

# Gene Transfer and Rare Diseases Workshop

NIH

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Rockville, MD – United States of America

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VP – Chief Medical Officer

# Pre-existing Conditions in GT development

# Stakeholders / Targets

- **Patients**
- **Physicians / Researchers**
- **Regulatory bodies (FDA + EMA)**
- **Investors / Partners / Shareholders**

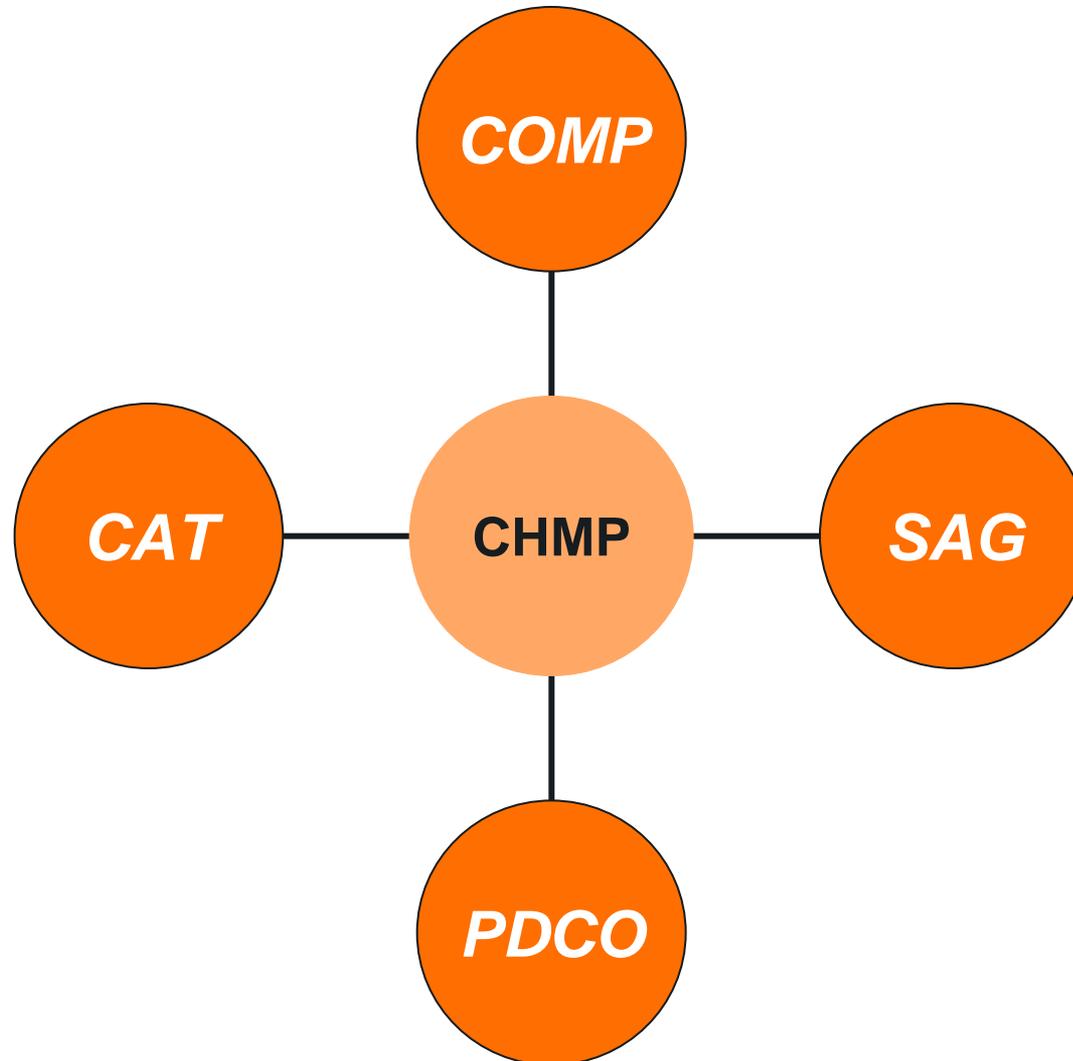
## *Support Conditions*

- ✓ **Grants Programmes/Frames**
- ✓ **Tax Reduction Schemes**
- ✓ **Patients Advocacy Associations**
- ✓ **Government Interest**
- ✓ **Research Institutions**

