

# Nano2Clinic

Cancer Nanomedicine - from the bench to the bedside



Funded by the European Union

## Best practice: Clinical translation of a orphan nanodrug



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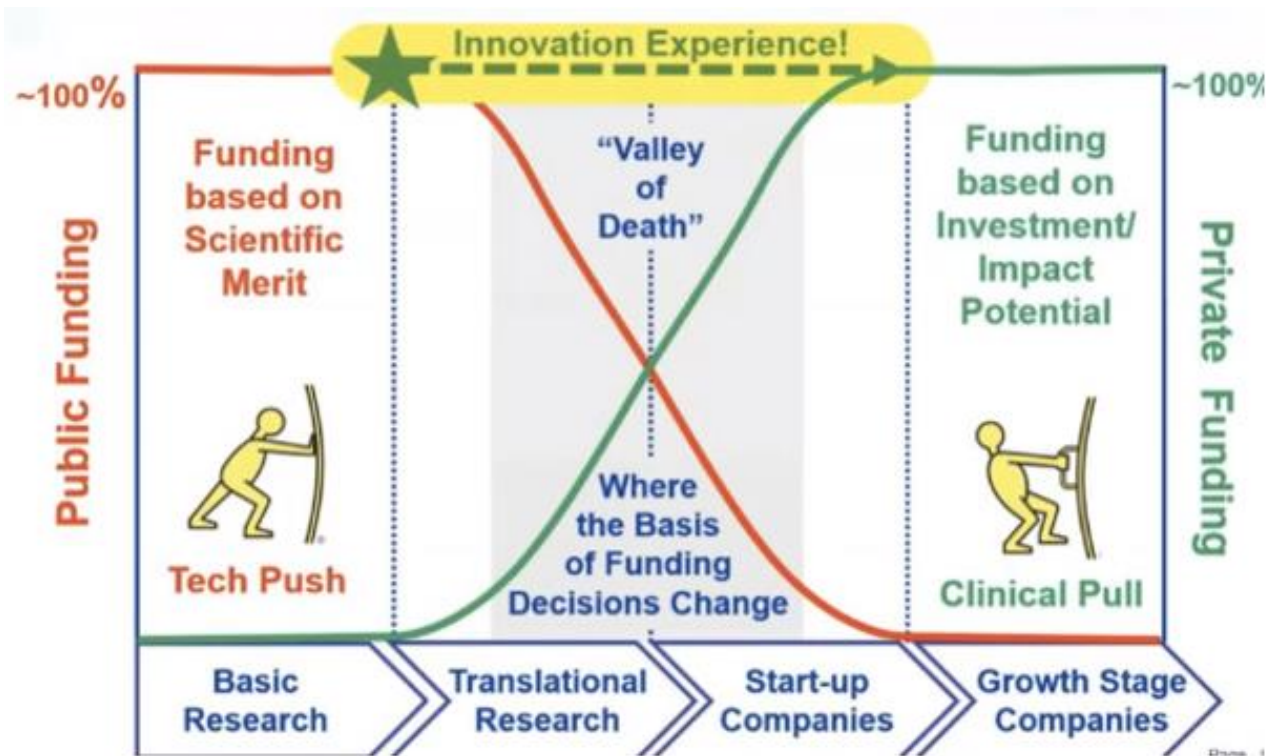
# Orphan Products: Hope for People With Rare Diseases

- A **rare disease** is defined by the EC as a **life-threatening** or **chronically debilitating** condition with a **very low prevalence** (< 1 in 2,000 people)
- **Evident limitations on the development of therapies**; fewer than 6% of rare diseases have an approved treatment option and if so, with limited effectiveness.
- **Main challenges to face:**
  - small market (low interest for orphan products since unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development)
  - poor understanding of the metabolic and biological basis of the disease
  - regulatory challenges: low patient recruitment for clinical trials, more stringent requirements for demonstrating safety and efficacy due to the limited treatment options available for patients with rare diseases, ...
- Overall, drug development for rare diseases is not financially viable without the **support of regulatory agencies and the funding and incentives through research and innovation framework programs**



# Public Funding to foster the clinical transition of orphan nanodrugs

Publicly funded research investment led by the European Commission has extensively supported the development of treatments for rare diseases



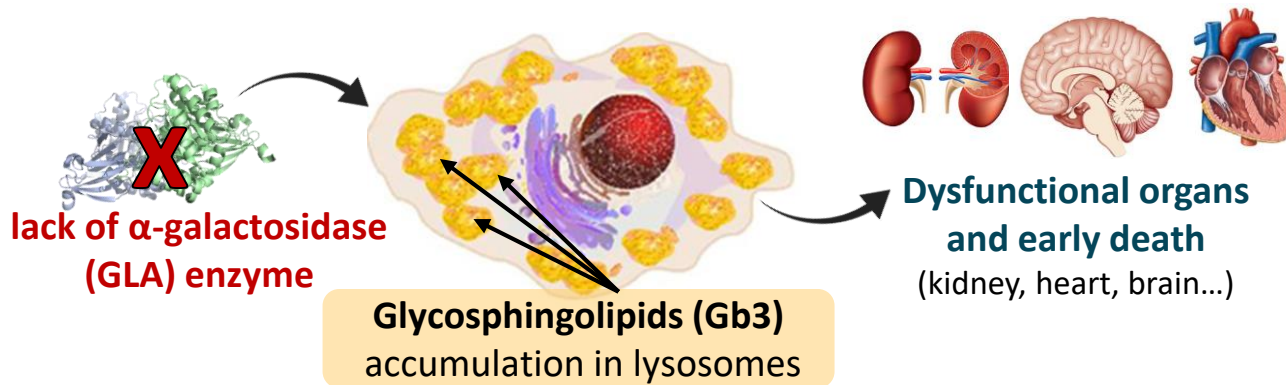
 SMART<sup>4</sup>FABRY (2017-2020)  
*(coordinators)*

