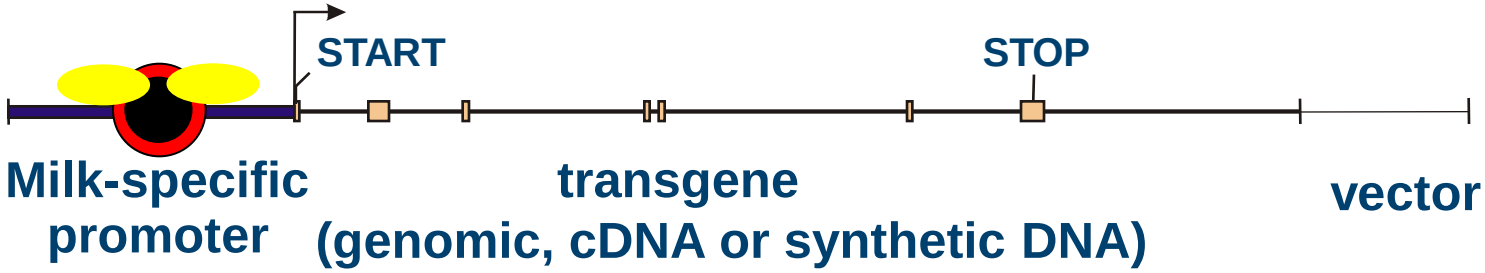
sobi
SWEDISH ORPHAN BIOVITRUM

Validation of transgenic production platforms

Regulatory approvals for therapeutic proteins

- **Recombinant human C1 Inhibitor from transgenic rabbits**
  - Marketing authorisation in Europe for treatment of acute HAE
  - Pivotal US Phase III clinical trial ongoing under Special Protocol Assessment (SPA)
    - SPA is an agreement between Pharming and FDA on the trial design
- **Recombinant human Anti-thrombin-III from transgenic goats**
  - Marketing authorisation in Europe and United States
  - Developed by GTC Biotherapeutics

Technology Platform – Expression of target protein in milk



Transgene: DNA stretch encoding protein X

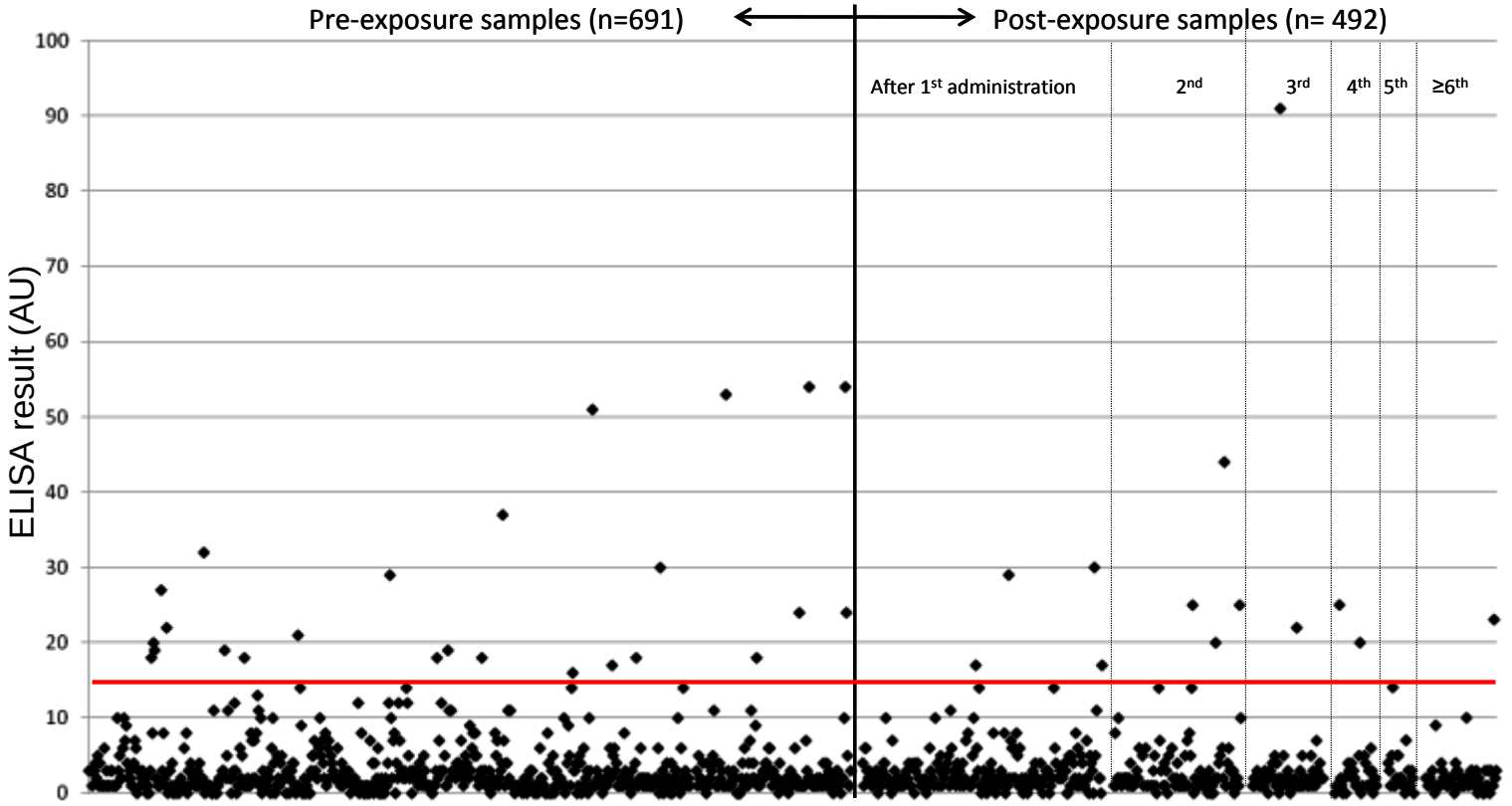
Promoter: Control of gene-expression; responsive to lactogenic hormones

