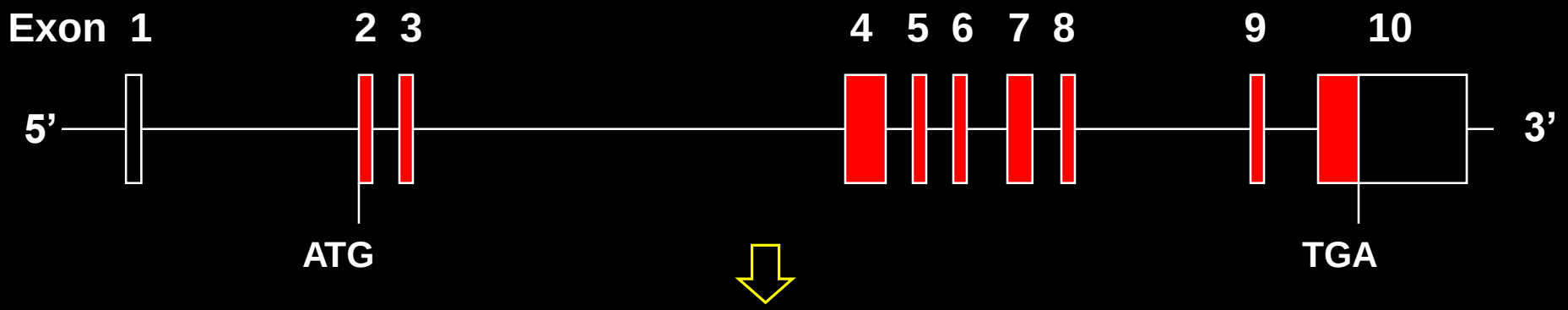
Lysosomal acid lipase deficiency

OMIM #278000

Lysosomal acid lipase

LIPA gene (10q23.2-q23.3) NG 008194

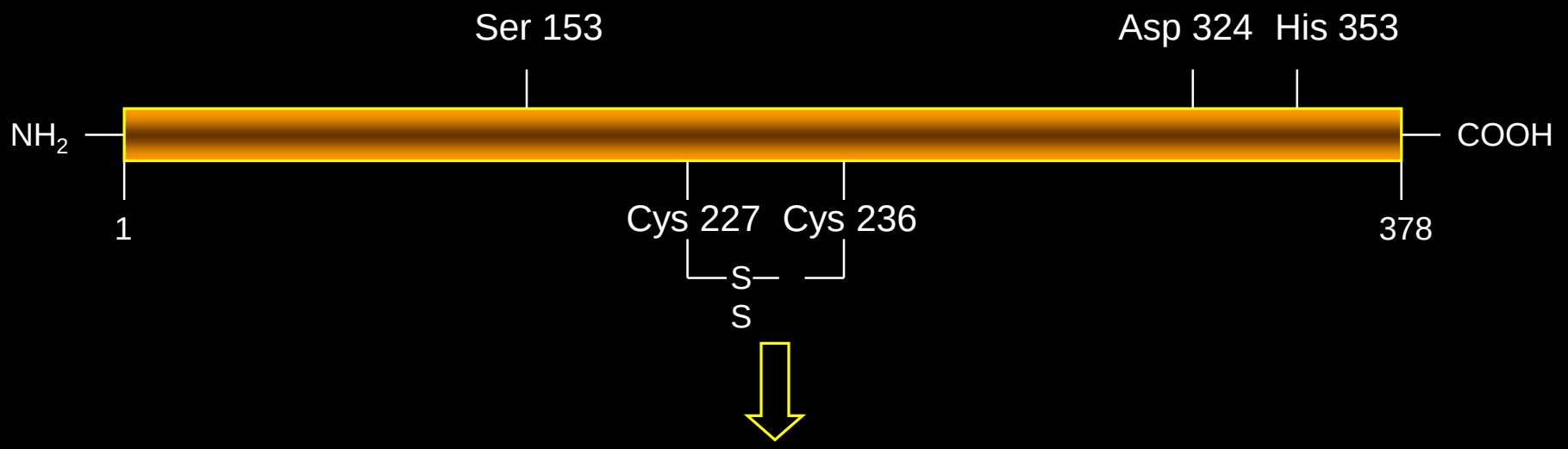


mRNA (2669 bp) NM 001127605

LAL 399 aa NP 000226 (SP 21 aa; mature 378 aa)

Virtually synthesized by all cells, including hepatocytes, fibroblasts and macrophages

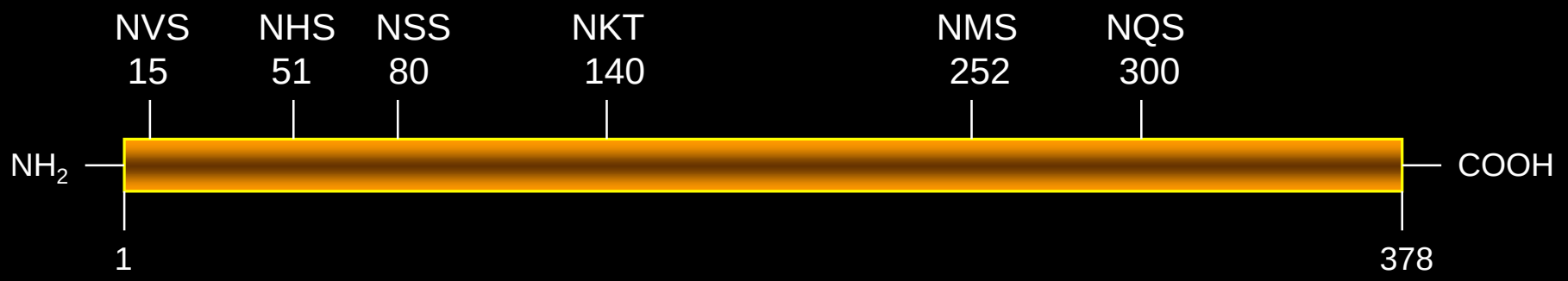
LAL - catalytic triad



Crucial role in determining LAL substrate specificity (**CE >> TG**): selective access of cholesteryl esters to the catalytic active site

Lohse P et al. J Lipid Res 1997; 38: 1896-905

LAL - glycosilation (42 → 54 kDa)