 **Phoenix** (2021-2025)

# The Challenge in Fabry Disease

## FABRY DISEASE

Lysosomal Storage Disorder  
(1 to 40,000 – 117,000 worldwide)



## Limitations in Enzyme Replacement Therapy

REPLAGAL  
Sterile Concentrate  
agalsidase alfa  
intravenous use  
3.5 ml

Fabrazyme  
agalsidase beta  
5 mg  
For Intravenous Infusion Only

- ✗ Rapid enzyme degradation
- ✗ Poor penetration of enzyme in endothelial cells
- ✗ High immunogenicity
- ✗ Short circulation half-life, poor biodistribution and limited efficacy
- ✗ Frequent dosing is required (EOW)
- ✗ High-cost treatment (>280 k€/year)

iv infusion every 2 weeks

The image shows two vials of enzyme replacement therapy: Replagal (agalsidase alfa) and Fabrazyme (agalsidase beta). To the right, a list of six limitations is presented, each marked with a red 'X'. Below the vials, the text 'iv infusion every 2 weeks' is written in red.

*The EU orphan status already expired*

1<sup>st</sup> January 2017 – 31<sup>st</sup> December 2020



*Advance a novel nanoliposome formulation of a novel GLA enzyme from an experimental PoC up to an advanced stage of preclinical development*



