Nano2Clinic

Cancer Nanomedicine - from the bench to the bedside

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the European Union

Best practice:
Clinical translation of a orphan nanodrug

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March 3rd, 2023

CSIC Consejo Superior de Investigaciones Científicas

ICMAB Institut de Ciència de Materials de Barcelona — Excelencia Severo Ochoa

ciber-bbn Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina

nanbiosis

NANOMOL Centre of Nanotechnology and Molecular Materials

tecnio catalonia Fins a 31/12/2023

ACCIÓ Generalitat de Catalunya

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)

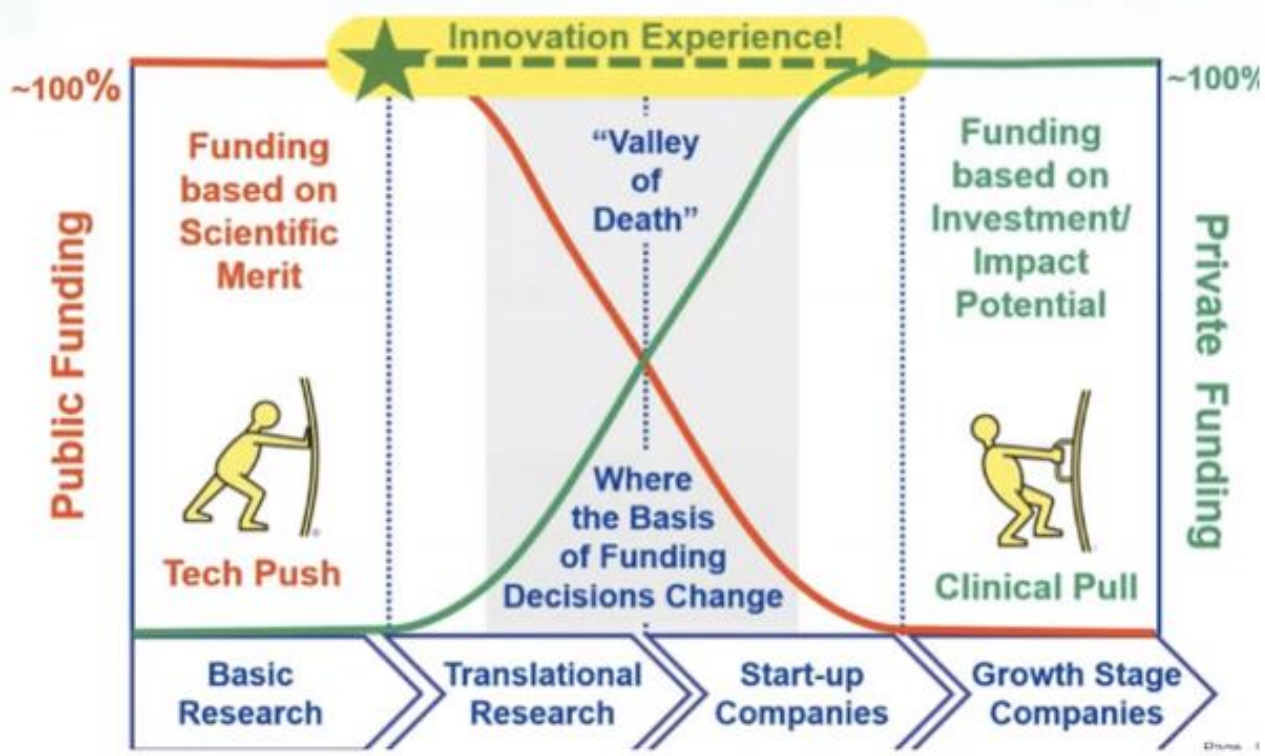
- **Evident limitations on the development of therapies;** fewer than 6% of rare diseases have an approved treatment option and if so, with limited effectiveness.