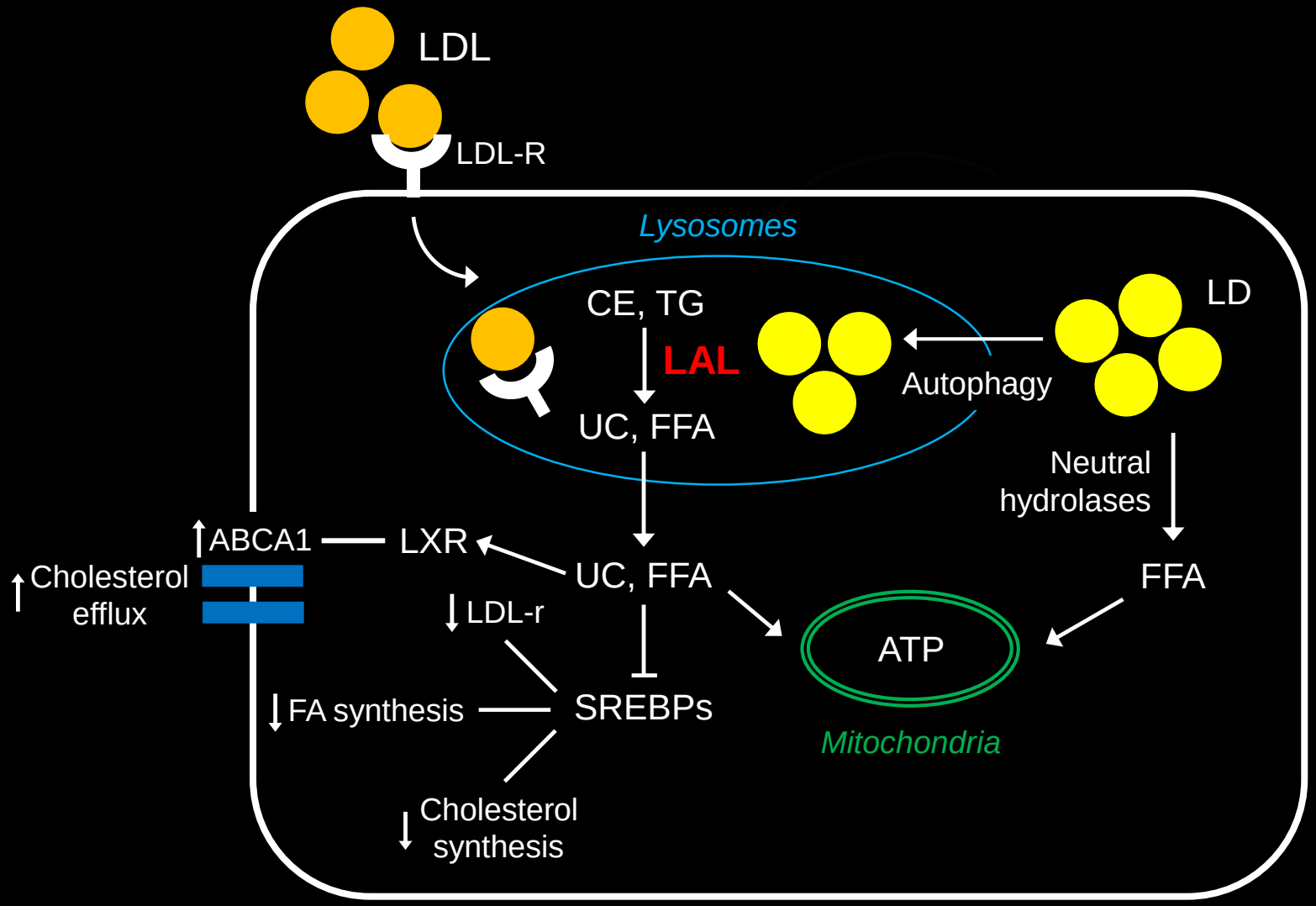
N-glycosilation sites at positions 15, 80 and 252 are conserved among members of the lipase family

N-glycosilation sites are not essential for LAL activity, but may be involved in the maintenance or stabilization of a fully active conformation (global folding and/or sulfide bond formation); however, glycosylation of Asn residues at position 140 and 252 seems to essential for the biosynthesis of active enzyme.

Zschenker O et al. J Biochem 2005; 137: 387-94

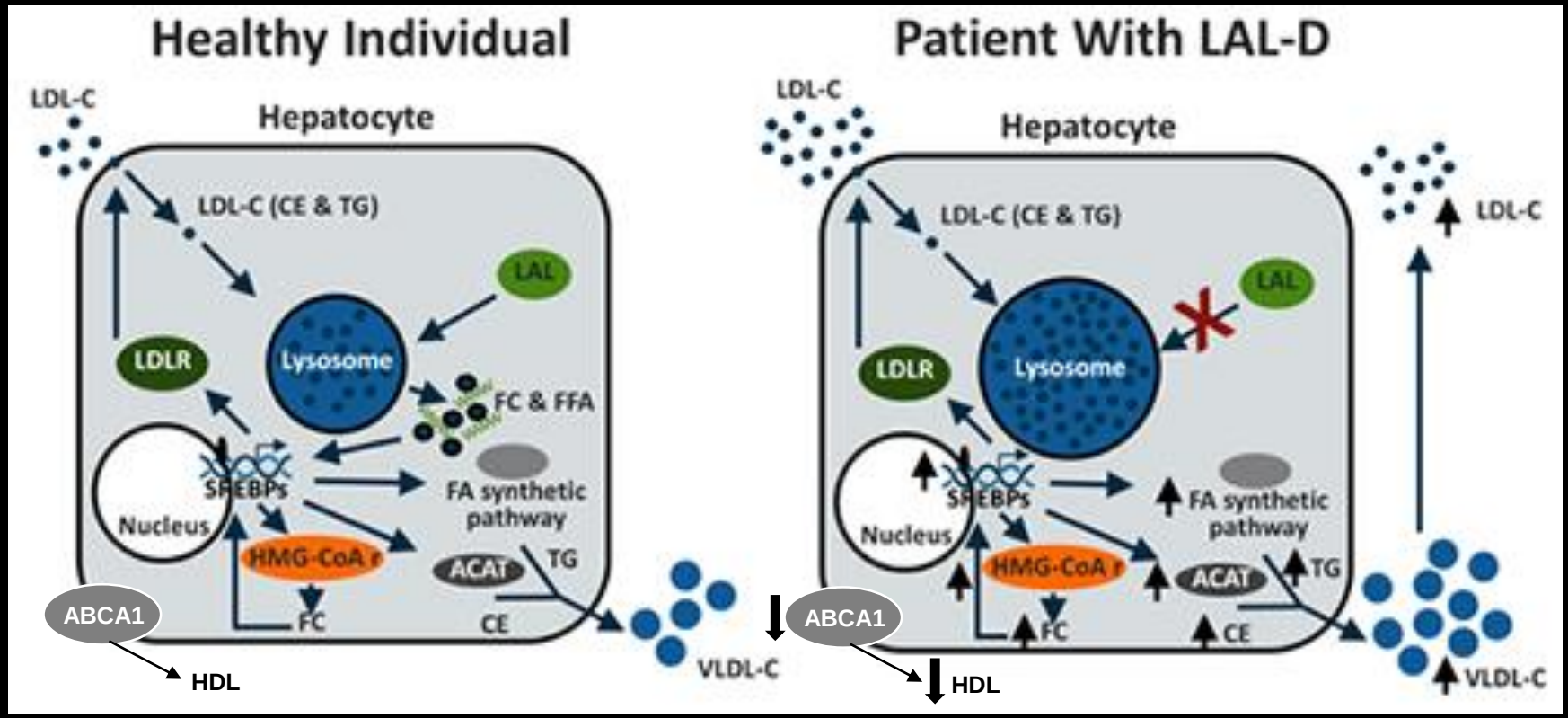
Lysosomal acid lipase - function

LAL catalyzes the hydrolysis of cholesteryl esters and triglycerides that have been internalized via receptor-mediated endocytosis of lipoproteins



Gomaraschi M et al. Trends Pharm Sci 2018;in press

Lysosomal acid lipase - Deficiency



http://www.medscape.org/846314_2

Liver lipid concentrations in LAL-D

(mg/g wet tissue)

	LAL-D	Controls
CE	95-187	1-1.4
TG	33-64	10-19

Higher proportion of cholesterol linoleate (C18:2) (41%), lower proportion of cholesterol oleate (C18:1) (33%) and normal proportion of cholesterol palmitate (C16:0) (14%) in comparison to controls.