<http://www.smart4fabry.eu/>

Interdisciplinary team

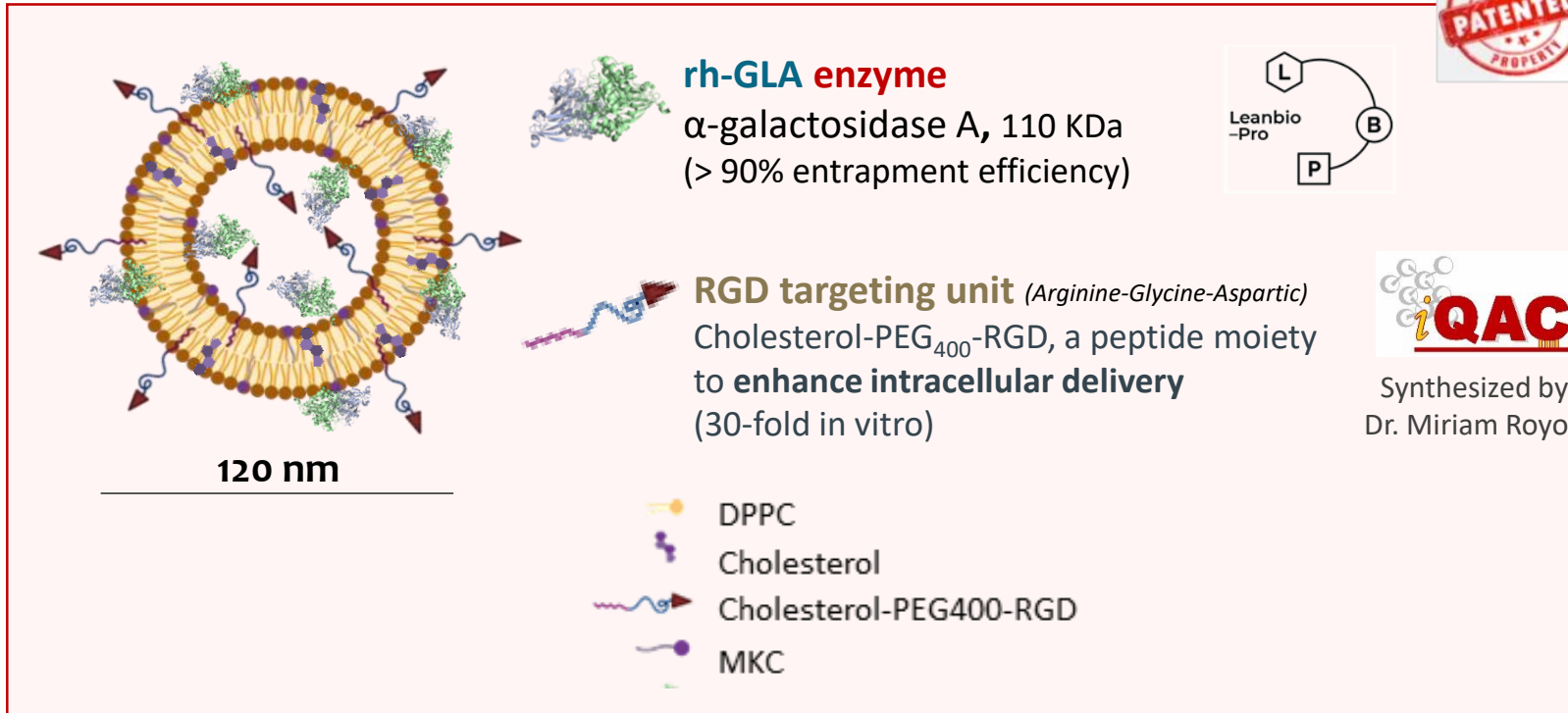
5,800 k€

Coord. Prof. Dr. Nora Ventosa



# RGD-targeted nanovesicles for GLA delivery in Fabry disease

## nanoGLA



PROTECTION

INTEGRIN  
TARGETING

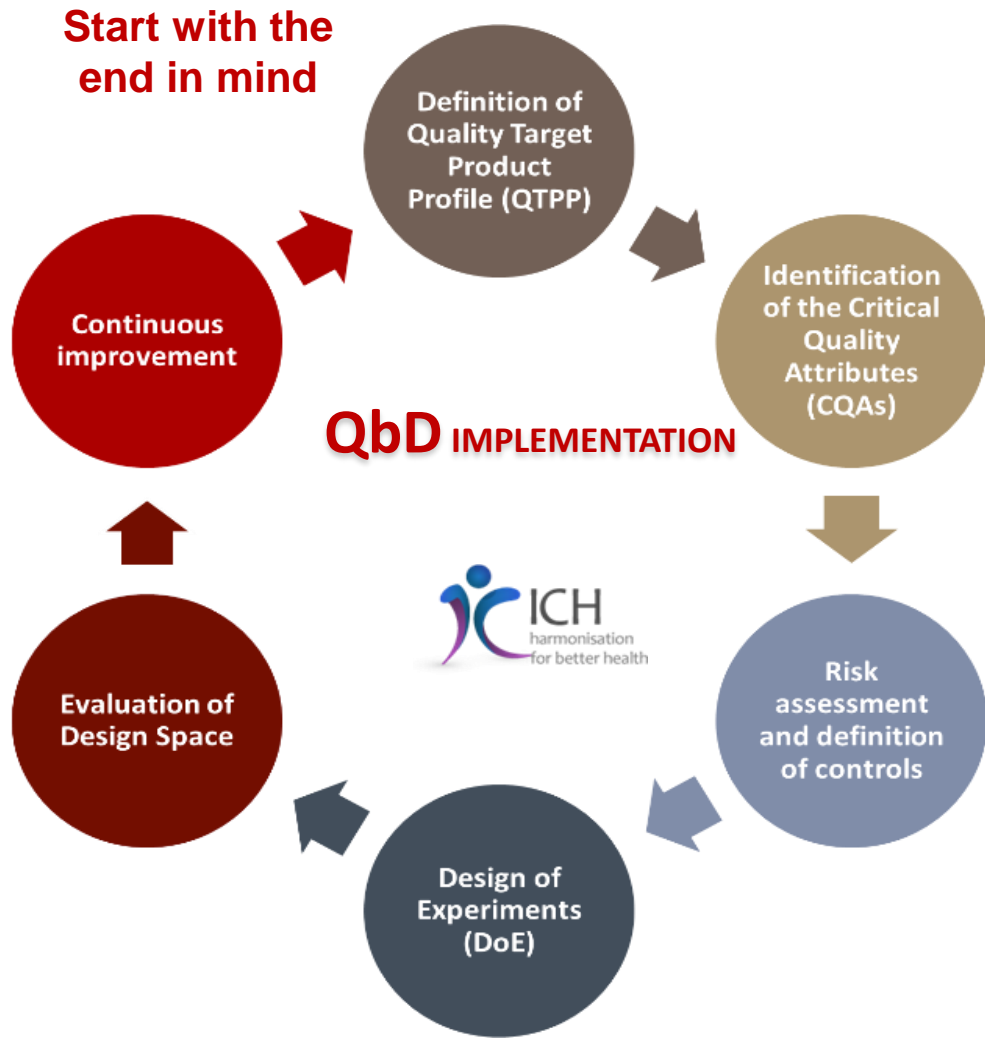
INTRACELULAR  
DELIVERY

## DELOS manufacturing process

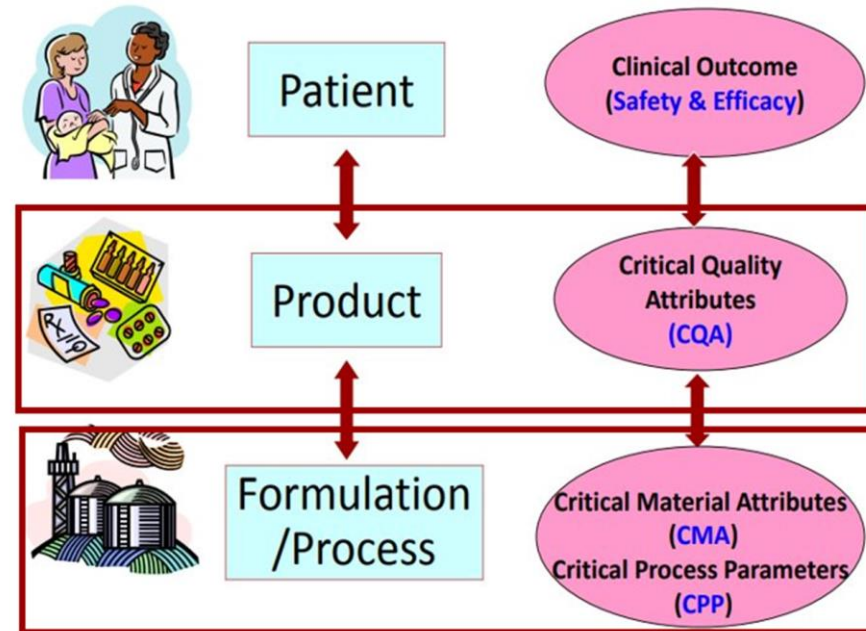


- Eco-efficient process
- High control of the molecular assembly
- Scalable
- GMP compatible