## Research Conditions

- **Several Research Programmes**
- **IP boundaries**
- **Communications / Publications**
- **Dispersed Consensus**
- **Experts / KOL  $\neq$  Researchers**

## EMA reviewers



# Glybera 1<sup>st</sup> GT Approved in Western World

<b>Submission:</b>	<b>end 2009</b>
<b>1<sup>st</sup> Neg Opinion:</b>	<b>Jun 2011</b>
<b>2<sup>nd</sup> Neg Opinion:</b>	<b>Oct 2011</b>
<b>EC rejection:</b>	<b>Jan 2012</b>
<b>CAT Positive:</b>	<b>Jun 2012</b>
<b>CHMP Positive:</b>	<b>Jul 2012</b>

# 1<sup>st</sup> Condition

## Company's Manufacturing

- Drug Substance to Drug Product
- GMP product at “first in patient administration”
- Validated Quality Assays, Characterisation and Specifications
- Validated Quality Delivery Process
- Reproducible Manufacturing

# uniQure Production System

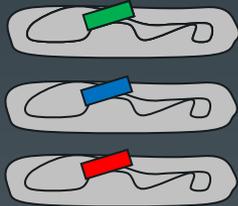
## Baculovirus based AAV production

- Modular
- High vector yields
- Reproducible / consistent
- GMP and Regulatory compliance
- Cost effective

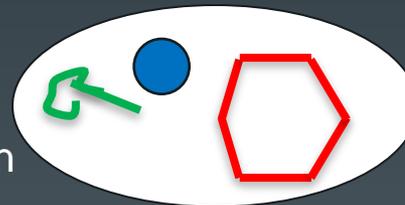
Bac-Vec

Bac-Rep

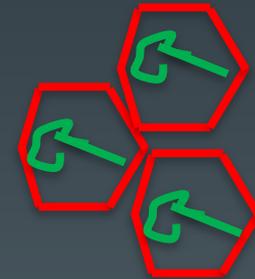
Bac-Cap



co-transfection



insect cell



therapeutic gene  
packaged in an AAV  
delivery shell

Bac-Vec delivers a therapeutic gene (PBGD gene)

Bac-Rep delivers replication protein

Bac-Cap delivers capsid protein (AAV5)

## 2<sup>nd</sup> Condition

# Toxicity Studies Before Clinical

- Small to large animals Tox Studies
- Short-, Medium- and Long-term studies
- Dose Selection Support
- Immunogenicity

# Information Needed to Start an Early- Phase Clinical Study

Product manufacture, characterization, and safety tests

Safety information to show that the proposed treatment is **reasonably safe** to administer in human, based on:

- **Pre-clinical studies** conducted in appropriate animal species/models
- Data from **previous** or **ongoing clinical studies**
- **Published** scientific data

## 3<sup>rd</sup> Condition

# Safety in Clinical Development

- Risk Based Approach
- Termination Procedure
- Anticipated Rescue Treatment

- **Starting dose or dose range**
- **Rationale of route of administration**
- **Delivery device**
- **Biological activity data:**
  - *Gene expression in target tissues*
  - *Measurable transgene product in target tissues*
  - *Immunogenicity*

