

uniQure

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ESOF
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uniQure – the New AMT



uniQure

Corporate Focus uniQure 2012

	Program	Priority	Strategic Objective
Development	Hemophilia B (plus)		Partner s/t to fund
	GDNF		Develop platform to partner in full or part
	Porphyria		Develop AAV5 expertise, option value
	Sanfilippo		Develop AAV5 expertise, option value, service revenues
Discovery			Target selection process initiated
Technology	Repeat injections		Fulfill regulatory requirements
	Gene switch		Fulfill regulatory requirements
	AAV5_Proof-of concept		Strengthen platform
	RNAi_Proof-of concept		Partner

Glybera:

not in the active portfolio, but in the back of our mind

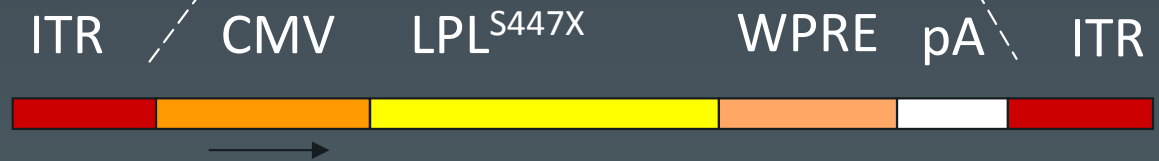
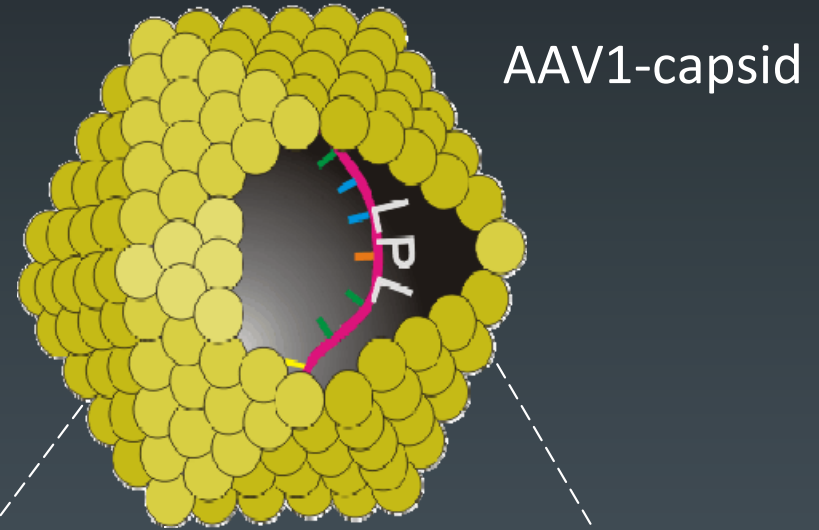
- ◆ **How is Glybera influencing uniQure's Portfolio:**
experience and established technology platforms
- ◆ **Lessons learned from Glybera:**
step up in clinical development
enter new ground,
e.g. re-administration, regulated gene expression,
gene targeting

What is Glybera

One time intramuscular injection

1×10^{12} gc/kg

Short term immunosuppression



AAV2-LPL^{S447X}

CT-AMT-010: dose response / mammalian cell produced

CT-AMT-011-01: dose response / insect cell produced

CT-AMT-011-02: single dose /insect cell produced

For what is Glybera?

Disease

LPLD - Lack of lipoprotein lipase
necessary in fat metabolism

Manifestations

Chylomicronemia
Pancreatitis (potentially lethal)
Diabetes mellitus
Atherosclerosis