# Quality by Design approach

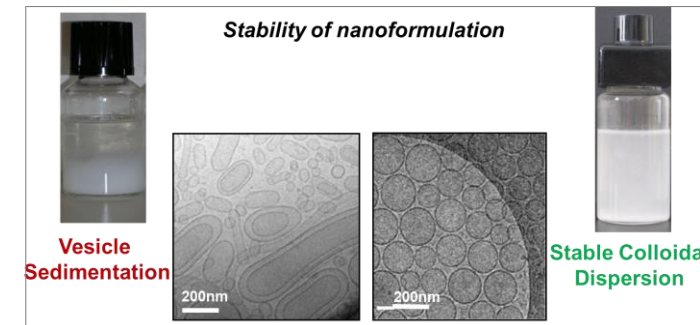
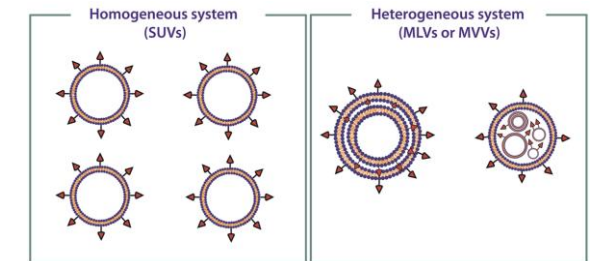
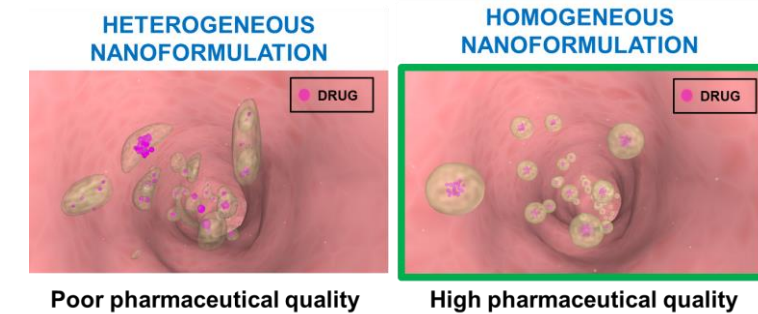


- Systematic methodology recommended by EMA and FDA to formulation and process development.



# Definition of the Product Quality: Quality Target Product Profile

## Pharmaceutical quality related to nanoscale properties



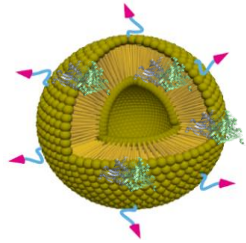
QTPP elements	Target
Dosage form	Nanoformulation
Dosage design	For targeted delivery
Administration route	Intravenous
<b>Quality attributes of the liposomal product</b>	
<b>Physico-Chemical (PC) properties:</b>	
Mean Particle Size and Particle Size Distribution (Pdl)	<b>Must meet the standards resulted from the specifications of similar approved products or from the current scientific research</b>
Particle morphology and lamellarity	
$\zeta$ -potential (liposome surface charge)	
Drug Entrapment Efficiency/Free drug substance	
Integration efficiency of Chol-PEGn-RGD in the vesicular membrane	
pH	
Dispersion stability	
Osmolality	<b>Preserve the enzymatic activity</b> <b>Lack of hemolytic activity and cytotoxicity</b> <b>Sterile and free of endotoxins</b>
Lipid and GLA degradation products	
<b>Biological properties:</b>	
Bioactivity	
Biocompatible	
Microbiological quality	

# NanoGLA and process development for scale-up & preclinical testing

Optimization based on QbD approach



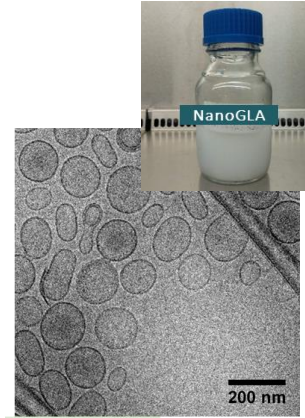
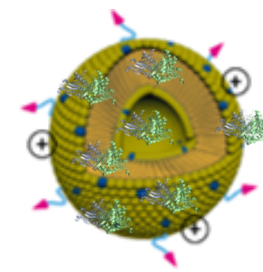
Initial nanoGLA formulation



Optimization of the composition and surface characteristics

Optimization of the manufacturing process

Final nanoGLA formulation



*Defined CQAs & specification in line with Relevant CMC Guidance and EMA recommendations (Scientific Advice)*

Nanoformulation with optimal characteristics for scale-up & preclinical testing



# Specific Relevant Guidance

NanoGLA is classified as **biologic** in a liposomal delivery system and will be subject to biological and other quality legislation

## Essential to refer to guidance relevant to both, drug substance and drug product

### a. Specific Guidance on Liposomal or other Nanodrug Delivery Systems:

- ✓ **Reflection paper EMA/CHMP/806058/2009/Rev.02 (February 2013)**  
(only indirectly relevant as neither Replagal or Fabrazyme are liposomal products)
- ✓ **FDA Final Guidance for Liposome Drug Products (April 2018)**
- ✓ **FDA Final Guidance for Industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (June 2014)**

### b. Guidance on Biotechnological Product

- ✓ **ICH Q6B guideline** “Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products”