- **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

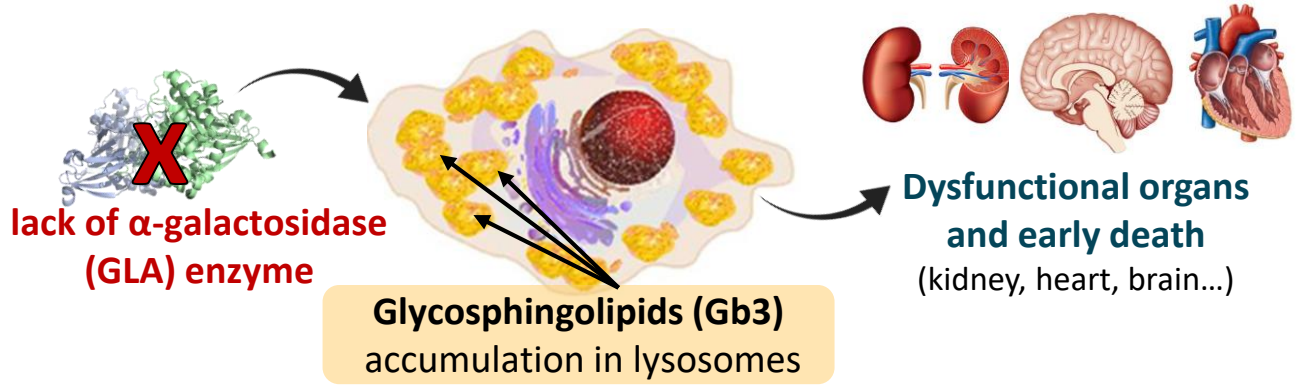


SMART4FABRY (2017-2020)
(coordinators)

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

iv infusion every 2 weeks

- ✘ 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)

The EU orphan status already expired

SMART⁴FABRY

1st January 2017 – 31st December 2020

European Commission | Horizon 2020 European Union funding for Research & Innovation

http://www.smart4fabry.eu/

Interdisciplinary team
5,800 k€

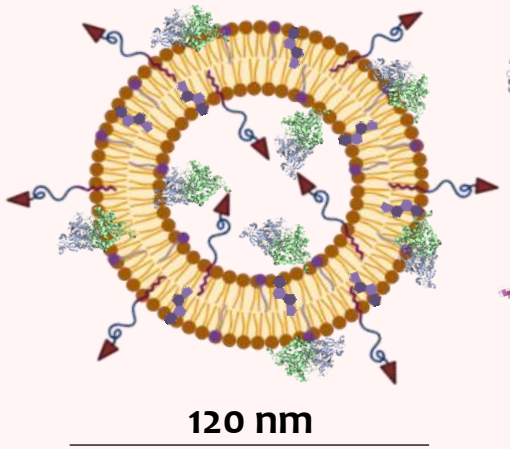
Coord. Prof. Dr. Nora Ventosa

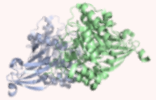
*Advance a **novel nanoliposome formulation of a novel GLA enzyme from an experimental PoC up to an advanced stage of preclinical development***

ciber-bbn · ICMAB · Leanbio Pro · Technion Israel Institute of Technology · AARHUS UNIVERSITY · NANOMOL TECHNOLOGIES · DDR Drug Development & Regulation · JOANNEUM RESEARCH · BNN · COVANCE · BioKeralty Research Institute

RGD-targeted nanovesicles for GLA delivery in Fabry disease

nanoGLA



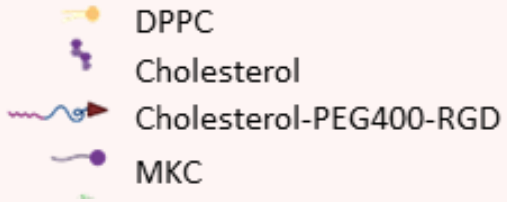


rh-GLA enzyme
α-galactosidase A, 110 KDa
(> 90% entrapment efficiency)

Leanbio –Pro

RGD targeting unit *(Arginine-Glycine-Aspartic)*
Cholesterol-PEG_{400}-RGD, a peptide moiety to **enhance intracellular delivery** (30-fold in vitro)