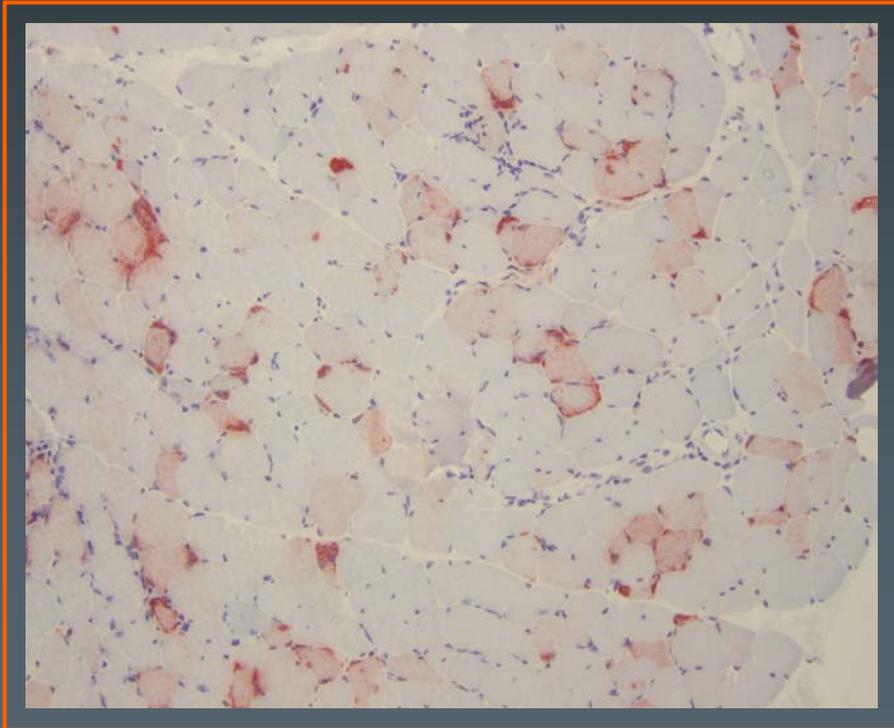
# Muscle Biopsy – LPL Expression

uniQure

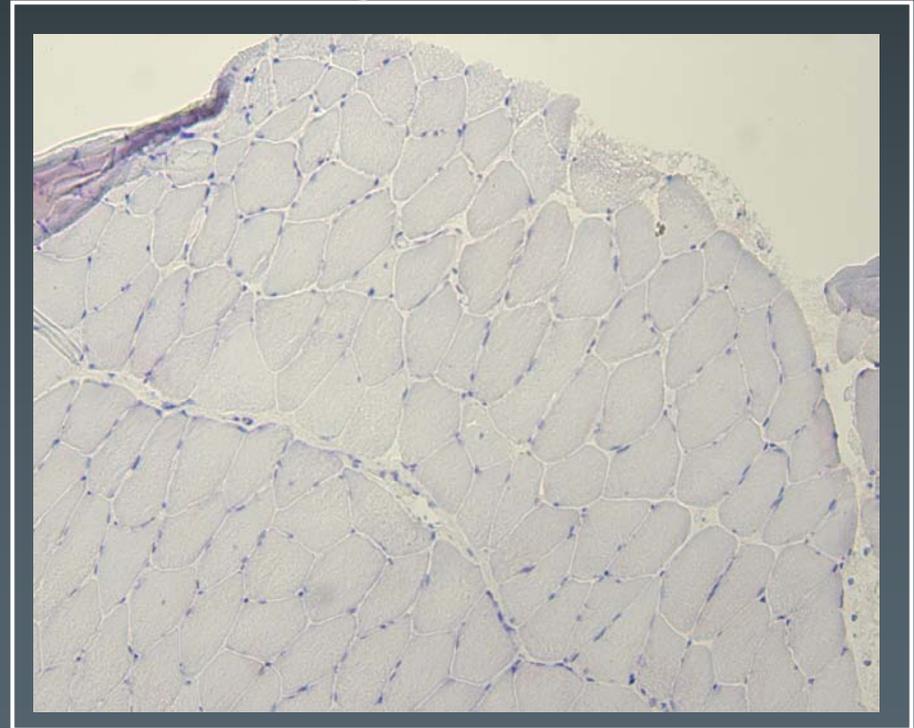
*Sustained LPL protein expression in muscle*