Lysosomal acid lipase deficiency

OMIM #278000
Wolman Disease
Cholesteryl Ester Storage Disease

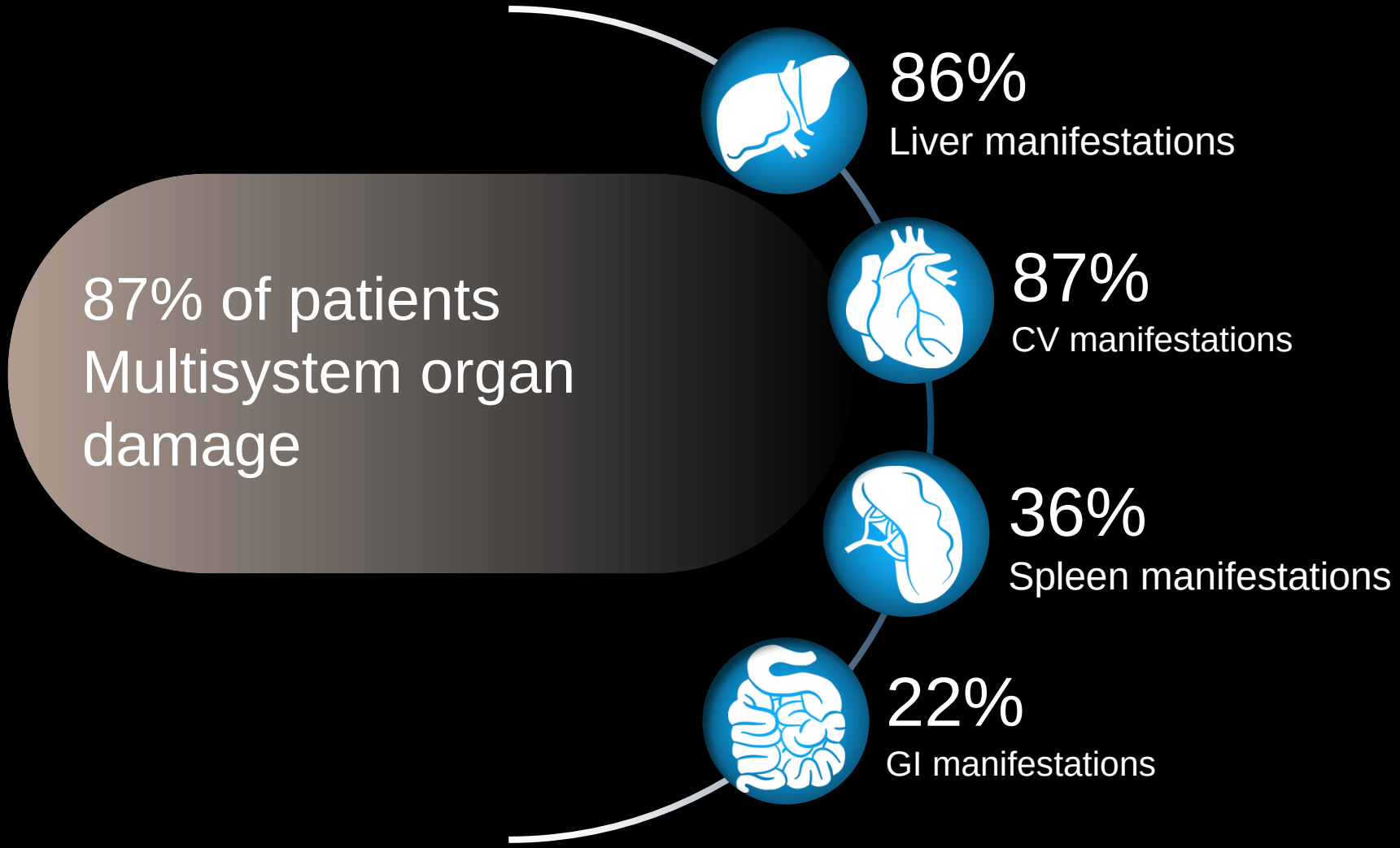
LAL-D: Wolman disease

- First characterized in 1961 by Israeli Dr. M. Wolman
- Autosomal recessive
- Prevalence: very rare
- Mutations which totally abolish LAL activity
- Fulminant neonatal-onset disorder characterized by massive storage of CE and TG predominantly in the liver, spleen, adrenals, bone marrow, lymph nodes and macrophages
- Massive hepatosplenomegaly, adrenal calcification, vomiting, diarrhea, anemia, thrombocytopenia, failure to thrive, respiratory failure, cachexia
- Death in the first 6-8 months of life

LAL-D: Cholesteryl Ester Storage Disease

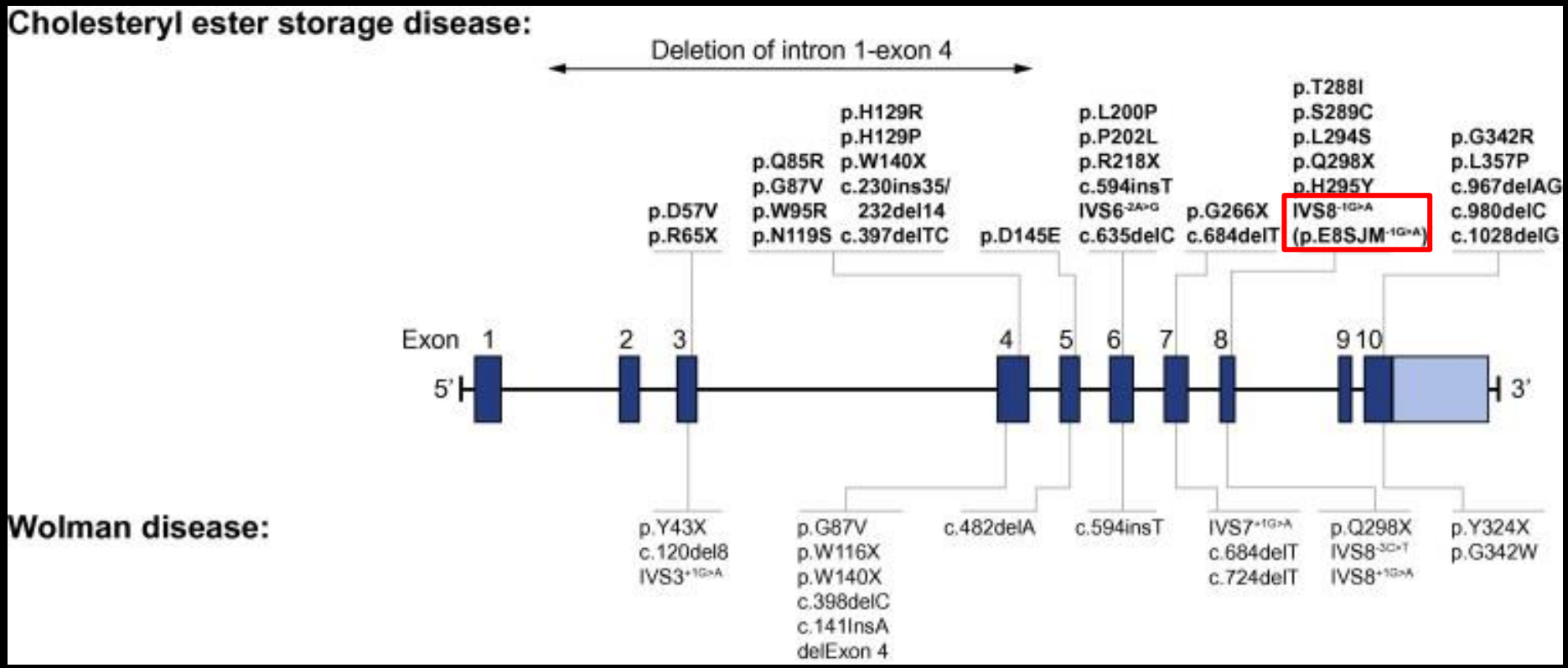
- First published mention by Fredrickson in 1963 in reference to a child with marked hyperlipidemia, whose enlarged liver was found to contain 18% of its wet weight as cholesteryl ester
- Autosomal recessive
- Prevalence in Caucasians 1/50.000-78.000; very rare in Asians and African
- Residual LAL activity (in fibroblasts 12-24% of controls)
- Present in childhood but frequently unrecognized until adulthood (broad spectrum of severity)
- Compatible with survival into middle age and beyond (liver failure or premature CVD)
- Massive accumulation of CE and to a lesser extent TG predominantly in hepatocytes, adrenal gland, intestine and monocyte-macrophages throughout the body
- Hepatomegaly and splenomegaly, dyslipidemia