iQAC
Synthesized by Dr. Miriam Royo



PROTECTION

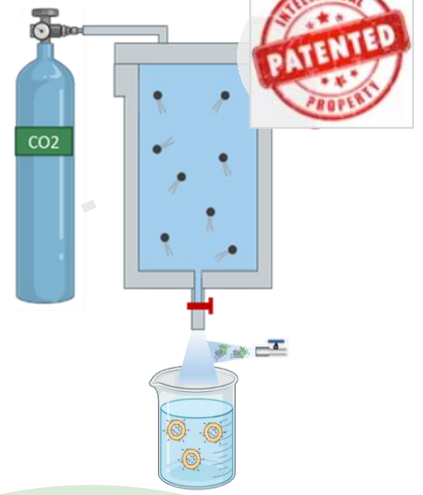
INTEGRIN TARGETING

INTRACELULAR DELIVERY

DELOS manufacturing process

NANOMOL
CENTRE OF NANOTECHNOLOGY AND MOLECULAR MATERIALS

NANOMOL TECHNOLOGIES



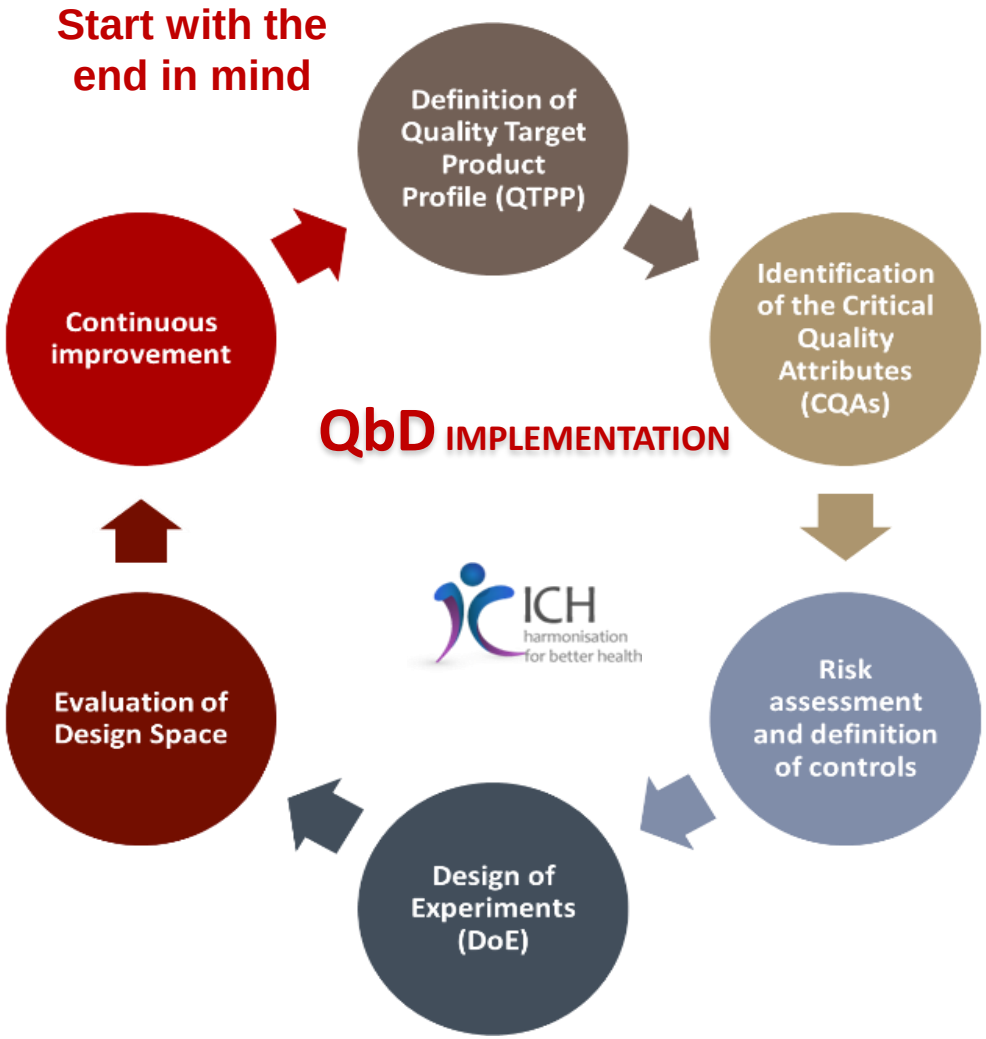
- Eco-efficient process
- High control of the molecular assembly
- Scalable
- GMP compatible

J. Tomsen-Melero et al. ACS Appl. Mater. Interfaces 2021.
J. Merlo, et al. Journal of Supercritical Fluids, In press
Cabrera, I. et al Adv. Healthc. Mater. 2016, 7, 829-840.