*52 weeks post-Glybera expression in 1 patient of CT-AMT-011-02*

**Injected muscle**



**Non-injected muscle**

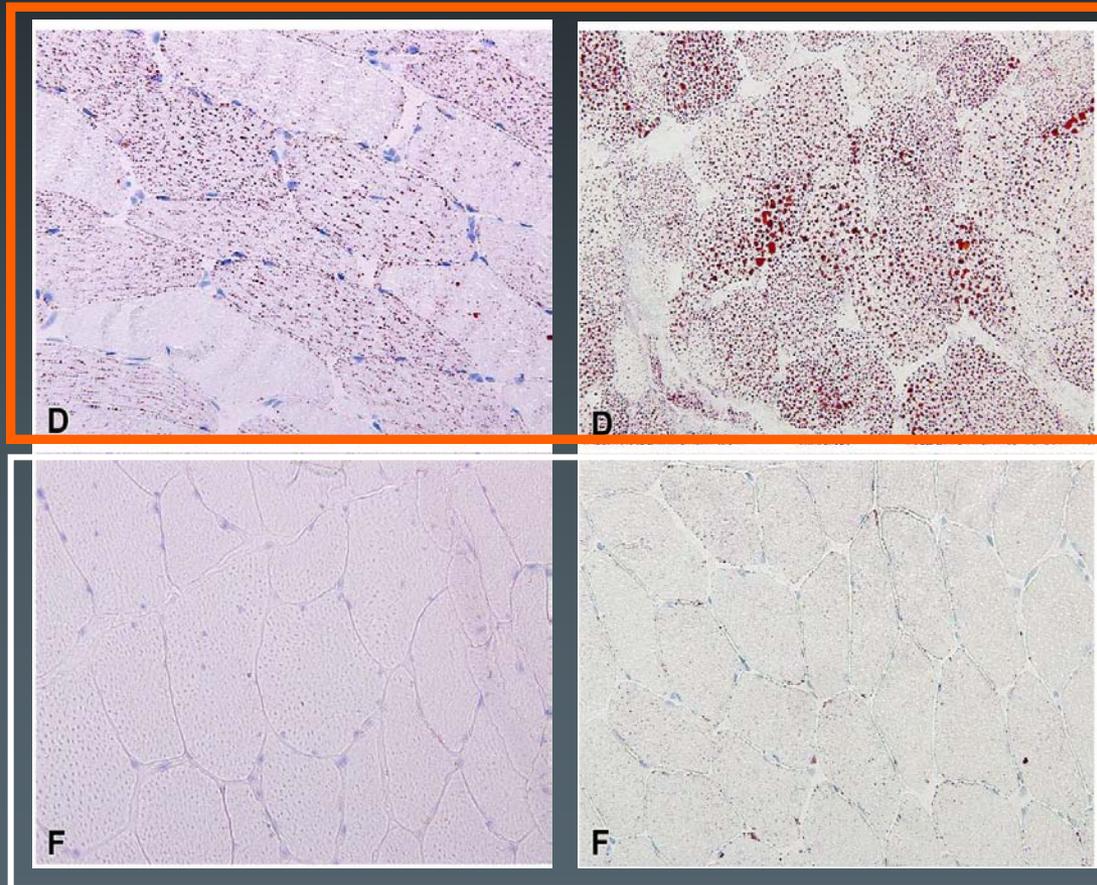


# Muscle Biopsy – Lipid Uptake

26 weeks post-Glybera LPL-mediated Lipid Uptake

$3 \times 10^{11}$  gc/kg (subj004)

$1 \times 10^{12}$  gc/kg (subj011)



Injected  
muscle

Non-injected  
muscle from  
same patient

Oil Red O stain in  
human muscle,  
26 weeks after  
treatment.  
Indicates FFA  
uptake from  
lipolysed CM.