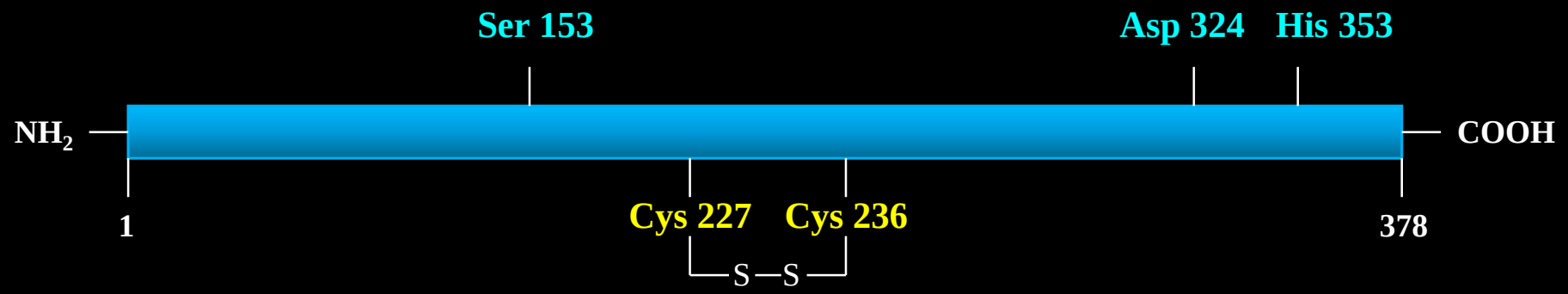
LAL-D: progressive multisystem organ damage



Bernstein DL, et al. *J Hepatol*. 2013;58(6):1230-1243.