### c. Guidance on Pharmaceutical Development

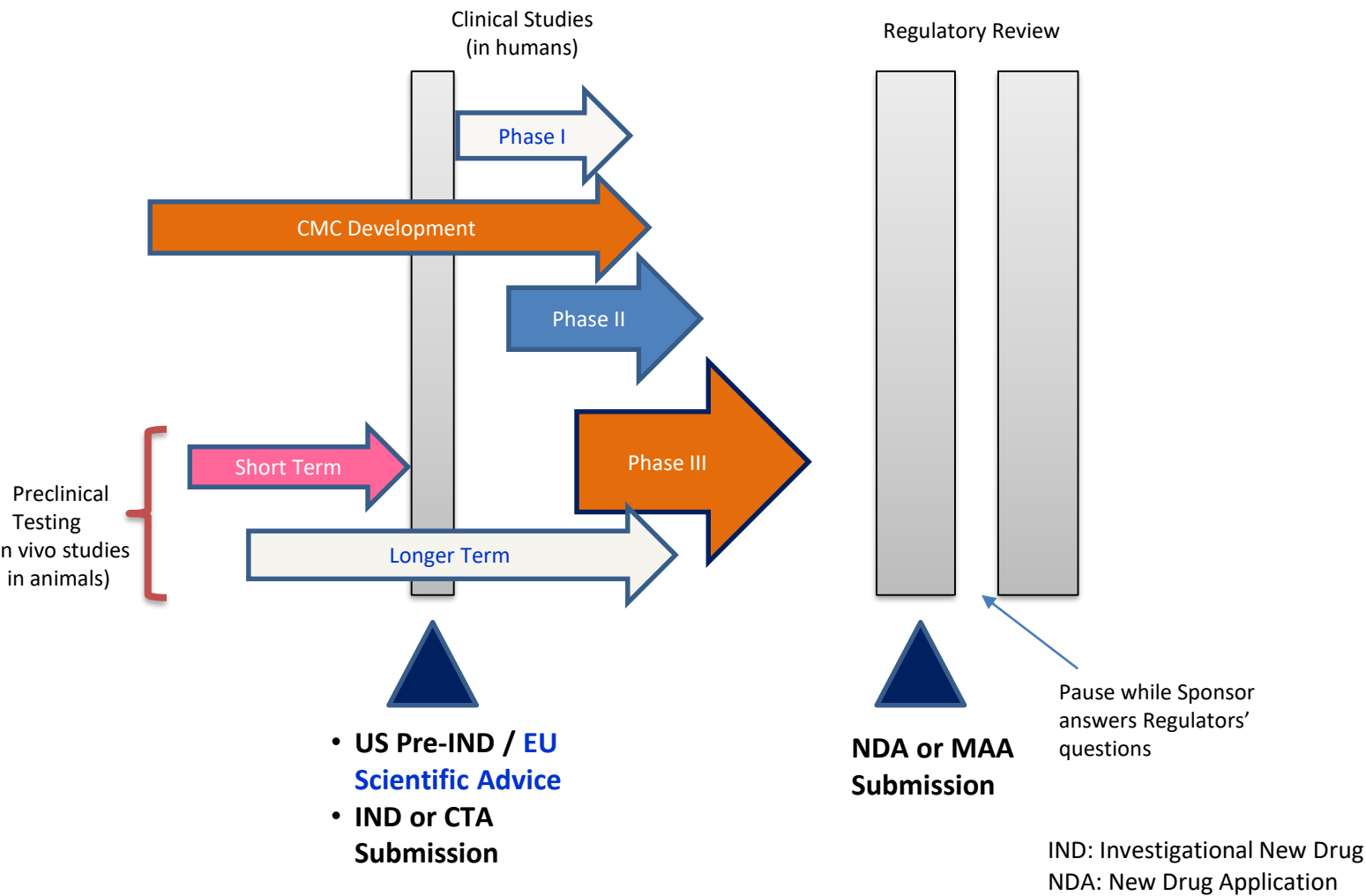
- ✓ **ICH Q8(R2), Q9 , Q10 & Q11 guideline**

In addition to the existing guidelines for conventional drugs about non-clinical / clinical trials



# Scientific considerations from regulatory agencies

## The Pharmaceutical Development Path: Chemistry, Manufacturing & Controls (CMC), nonclinical, and clinical studies



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH



**Scientific considerations** are given by the regulatory agencies in the frame of preparing the drug product for:

- the **clinical trial application (CTA)**
- the **future marketing-authorisation application (MAA)**