## 4<sup>th</sup> Condition

# Efficacy End-Points

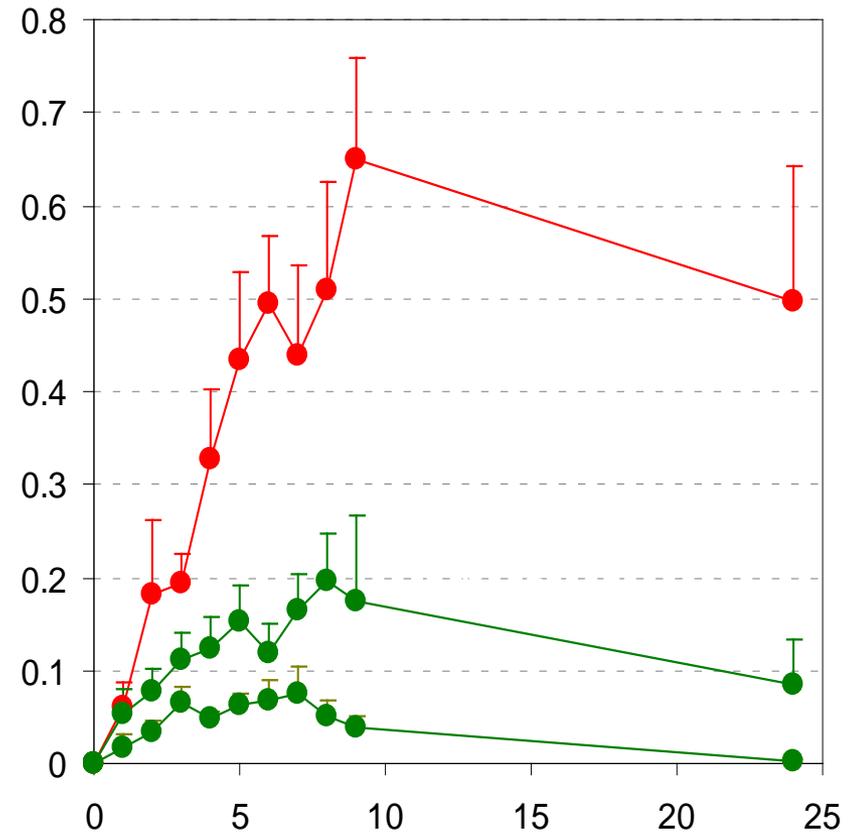
- Primary
- Secondary
- Expanded

## Collecting Data: Biologic Activity

- *Duration and level of gene expression*
- *Duration and level of transgene proteins*

# Biological response to Glybera

- Improves post-prandial metabolism of newly-formed, large CM (reduced peak level, reduced AUC)
- In all patients evaluated so far
- Persistent effect (observed at 14 and 52 weeks after GT)



## Results for definitive cases of pancreatitis

- Reduction of risk by more than 50 % post treatment
- Consistent results for different length of historic control
- Hazard Ratios between 0.41 – 0.49

# Shorter Hospital Stay / Lower Complexity After Treatment

**Table 8 Duration of hospitalization**

Event		pre treatment (N=17)	post treatment (N=17)	untreated (N=5)
definite pancreatitis	Subjects with a hospitalization	14	3	4
	Median (min-max)	28.0 (0-1119)	0.0 (0-19)	53.0 (0-610)
probable pancreatitis	Subjects with a hospitalization	8	1	3
	Median (min-max)	0.0 (0-96)	0.0 (0-4)	7.0 (0-77)
abdominal pain	Subjects with a hospitalization	10	1	4
	Median (min-max)	3.0 (0-367)	0.0 (0-5)	8.0 (0-212)
other	Subjects with a hospitalization	13	0	3
	Median (min-max)	12.0 (0-95)	0.0 (0-0)	7.0 (0-20)

For subjects with no events the duration of hospitalization is set to 0 days; Sources: Table [14.3.3](#)

Source: CSR 011-03

## 5<sup>th</sup> Condition

### Long-term Follow-up Program and Registry

- Safety
- Efficacy

**All Challenges Represent Opportunities for  
Cutting Edge Therapeutic Innovation when  
Researchers, Industry, Investors and  
Regulatory Authorities work together for the  
Benefit of Patients with No Efficient Treatment**

**Thank You for Your Kind Attention !**

**Dr. Carlos R. Camozzi**  
**VP – Chief Medical Officer**  
**uniQure B. V.**