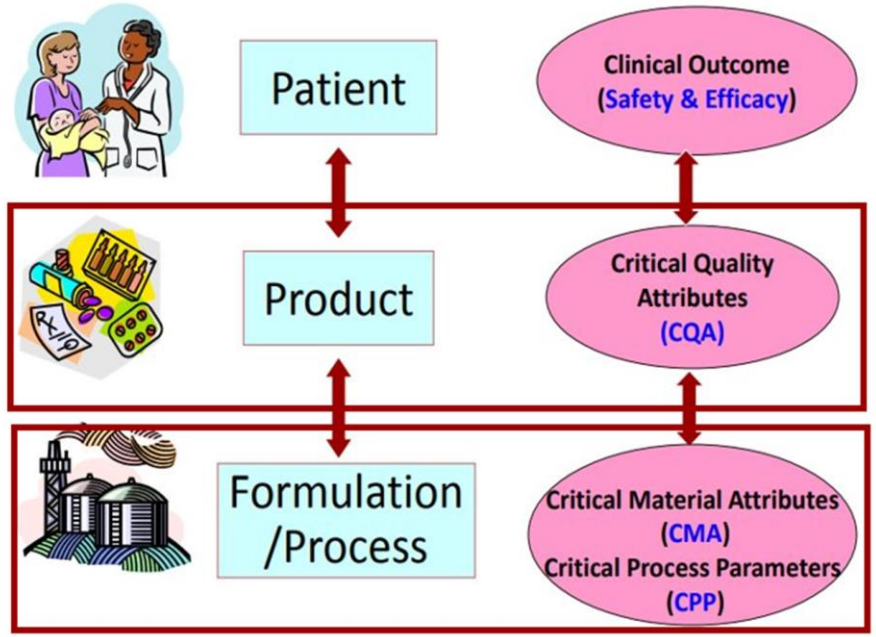
*Granted patent WO/2014/001509, major holders CSIC & CIBER-BBN (**2012**)*

*IP protection of nanoGLA through a selection patent application, PCT/EP2022/051727 (**2021**)*

Quality by Design approach



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

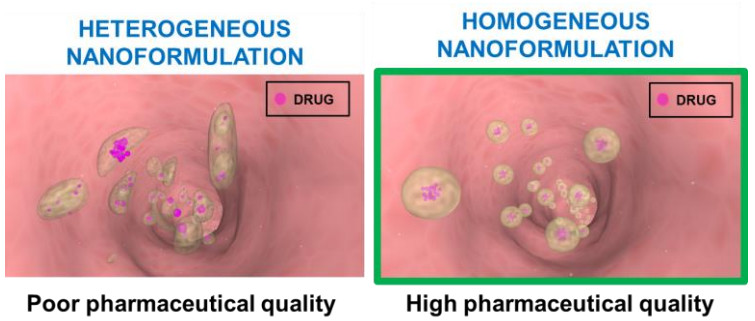


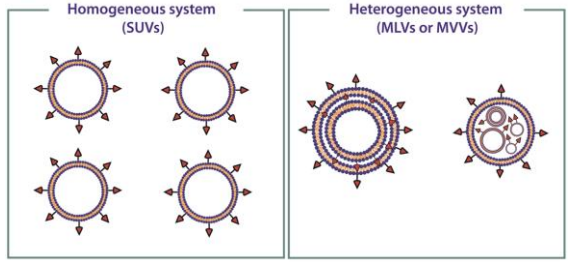
ICH Guideline Q9 - Quality Risk Management. *QUALITY RISK MANAGEMENT Q9, Step 4*.
ICH Guideline Q10 - Pharmaceutical Quality System. *PHARMACEUTICAL QUALITY SYSTEM Q10, Step 4*.
ICH Guideline Q8 - Pharmaceutical Development. *PHARMACEUTICAL DEVELOPMENT Q8(R2), Step 4*.

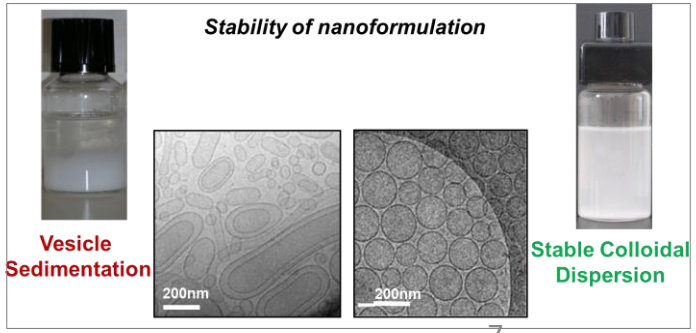
Definition of the Product Quality: Quality Target Product Profile

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

Pharmaceutical quality related to nanoscale properties







NanoGLA and process development for scale-up & preclinical testing

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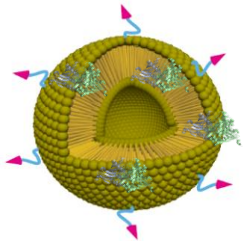
Optimization based on QbD approach