# Regulatory Support: Scientific Advice (SA) (CHMP-EMA)

In col. with

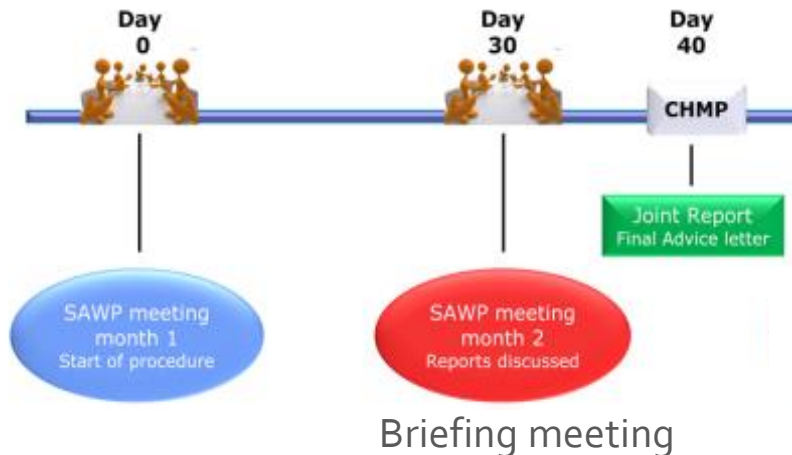


## ○ Preparation of the Briefing Document:

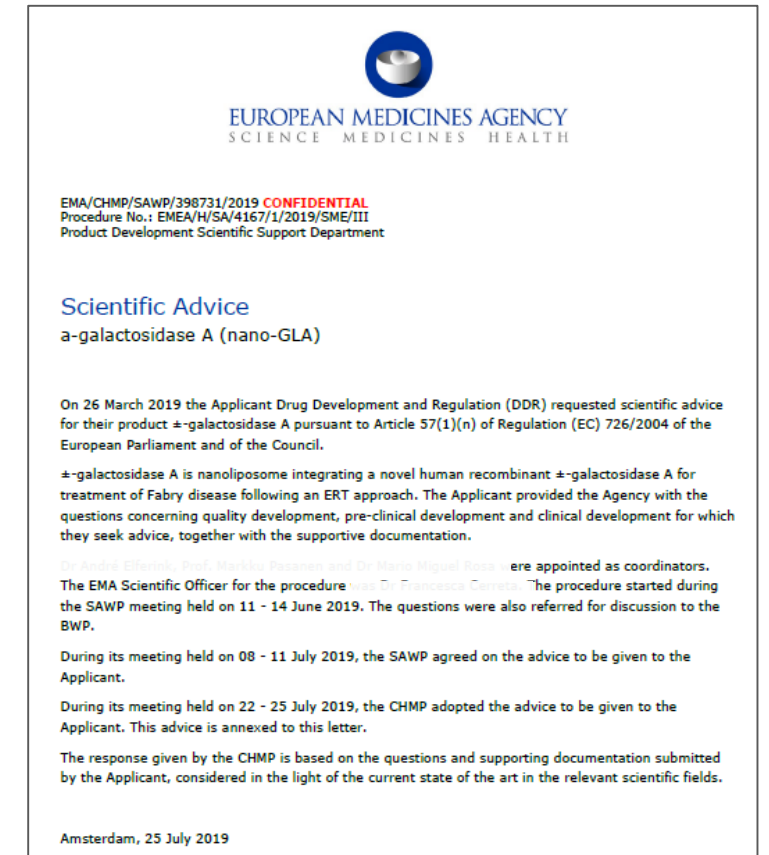
Contains **scientific questions** regarding:

- **Quality** (Critical Quality Attributes, specifications, stability programme, etc.)
- **Non-clinical** (Toxicity and safety studies design)

## ○ Submission and Procedural timelines:



SA is issued by the Committee for Medicinal Products for Human Use (CHMP)



63 pages

*Recommendations have been taking into consideration for pharmaceutical development*



# Main Preclinical Achievements

## Competitive advantages of the nanoGLA regarding the current solutions

**NanoGLA shows higher effectivity than current authorized ERT for Fabry Disease in a in vivo Fabry mouse model**

*(data still not published)*



# Orphan Drug Designation (ODD)



To qualify for orphan designation, a medicine must meet a number of criteria:

1 it must be intended for the treatment, prevention or diagnosis of a disease that is **life-threatening** or **chronically debilitating**

2 the **prevalence** of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;

3 no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of **significant benefit** to those affected by the condition.

# Orphan Drug Designation (ODD)

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Which are the advantages? Which are the incentives?



1

**Protocol assistance** from the EMA about the trials needed to demonstrate the quality, safety, and efficacy of the medicine