Advantages over plasma derived products

- No supply limitations
- Safety and purity
  - Highly purified protein
  - No risk of human blood/plasma borne disease
- Allows high dose per vial and exploration of different dosing regimens
  - Rhucin 2100 units of rhC1INH per vial
  - Contributes to efficacy outcome
- Competitive cost of goods with significant potential for economies of scale

Reassuring immuno-safety profile:

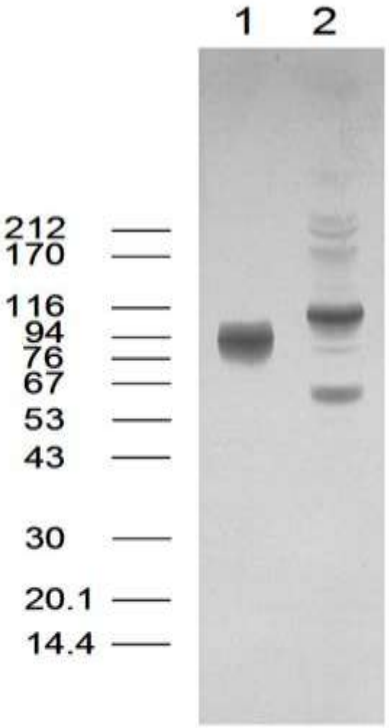
Low potential to induce antibodies against C1INH



Reference: Immunological Assessment, 2011

Rhucin® (rhC1 INH) is highly purified

Non-reduced SDS-PAGE analysis of rhC1INH and commercially available plasma derived C1INH .



- Rhucin < 20 ppm non-product related impurities
- Commercially available plasma derived human C1INH ~ 250,000 ppm non- product related impurities
- As C1 Inhibitors may have to be dosed relatively high, (~200mg/ day+) the absolute amounts of impurities dosed/day with plasma derived C1 Inhibitors can become significant

Lane 1: Ruconest /Rhucin

Lane 2 :Commercially available plasma derived human C1INH

Proteins; 100 ng/lane, were visualized by silver-staining.

The transgenic rabbit production platform for recombinant human proteins:

A competitive and proven production system

An alternative to cell based production systems

Advantages of the Transgenic Mammal Platform Over Cell Cultures – Technical Aspects

- GMP conform, validated production process – like cell cultures
- Stable genetic information, no risk of losses of expression
- No need for sterile (up- stream manufacturing) environment, “self protecting/ immune competent” bioreactors
- Generally higher yields (up to more than 10 g/ l)
- Glycosylation pattern generally more similar to human
  - Low immunogenicity potential
- Ideally suited for complex and/or highly glycosylated proteins that are poorly expressed in cell cultures

Comparison of expression levels

Recombinant human C1 inhibitor expression levels produced by different expression systems.

Expression system	Expression level (g/L)	Volume (L) for 100 Kg (50% yield)	Number of humans/animals per year
Human plasma	0.25	800,000	800,000
COS[1]	0.005	40,000,000	-
Pichia Pastoris[2]	0.1	2,000,000	-
Rabbit	**15**	**13,500**	**1,350**

COS cells are commonly used to produce recombinant proteins.

Pichia Pastoris is a species of yeast also frequently used to express recombinant proteins.

Expression levels for rabbit refer to expression levels in the mammary gland.

Values for human plasma are shown for reference.

[1] *Eldering E, Nuijens JH, Hack CE. Expression of functional human C1 inhibitor in COS cells. J Biol Chem 1988; 263: 11776-11779.*

[2] *Bos IG, de Bruin EC, Karuntu YA, Modderman PW, Eldering E, Hack CE. Recombinant human C1-inhibitor produced in Pichia pastoris has the same inhibitory capacity as plasma C1-inhibitor. Biochim Biophys Acta 2003; 1648: 75-83.*

Advantages of the Transgenic Mammal Platform Over Cell Cultures – Commercial Aspects

- Very low upfront investment and low maintenance costs
- Easy to contain, control and transport
- Speed of Development: Comparable “time to first production”
- No up-scaling problems, size of individual bioreactor constant
- No or few comparability issues if additional (milk) production sites are implemented
- Unique early (low cost) bulk holding stage (frozen milk)
  - minimizes unnecessary early stage down- stream manufacturing investments
  - extends the shelf life of the compound
  - increases flexibility in the (early post- launch) supply chain
- Production and purification of large quantities of protein relatively easy to achieve – hence relatively low COGS.