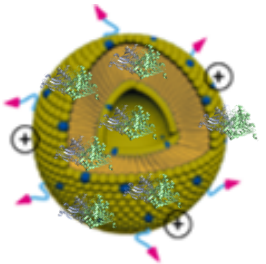
Initital nanoGLA formulation

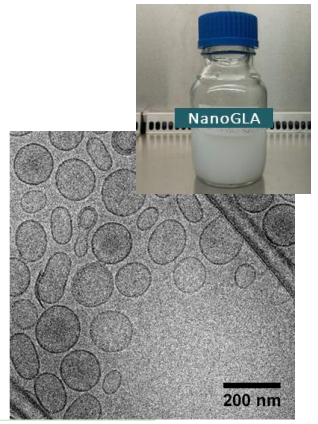


Optimization of the composition and surface characteristics

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"

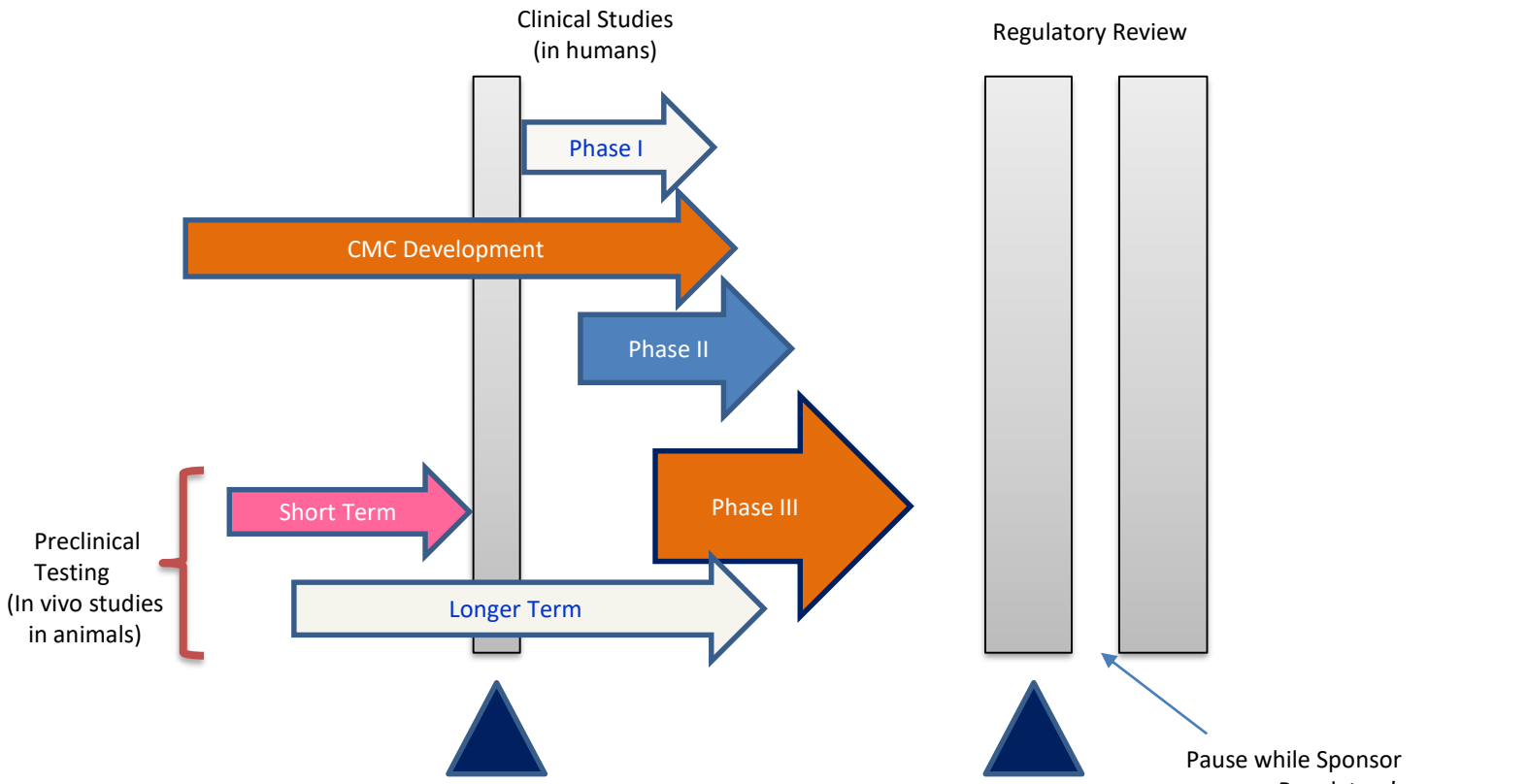
c. Guidance on Pharmaceutical Development

- ✓ **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



IND: Investigational New Drug
NDA: New Drug Application

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 DDR Drug Development & Regulation