2

**Fee reductions/exemption** during the procedures

3

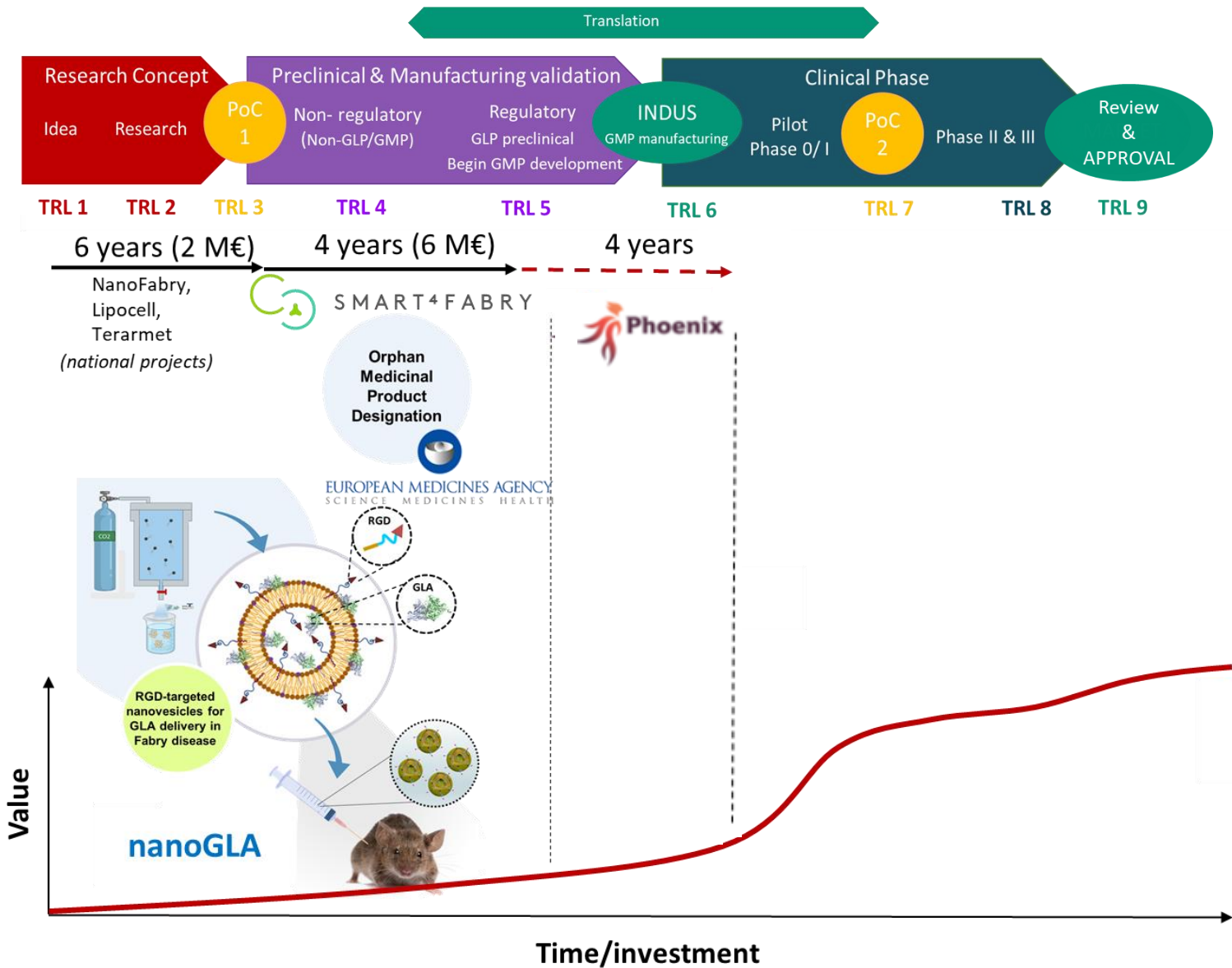
**Exclusivity in the market for 10 years** after being approved, and 12 years for pediatric drugs.

**This designation has important implications for the translation of the new therapeutic product from bench to bedside**

# Milestones achieved in the frame of S4F

- ✓ **Advanced the development of a novel nanopharmaceutical for the Fabry disease treatment up to the Regulatory Preclinical Phase (TRL5) with the achievement of important milestones:**
  - ✓ **Orphan Drug Designation:**
    - Improved efficacy in preclinical models compared to authorized treatments for Fabry disease
  - ✓ **Initiated the first GLP toxicity studies**
  - ✓ **Patent application to protect the nanoGLA product**  
*(PCT/EP2022/051727)*

# Further development to reach TRL6: EUH2020 PHOENIX



48 months (from 2021 to 2025)

14M€ project budget

To enable the **development and industrial production of nanopharmaceuticals** (from lab to industrial scale, **TRL6**), by providing a new infrastructure available to research labs, SMEs and start-ups.



# Phoenix Consortium



- ❑ 11 partners across Europe (public and private entities)
- ❑ Coordinated by the Luxembourg Institute (LIST), and the German SME MyBiotech
- ❑ 3 companies and 1 public institution from Spain:

- Nanomol Technologies
- Leanbio
- Grace Bio
- CSIC: ICMAB & INMA



Horizon 2020  
European Union funding  
for Research & Innovation

# Testing Phoenix OITB: Demo Cases



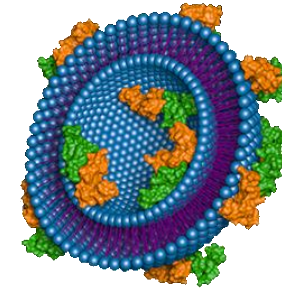
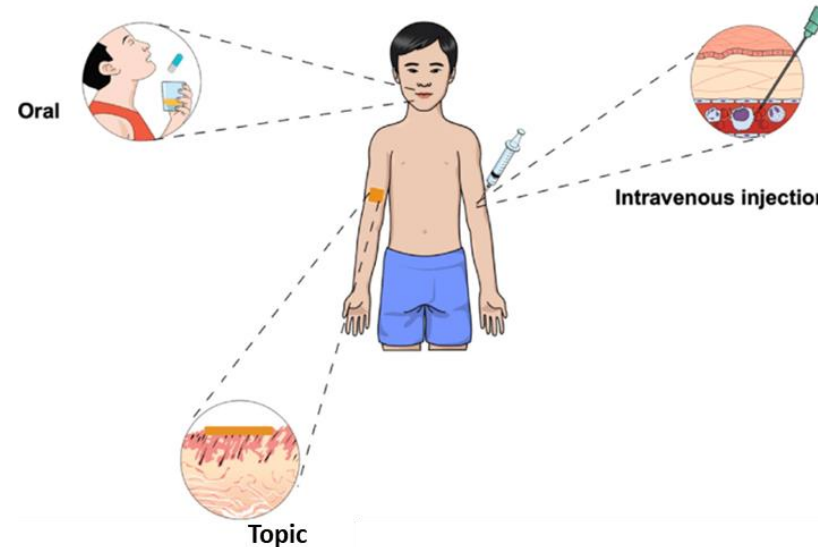
4 demo-cases are contributing for service portfolio establishment:

## 4 nanopharmaceutical types

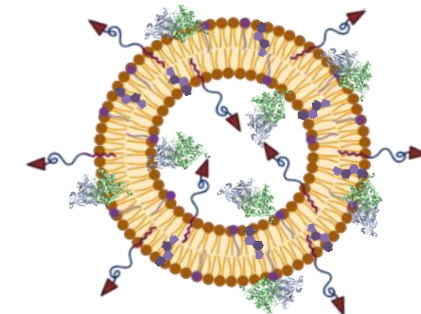
- Nanocrystals
- Vesicles
- Particle conjugates
- Polymeric diagnostic agent

## 3 delivery routes:

- Intravenous
- Oral
- Topic



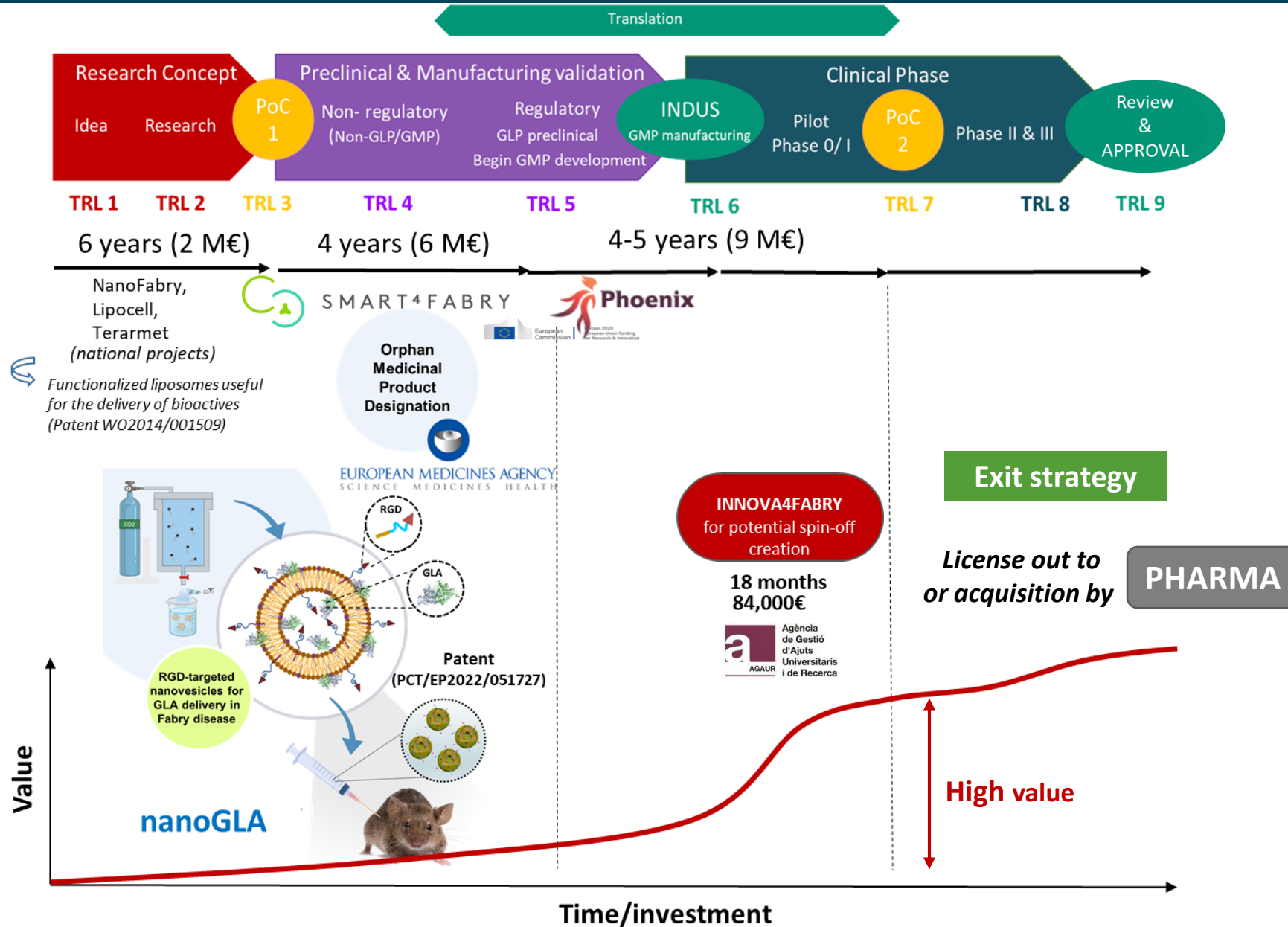
**Antimicrobial lipid nanovesicles**  
For the topical treatment of infections



**nanoGLA**  
For the i.v. treatment of rare Fabry disease

*Produced with the CO<sub>2</sub>-based,  
DELOS platform* 18

# Final overview (and future perspectives) of nanoGLA development



# Conclusions

## Take home messages

- Developing nanodrugs for rare diseases can be very challenging, since it must to face the significant challenges of both, the nanopharmaceuticals and orphan products' development;
- The support of regulatory agencies and the public funding research investment led by the European Commission is fostering the development of therapies for rare diseases;
- In the frame of the Smart4Fabry EU-project, we have developed a novel, patent protected, and potentially more effective therapy for Fabry disease treatment up to an advanced stage of preclinical development and with the achievement of the Orphan Drug Designation;
- Currently, with the Phoenix EU-project, together with the project Innova4Fabry, a smooth transfer of this novel therapy to clinical phase is pursued.

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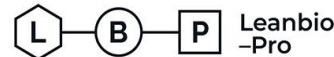
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# Thank you for your attention!