LIPA gene mutations

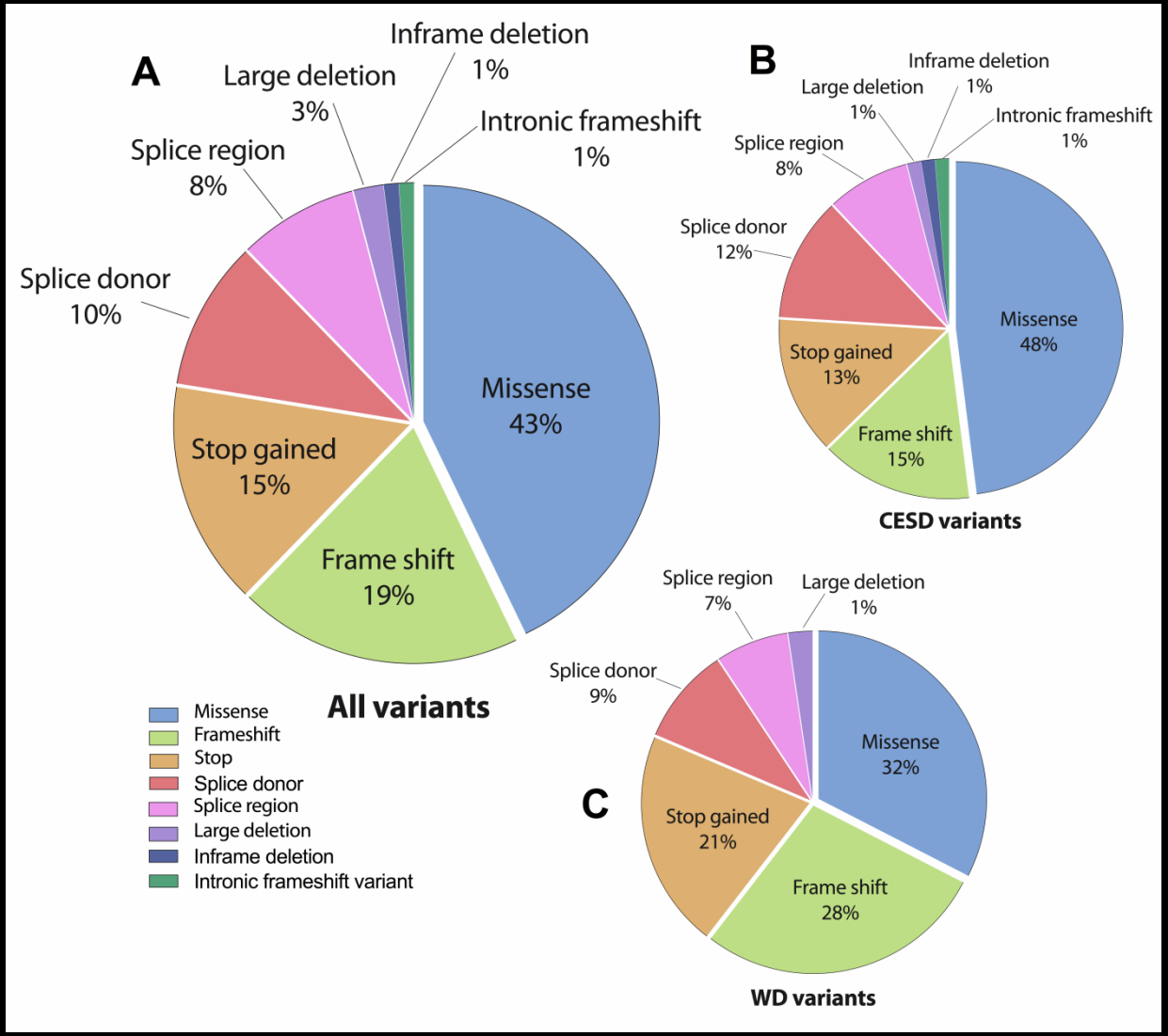




LIPA gene mutations

120 disease-causing *LIPA* variants associated with LAL-D

Prevalence of LAL-D: 1 per 177,452

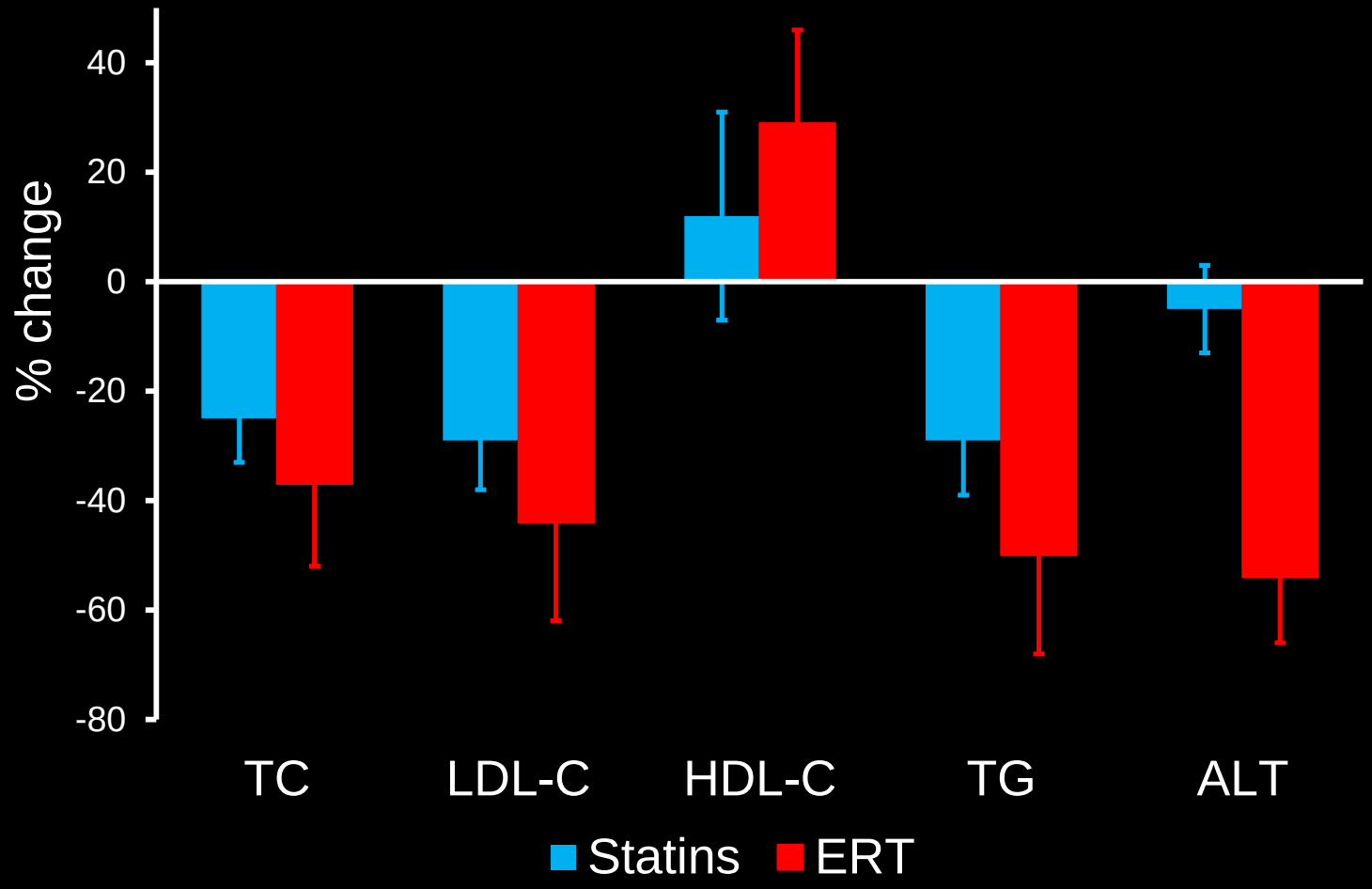


Carter et al. J Hepatology 2018; in press

Treatment of LAL-D

- Lipid-lowering agents
- Liver transplantation
- Enzyme replacement therapy

Lipid-lowering agents in LAL-D: statins



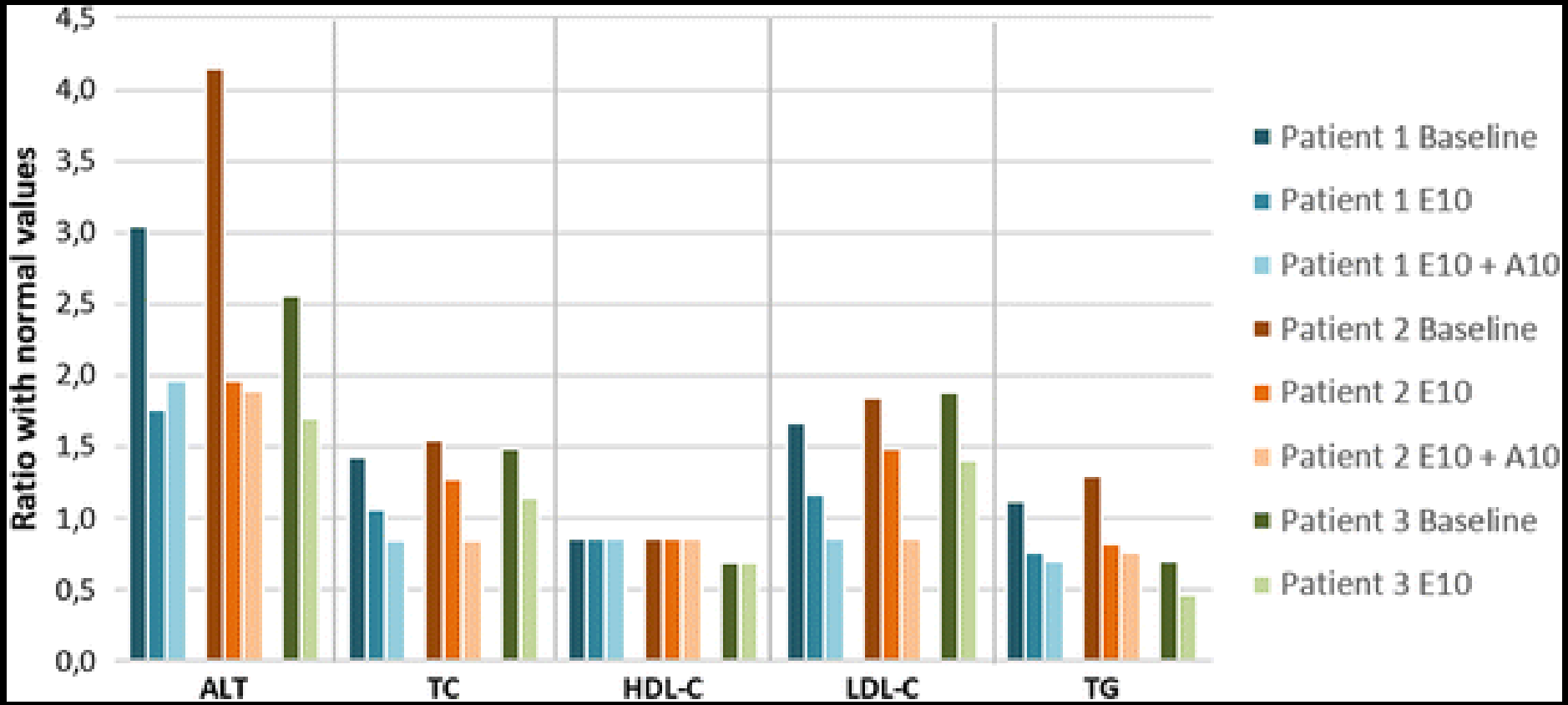
Pisciotta L et al, Atherosclerosis 2017;265:124

Data are mean±SD, n=6 for statins and n=4 for ERT

Lipid-lowering agents in LAL-D: ezetimibe

Ezetimibe in CESD patients

Follow-up: 9-10 years



Di Rocco M, Orphanet J Rare Dis. 2018 Jan 27;13(1):24

ERT for Lysosomal Storage Disorders

Goals of treatment

- The levels of storage within cells or organs of the individual should be reduced
- The natural history of the disease should be altered favorably
- Effective treatment should leave minimal residual disease
- The treatment should be safe
- The treatment should be affordable

ERT for Lysosomal Storage Disorders

Not all storage diseases are suitable targets for ERT

- ✓Irreversible damages early in life
- ✓CNS involvement
- ✓Enzyme features: stability, delivery to target cells, antigenicity
- ✓Biotechnological issues
- ✓Financial issues

ERT for Lysosomal Storage Disorders

Reduction of lysosomal substrate load in patient's cells and tissues
Improvement of clinical outcomes