Treatment

AAV-based gene therapy - LPLD gene
to restore body's natural fat metabolism



Secreted into the circulation as a catalytically active enzyme

Mainly bound to endothelium

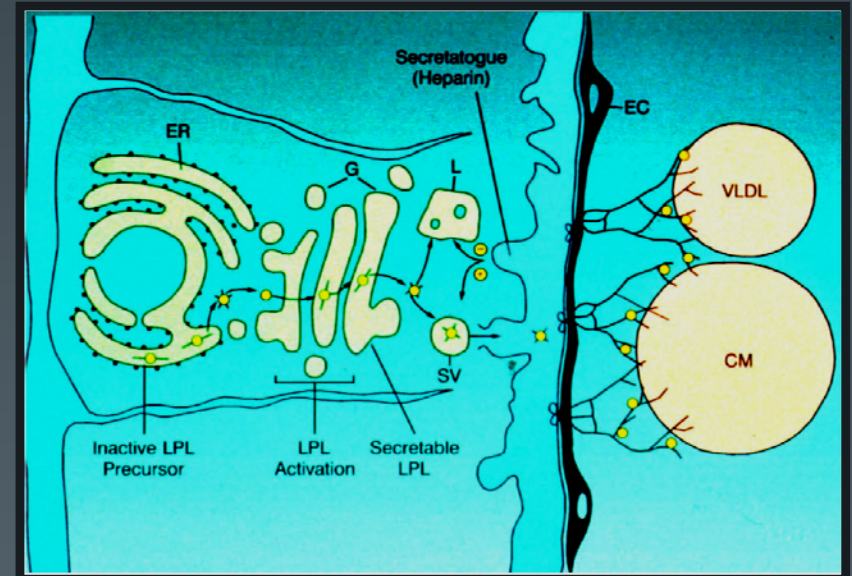
Substrate: triglycerides
(in chylomicrons and VLDL)

Crucial function in lipid metabolism

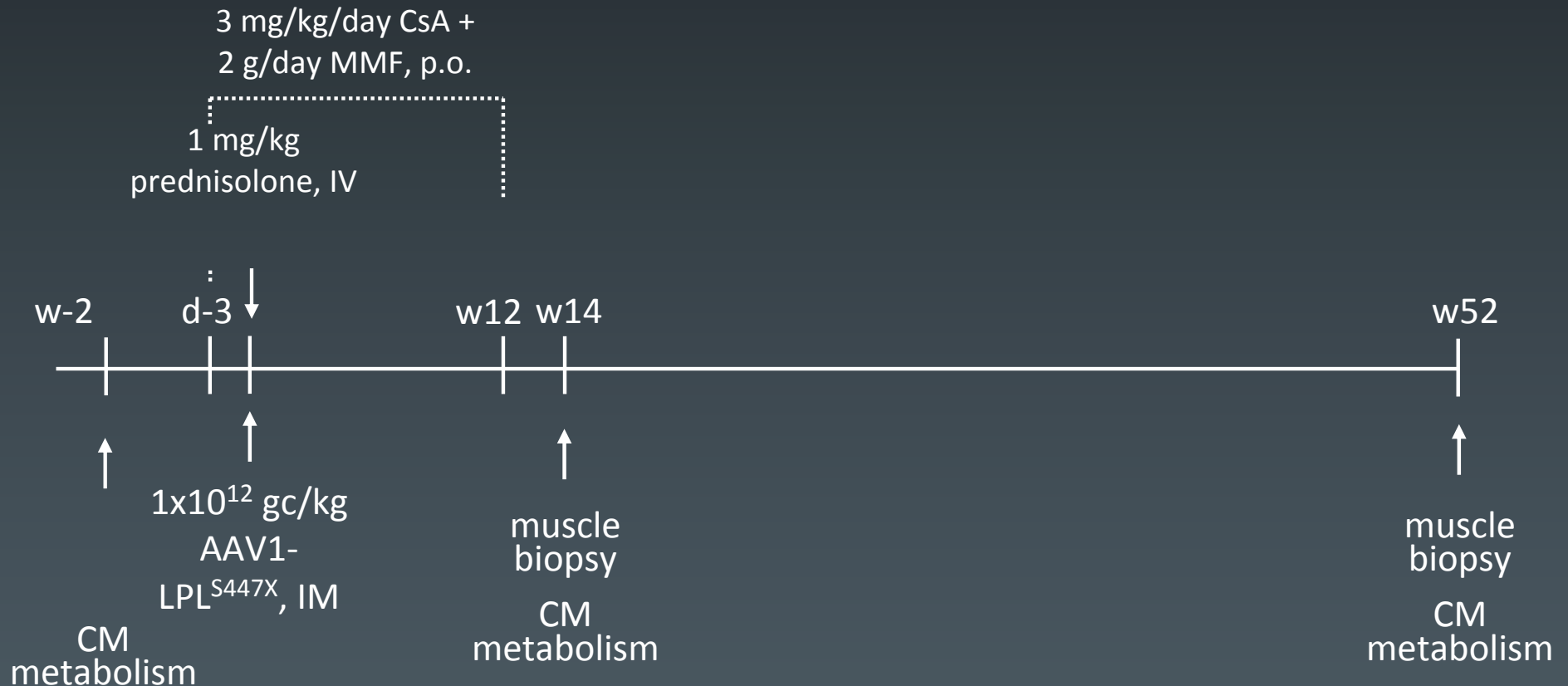
- hydrolysis of triglycerides
- lipoprotein binding: bridging function