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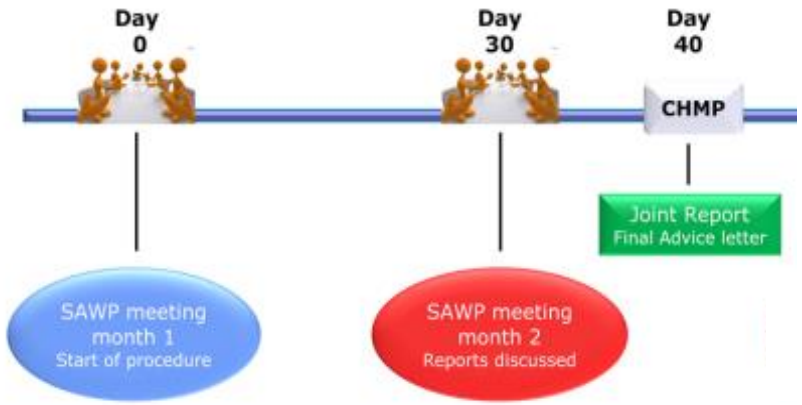
- **Preparation of the Briefing Document:**

  Contains **scientific questions** regarding:

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

- Submission and Procedural timelines:



Briefing meeting

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/CHMP/SAWP/398731/2019 CONFIDENTIAL
Procedure No.: EMEA/H/SA/4167/1/2019/SME/III
Product Development Scientific Support Department

Scientific Advice
a-galactosidase A (nano-GLA)

On 26 March 2019 the Applicant Drug Development and Regulation (DDR) requested scientific advice for their product ±-galactosidase A pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

±-galactosidase A is nanoliposome integrating a novel human recombinant ±-galactosidase A for treatment of Fabry disease following an ERT approach. The Applicant provided the Agency with the questions concerning quality development, pre-clinical development and clinical development for which they seek advice, together with the supportive documentation.

[redacted] were appointed as coordinators. The EMA Scientific Officer for the procedure was Dr Francesca Cerreta. The procedure started during the SAWP meeting held on 11 - 14 June 2019. The questions were also referred for discussion to the BWP.

During its meeting held on 08 - 11 July 2019, the SAWP agreed on the advice to be given to the Applicant.

During its meeting held on 22 - 25 July 2019, the CHMP adopted the advice to be given to the Applicant. This advice is annexed to this letter.

The response given by the CHMP is based on the questions and supporting documentation submitted by the Applicant, considered in the light of the current state of the art in the relevant scientific fields.

Amsterdam, 25 July 2019

63 pages

Recommendations have been taking into consideration for pharmaceutical development

Main Preclinical Achievements

SMART4FABRY

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)

Achieved

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Orphan Drug Designation

EU/3/20/2396

Orphan Drug Designation (ODD)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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)

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.