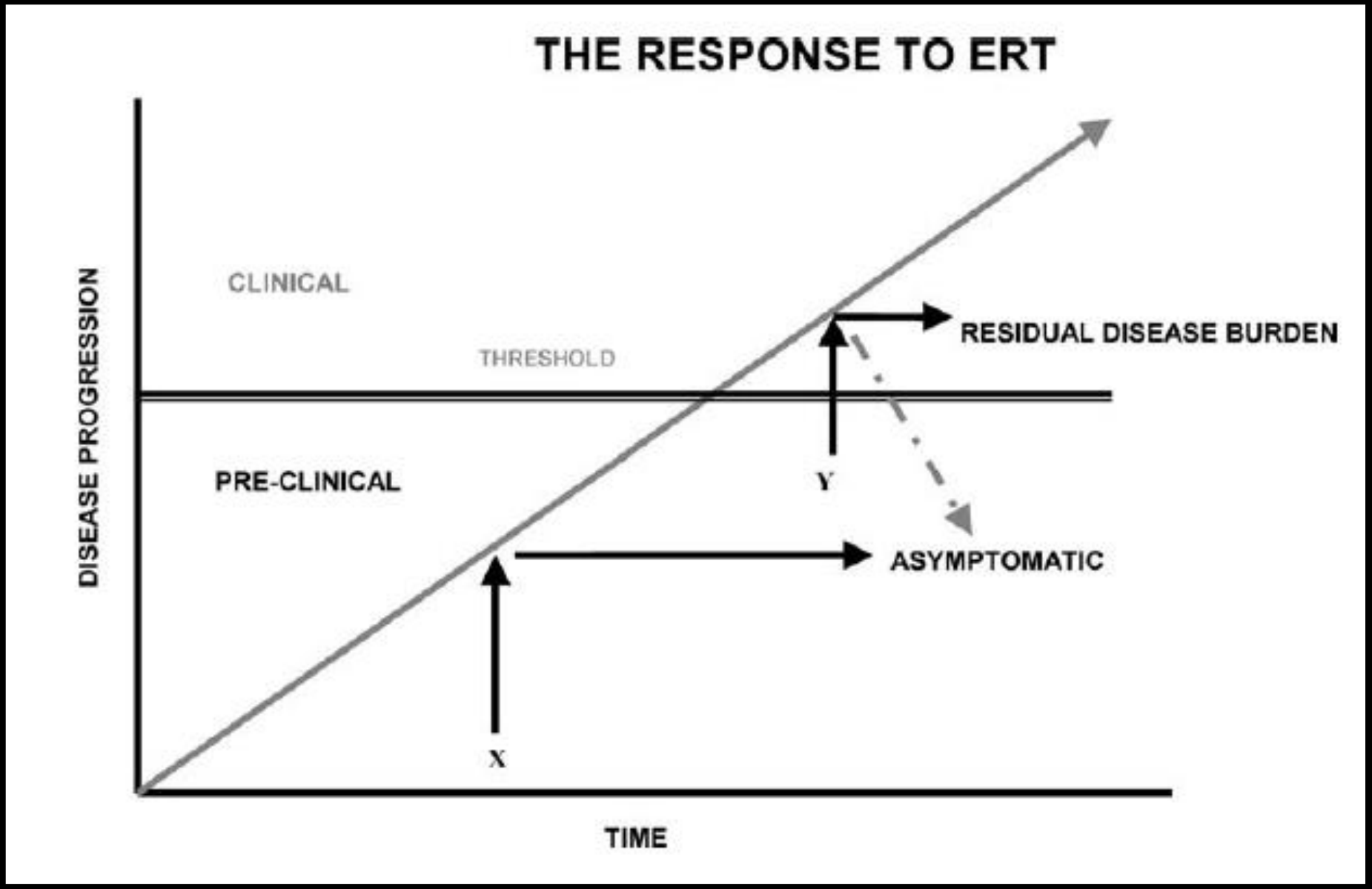
<u>Limits</u>

✓Inability of the r-enzymes to cross the blood-brain barrier (the CNS manifestations do not respond well to ERT)

✓Delivery of infused enzyme to different disease-relevant cells may be insufficient

✓Infused enzymes may be immunogenic (limiting efficacy)

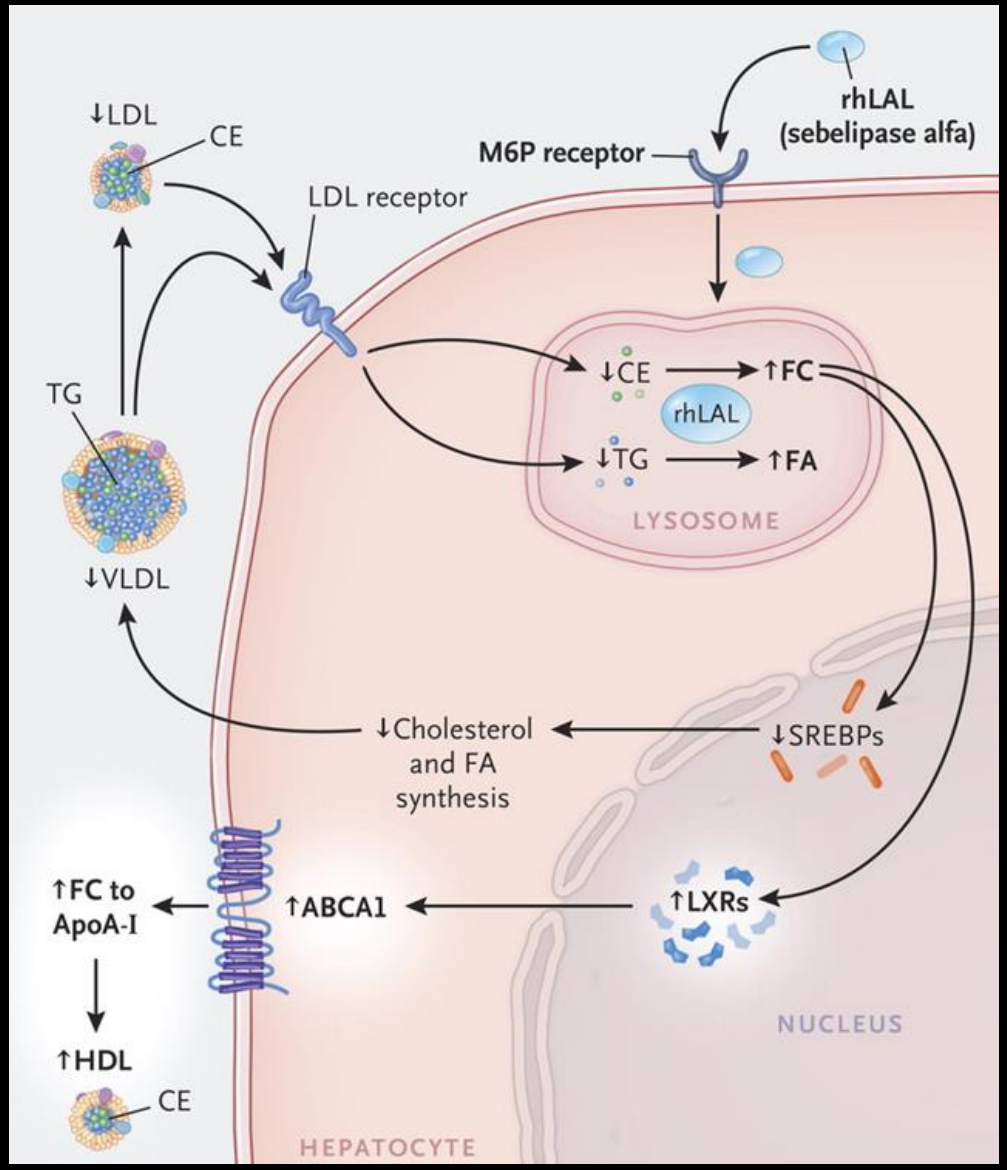
ENZYME REPLACEMENT THERAPY in LSD



ERT for LAL-D: sebelipase alfa

- *Sebelipase alfa* is recombinant human LAL for the enzyme replacement therapy of LAL Deficiency
- Received orphan drug designations in both the US and EU in 2010 for *sebelipase alfa* for LAL Deficiency
- Approved by FDA and EMA in late 2015
- *Sebelipase alfa* is a glycoprotein with six potential N-linked glycosylation sites (N-acetylglucosamine and mannose terminated N-linked structures); N-glycans containing terminal mannose-6-phosphate moieties which allow for targeting to a wide variety of cells expressing the mannose-6-phosphate receptor

ERT for LAL-D: sebelipase alfa



ARISE Phase III trial of *sebelipase alfa* for CESD

Acid Lipase **R**eplacement **I**nvestigating **S**afety and **E**fficacy **(ARISE)**

A Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Sebelipase Alfa in Patients with LAL Deficiency

Endpoints	**Primary:** Normalization of ALT **Secondary:** Decrease in cholesterol, normalization of AST, decrease in triglycerides, increase in HDL-c, decrease in liver fat content, improvement in hepatic histology, decrease in liver volume
Eligibility	**Inclusion:** ≥ 4 years males/females, deficiency of LAL enzyme activity, ALT ≥ 1.5x ULN **Exclusion:** Severe hepatic dysfunction, previous hematopoietic or liver transplant procedure
Duration	20-week double-blind treatment period and an open-label extension period of up to 130 weeks
Sebelipase Dose	Bi-weekly infusions of 1.0 mg/kg
Patient No.	n = 66