Expression:

- heart muscle, adipose tissue, skeletal muscle



Design 3rd clinical study AMT-011-02



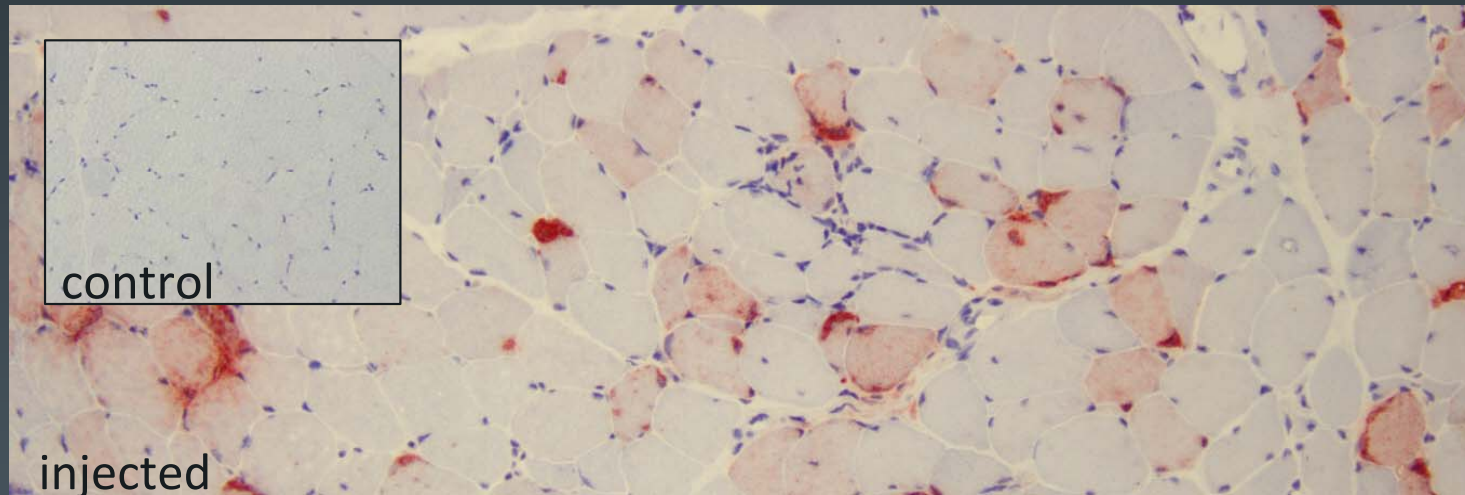
- 5 subjects, 1×10^{12} gc/kg AAV1-LPL^{S447X} + CsA/MMF (oral) + prednisolone (IV)
- 1 month run-in + 1 year follow-up

(ECOGENE-21 Clinical Trial Center, Chicoutimi, Quebec, Canada)