Advantages of the Transgenic Rabbit Platform Over Other Transgenic Mammals

- High and fast reproduction rate – hence extremely versatile and easy to "fine- tune" the development of the founder through classic breeding steps
- No transfection of any rabbit pathogens to humans observed or known
- Rabbits feature "human type" glycosylation pattern
- Extremely easy to contain, control and transport
- Relatively high expression of protein
- Ideal for production of pharmaceutical (volumes of) proteins

Advantages of the Transgenic Mammal Platform
Broad & Strong IP coverage

- Solid protection in the US for DNA constructs in the generation of any transgenic mammal producing any recombinant protein in milk - until 2027
- Broad IP coverage (owned/in-licensed) for several competitive methods for generating transgenic mammals
- Long lasting protection for Pharming products (including recombinant human C1 inhibitor) in numerous countries (incl. US, EP, AU, JP, CA) until 2025/2026
  - In addition, pending applications for use of rhC1 inhibitor in other indications such as Ischemia Reperfusion Injury (IRI)
- New IP possible for products that have thus far not been produced on transgenic mammals
  - Process and “animal” IP
  - Product by process IP

Successful expression of many recombinant human proteins in milk of transgenic animals achieved by Pharming and others

- **Plasma Proteins**
  - Serpins: C1 Inhibitor, α1-antitrypsin and Antithrombin-III
  - Clotting Factors VII, VIII, IX and von Willebrand Factor
  - Albumin and Fibrinogen
- **Metabolic enzymes**
  - α–Glucosidase
- **Monoclonal antibodies**
  - High expression levels in various species: up to 30 g/L reported
- **Hormones**
  - Human Growth Hormone, Follicle Stimulating Hormone
- **Structural proteins**
  - Collagen
- **Others**
  - Protein vaccines
  - Lactoferrin and Lysozyme
  - Bile-salt stimulated lipase

Example: blood clotting factors

Blood factor	Market attractiveness
Factor VIII	Used to treat Haemophilia A •Current global market is ~US$ 5B •Need for affordable treatments in emerging markets •Unmet medical need remains, despite current and recombinant products in development
Factor VII	Used to treat patients that develop antibodies (inhibitors) to FVIII • Sales of approximately US$ 1.4B
Factor IX	Used to treat Haemophilia B • Sales of order ~US$ 1B

Manufacturing FVIII protein in mammalian cell culture is very expensive

Very costly to express each gram of protein

- Capital and operating costs of production systems in CHO or BHK cells are large
- FVIII is unstable and subject to degradation from proteases (enzymes) in cell culture
- Expression level of FVIII is very low compared to other recombinant proteins

Very costly to purify protein from the cell culture media

- Protein needs to be extracted using affinity columns rather than cheaper purification methods
- Because of low expression level : lot of affinity columns required

Producing FVIII in milk of transgenic rabbits will have lower cost of goods

Formulated and put into an injectable dosage form.

Purify FVIII from milk using low-cost purification methods

Breed transgenic rabbits that produce FVIII in milk

Treatment opportunities

- Treat patients that cannot afford any treatment today and serve emerging markets
- Treat development of 'inhibitors' by tolerising patients (which requires large quantities of FVIII)
- Opportunity to make prophylactic treatment more widely available

With proper treatment, people with hemophilia can live perfectly healthy lives. Without it, many will die young or, if they survive, suffer joint damage that leaves them with permanent disabilities. Tragically, only about 25 percent of the estimated 400,000 people with hemophilia receive adequate treatment. (World Federation of Hemophilia website)


RUCONEST™ 2100 U
Powder for solution
for injection
Conestat alfa
For intravenous use.
One vial contains 2100 U of conestat alfa, corresponding to 2100 U/14 ml after reconstitution, or a concentration of 150 U/ml.
Excipients: Sucrose, Sodium citrate (E331), Citric acid (E330).
Do not store above 25°C. Store in the original package in order to protect from light. Keep out of the reach and sight of children.
Medicinal product subject to medical prescription. Read the package leaflet before use.
1 vial.
PHARMING
RUCONEST™ 2100 U
Pulver till injektionsvätsk
Conestat alfa / Konestat
For intravenous use. 2100 U
leaflet before use. After
the solution contains 150 U
För intravenös användning.
före användning. Efter
innehåller lösningen 150 E
Tarkoitettu suonensisäiseen
Lue pakkausseloste ennen
valmiiksi sekoittamalla 14 ml
liuos sisältää 150 U alfakonestaatt