The new engl and jour nal *of* medicine

Original Article

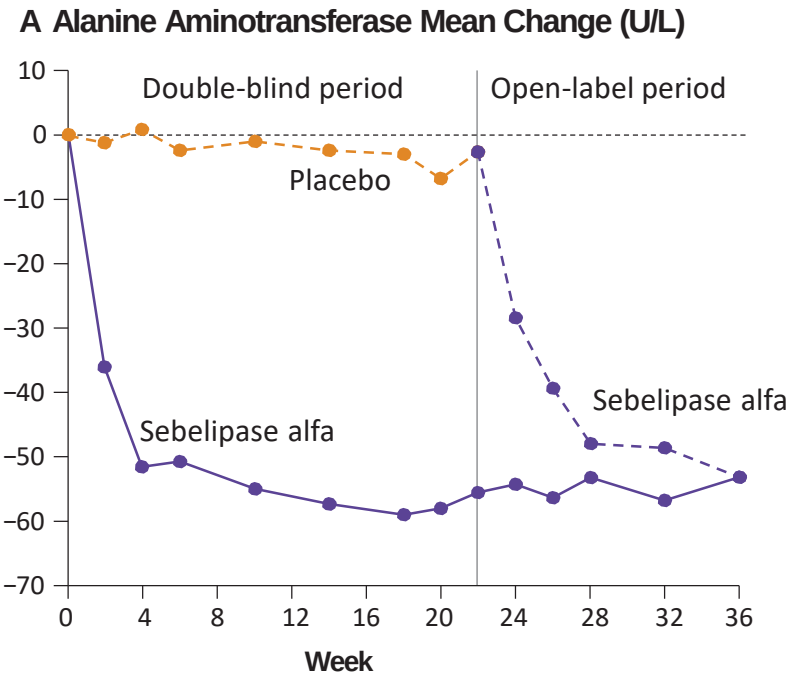
A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency

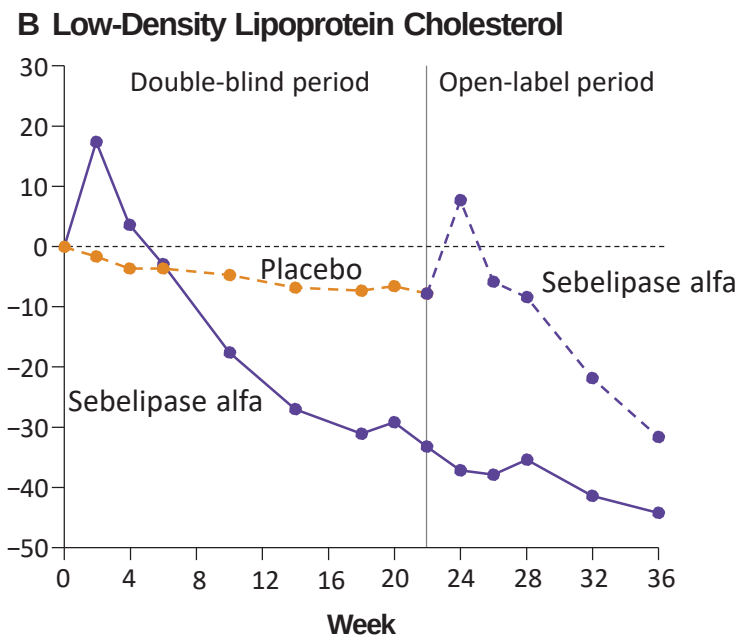
B.K. Burton, M. Balwani, F. Feillet, I. Barić, T.A. Burrow, C. Camarena Grande, M. Coker, A. Consuelo-Sánchez, P. Deegan, M. Di Rocco, G.M. Enns, R. Erbe, F. Ezgu, C. Ficicioglu, K.N. Furuya, J. Kane, C. Laukaitis, E. Mengel, E.G. Neilan, S. Nightingale, H. Peters, M. Scarpa, K.O. Schwab, V. Smolka, V. Valayannopoulos, M. Wood, Z. Goodman, Y. Yang, S. Eckert, S. Rojas-Caro, and A.G. Quinn

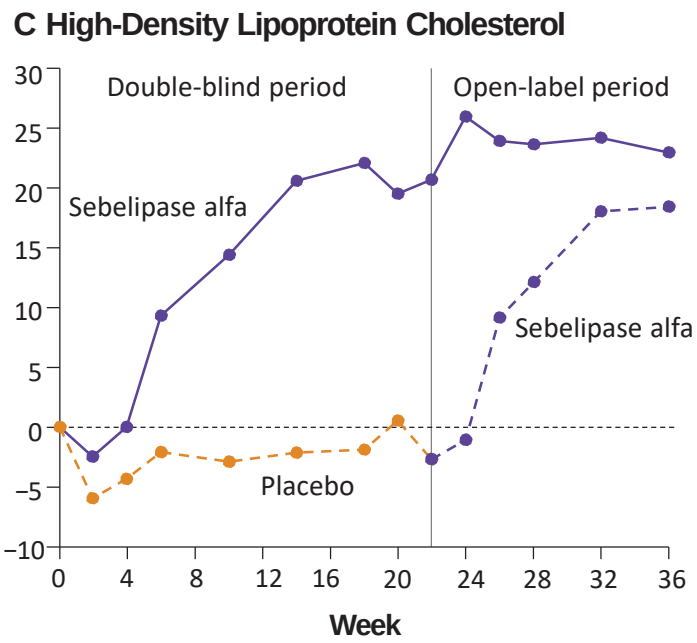
n engl j med 373;11 nejm.org September 10, 2015

Table 2. Primary and Secondary Efficacy Assessments.*

End Point	No. of Patients	Sebelipase Alfa	Placebo	P Value
Primary end point: normalization of alanine aminotransferase level — no./total no. (%)	66	11/36 (31)	2/30 (7)	0.03
Secondary end points				
Change from baseline in LDL cholesterol level — percentage points	66	−28.4±22.3	−6.2±13.0	<0.001
Change from baseline in non–HDL cholesterol level — percentage points	66	−28.0±18.6	−6.9±10.9	<0.001
Normalization of aspartate aminotransferase level — no./total no. (%)	65†	15/36 (42)	1/29 (3)	<0.001
Change from baseline in triglyceride level — percentage points	66	−25.5±29.4	−11.1±28.8	0.04
Change from baseline in HDL cholesterol level — percentage points	66	19.6±16.8	−0.3±12.4	<0.001
Change from baseline in hepatic fat content — percentage points‡	57§	−32.0±26.8	−4.2±15.6	<0.001
Reduction in steatosis — no./total no. (%)¶	26‖	10/16 (62)	4/10 (40)	0.42
Change from baseline in liver volume — percentage points	60**	−10.3±10.5	−2.7±10.1	—††


A Alanine Aminotransferase Mean Change (U/L)
Double-blind period
Open-label period
Placebo
Sebelipase alfa
Sebelipase alfa
10
0
−10
−20
−30
−40
−50
−60
−70
0
4
8
12
16
20
24
28
32
36
Week

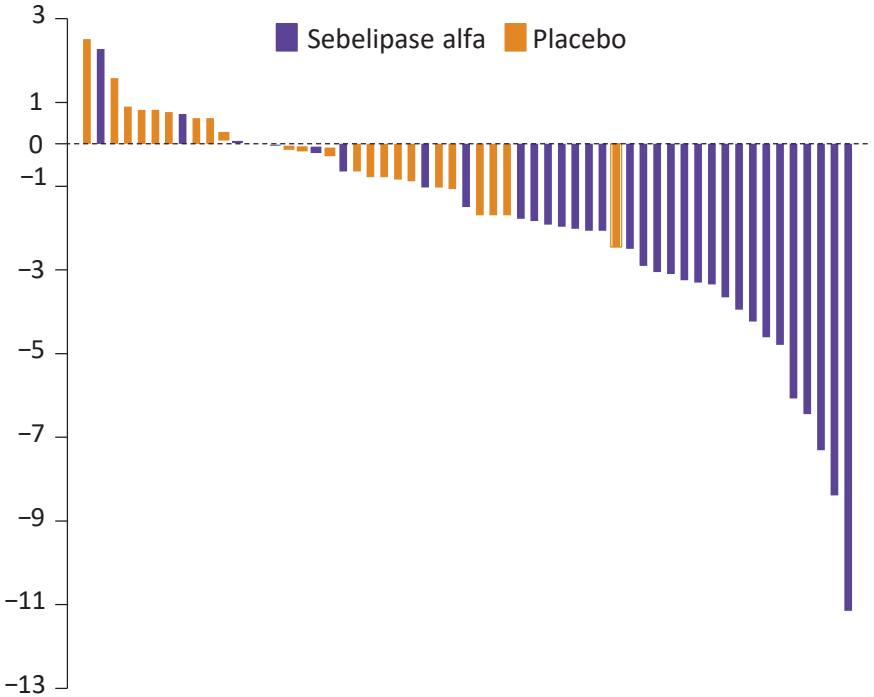

B Low-Density Lipoprotein Cholesterol
Mean Change (%)
Double-blind period
Open-label period
Placebo
Sebelipase alfa
Sebelipase alfa
30
20
10
0
−10
−20
−30
−40
−50
0
4
8
12
16
20
24
28
32
36
Week