Long term safety data of Glybera

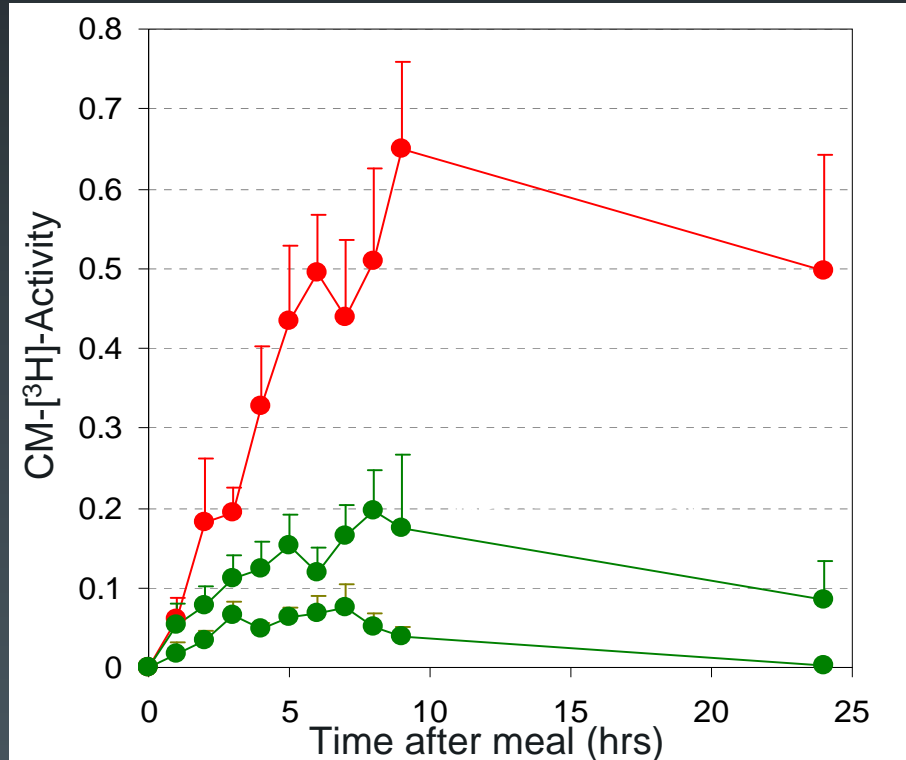
- Follow-up period is up to 5 years post-dosing (for recommended Glybera dose)
- **No major safety concerns:**
 - Most frequently reported AEs were local reactions (bruising, myalgia, muscle pain), headache, and nausea
 - All of these were transient and of mild to moderate intensity
 - No pattern of significant changes in laboratory parameters (other than plasma lipids)
 - No clinical evidence of long-term effects on muscle function or loss of LPL expression in muscle
- **Well tolerated treatment**

LPL vector DNA and expression



LPL^{S447X} expression in muscle, 1 year post administration

Effect on postprandial CM metabolism



- disturbed CM metabolism in untreated LPL deficient patients; majority circulates as large/buoyant CM
- greatly improved CM metabolism after treatment (1×10^{12} gc/kg AAV1-LPL^{S447X}); minority circulates as large/buoyant CM
- persistence up to 1 year after treatment

Immune response – a hurdle for re-administration?

What type of immune response was observed during clinical development of Glybera

Some of the lessons we learned for the future

Systemic immune response

	T cells				antibodies			
	AAV		LPL		AAV		LPL	
	B	A	B	A	B	A	B	A
01-001	-	1/9	-	-	+	++	-	-
01-002	-	5/8	-	-	+	++	-	-
01-003	-	1/8	-	-	-	++	-	-
02-001	-	2/8	-	-	+	++	-	-
02-002	-	1/8	-	-	-	++	-	-

Local Immune response

Gene expression despite systemic immune response triggered a detailed analysis of the local immune response

- **Granzyme B and Fas ligand – both are markers for cytolytic activity**
 - > expression not observed in LPL expressing muscle tissue
- **Fox P3 and CD24 – both are markers for T-regulatory cells**
 - > expression observed in LPL expressing muscle tissue

Those studies suggest a type of local tolerance

Summary Glybera

- **No safety concern**
 - > no CPK increase
- **Systemic immune response against AAV capsid proteins but not LPL**
- **Local immune response is indicating local tolerance**
- **Local long term (monitored for 1 year) expression of LPL despite local immune response**
- **Systemic activity of LPL**
- **Decreased risk for pancreatitis (followed for 3-5 years)**

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