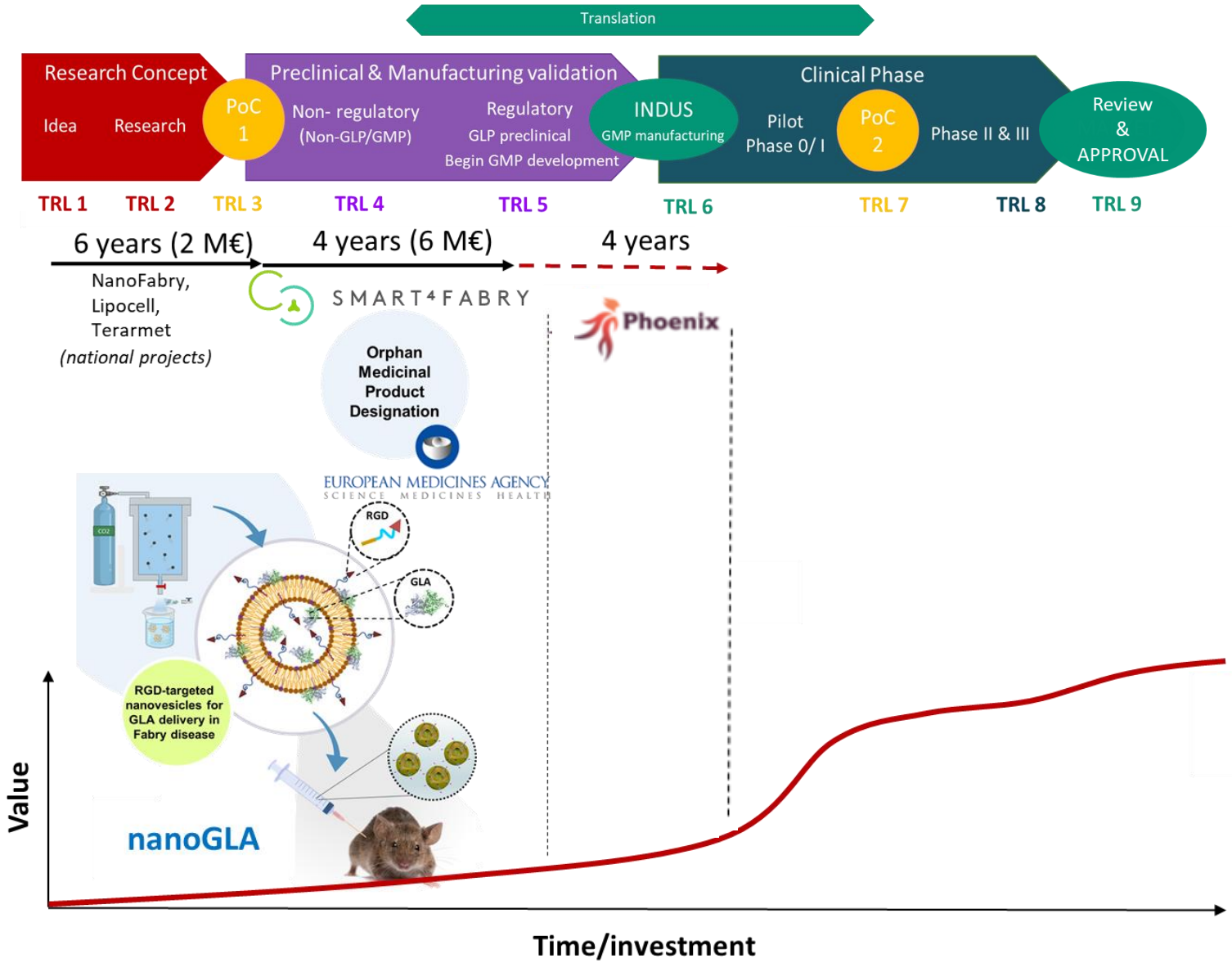
This designation has important implications for the translation of the new therapeutic product from bench to bedside

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



Phoenix

European Commission | Horizon 2020 European Union funding for Research & Innovation

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

Testing Phoenix OITB: Demo Cases

Phoenix

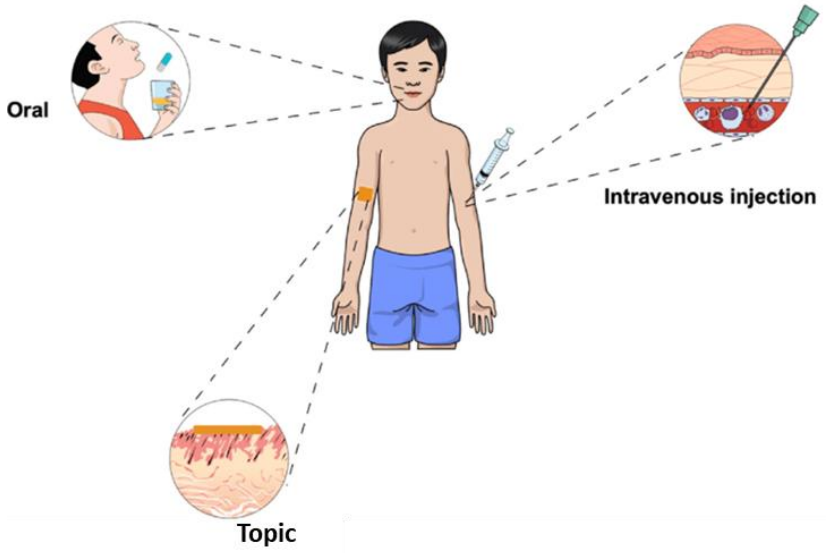
4 demo-cases are contributing for **service portfolio establishment:**

4 nanopharmaceutical types

- ❑ Nanocrystals
- ❑ Vesicles
- ❑ Particle conjugates
- ❑ Polymeric diagnostic agent

3 delivery routes:

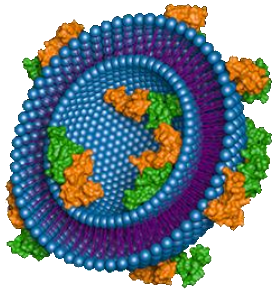
- ❑ Intravenous
- ❑ Oral
- ❑ Topic



ICMAB INSTITUT DE CIÈNCIA DE MATERIALS DE BARCELONA EXCELENCIA SEVERO OCHOA

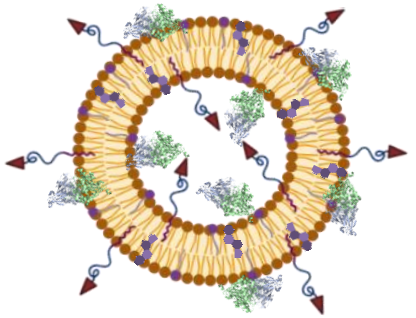
CSIC CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS

NANOMOL TECHNOLOGIES



Antimicrobial lipid nanovesicles

For the topical treatment of infections

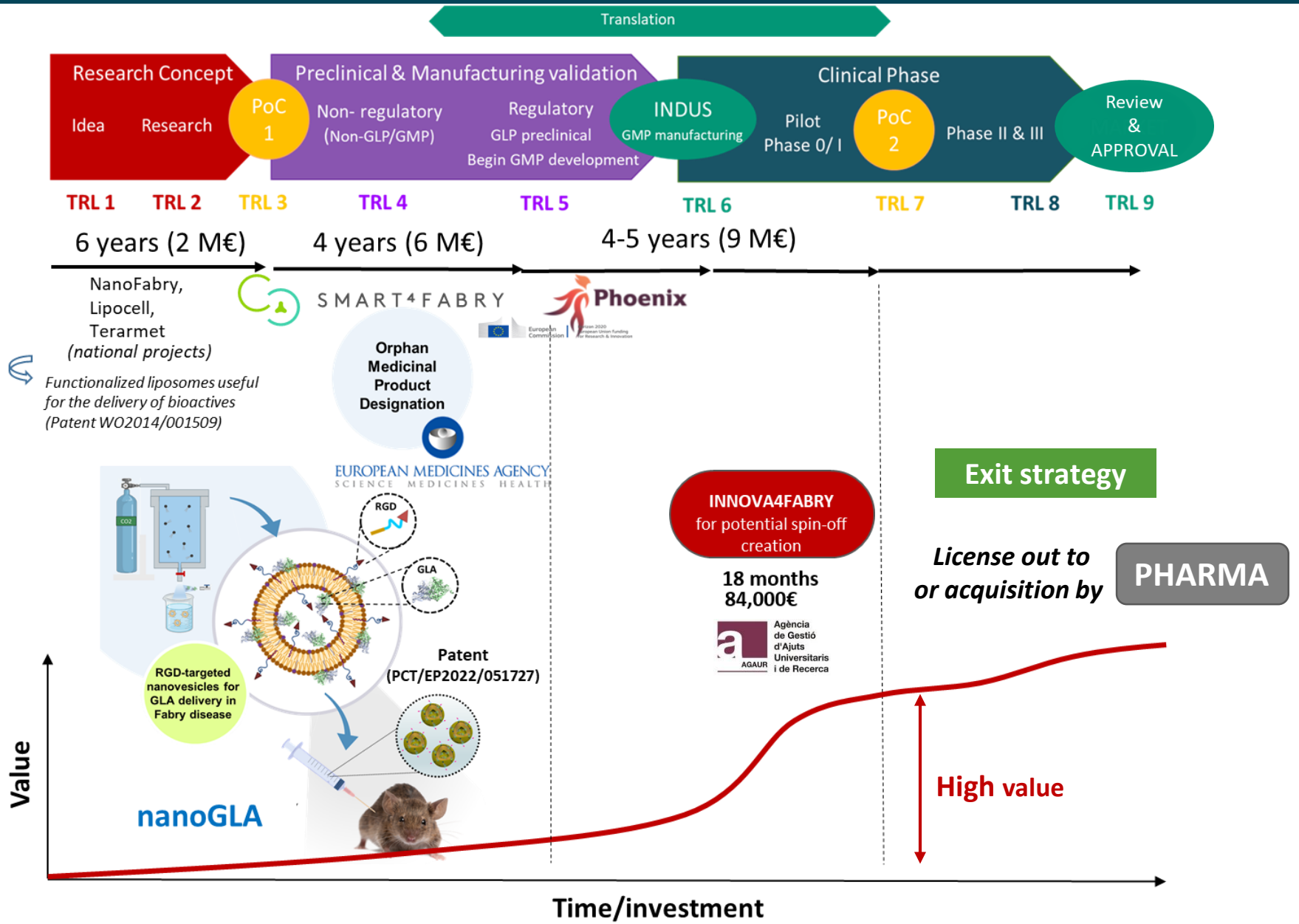


nanoGLA

For the i.v. treatment of rare Fabry disease

Produced with the CO_2-based, DELOS platform

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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Thank you for your attention!