C High-Density Lipoprotein Cholesterol
Double-blind period
Open-label period
Sebelipase alfa
Sebelipase alfa
Placebo
30
25
20
15
10
5
0
−5
−10
0
4
8
12
16
20
24
28
32
36
Week

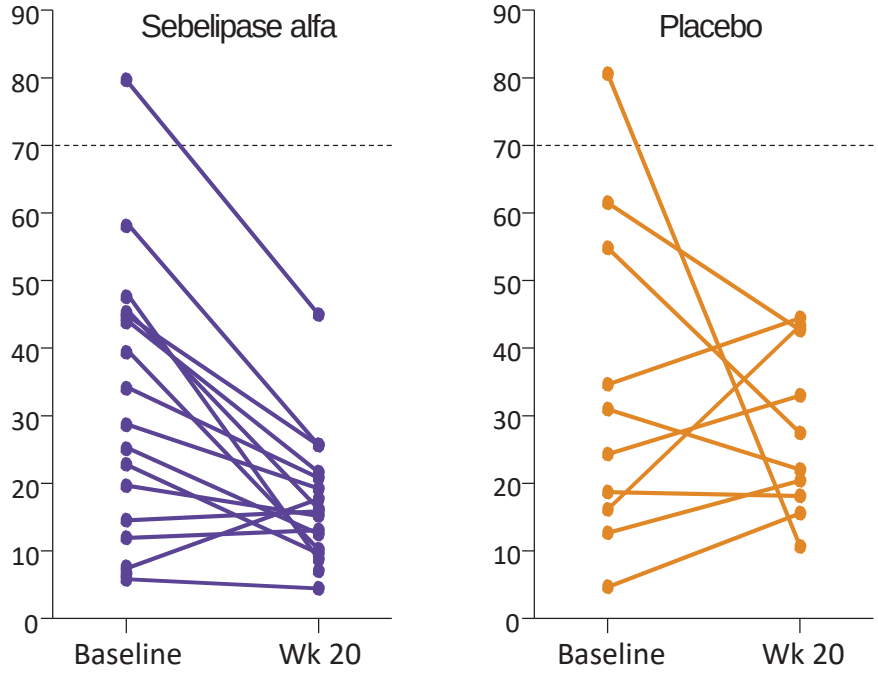
Acid Lipase Replacement Investigating Safety and Efficacy **(ARISE)**

A Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Sebelipase Alfa in Patients with LAL Deficiency

A Change in Hepatic Fat Content from Baseline to Wk 20



B Change in Steatosis from Baseline to Wk 20



ERT for Wolman Disease

Jones et al. Orphanet Journal of Rare Diseases (2017) 12:25
DOI 10.1186/s13023-017-0587-3

Orphanet Journal of Rare Diseases

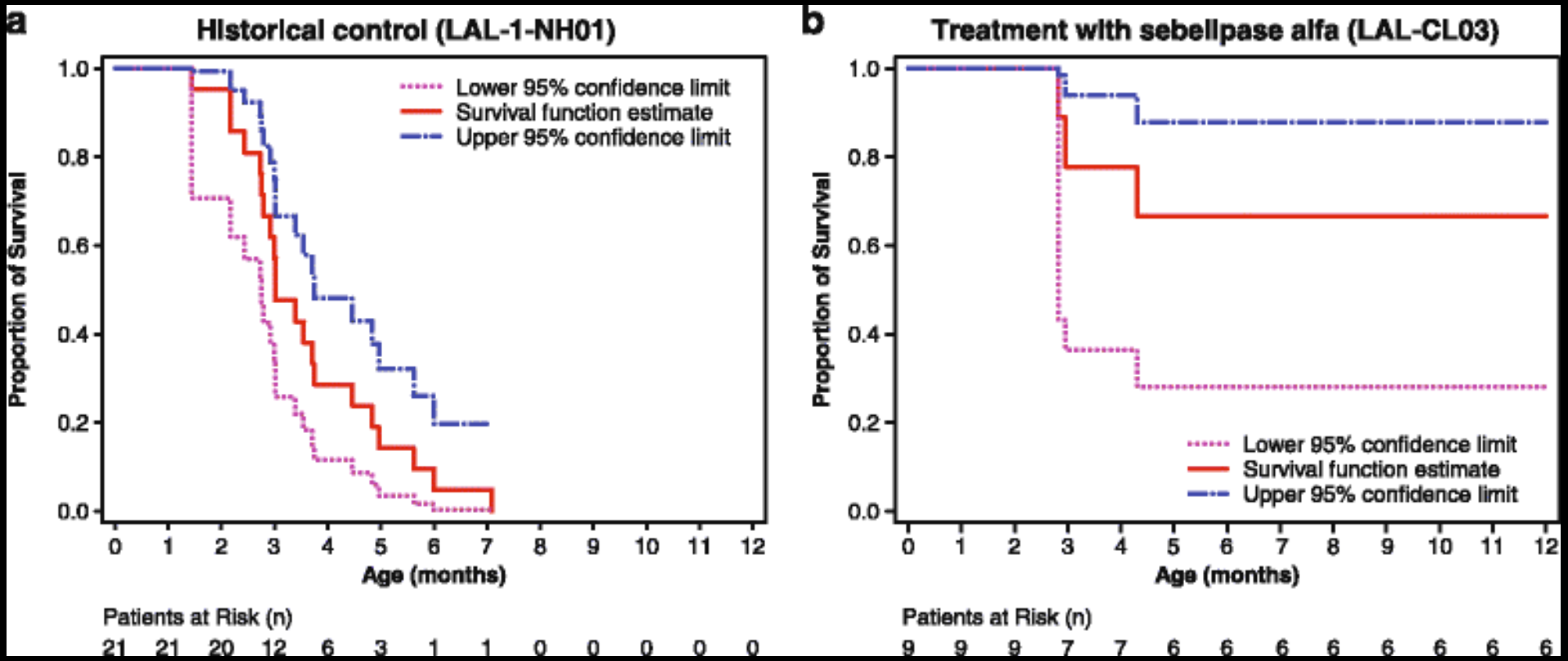
RESEARCH Open Access

Survival in infants treated with sebelipase Alfa for lysosomal acid lipase deficiency: an open-label, multicenter, dose-escalation study

Simon A. Jones[1*], Sandra Rojas-Caro[2], Anthony G. Quinn[2,11], Mark Friedman[3], Sachin Marulkar[3], Fatih Ezgu[4], Osama Zaki[5], J. Jay Gargus[6], Joanne Hughes[7], Dominique Plantaz[8], Roshni Vara[9], Stephen Eckert[2], Jean-Baptiste Arnoux[10], Anais Brassier[10], Kim-Hanh Le Quan Sang[10] and Vassili Valayannopoulos[10,12]

Nine patients; median age at baseline was 3.0 months (range 1.1-5.8 months)

ERT for Wolman Disease



Orphanet J Rare Dis. 2017