Pompe Disease and Its Beyond Therapeutics of Pompe disease: yesterday, today and tomorrow

Dr SHENG Bun

Consultant

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14 Oct 2023

Disclosure

I am the regional representative of the Sanofi international Pompe registry advisory board and the local PI of rare disease registry program sponsored by Sanofi

I am a member of the Amicus APAC regional advisory board on Fabry disease

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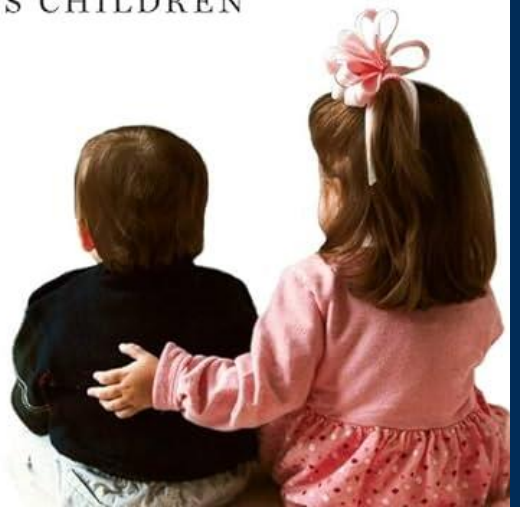
—*New York Post*

THE BOOK THAT INSPIRED THE MOVIE
EXTRAORDINARY MEASURES
STARRING
BRENDAN FRASER
and
HARRISON FORD

The Cure

HOW A FATHER RAISED $100 MILLION AND BUCKED THE MEDI[illegible] ESTABLISHMENT IN A QUEST TO SAVE HIS CHILDREN

Geeta Anand



"An inspirational story about business, medical science, and one father's refusal to give up hope."
—*Boston Globe*

"[A] heart-wrenching account of a father's extraordinary efforts to save his children."
—*Booklist*

[illegible] Pulitzer Prize-winning investigative repo[illegible]r and feature writer for the *Wall Street Journal*. Formerly a political reporter for the *Boston Globe*, she now specializes in health care, education, and environmental challenges in India. She lives in Mumbai with her husband and two daughters.

www.thecurebook.com

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Author photograph by Harry Zemike

The rivet[illegible]
John and Ai[illegible]
to find a cure[illegible]
that insp[illegible]
Extraord[illegible]

With three bea[illegible] and financia[illegible] Crowley were on top[illegible] youngest children, fi[illegible] five-month-old Patric[illegible] disease and given on[illegible] accept a death sent[illegible] consultant job and in[illegible] technology start-up[illegible] find a cure. Battling[illegible] interest accusations,[illegible] and Aileen would be[illegible] valiantly fought, and[illegible] tionary new [illegible]tme[illegible] hope[illegible] Meg[illegible]n Patri[illegible] [illegible]milli[illegible] affl[illegible]ed by[illegible] [illegible]the[illegible] inspi[illegible]r *Extraordinary Meas*[illegible] and Harrison Ford, [illegible] story of cutting-edge[illegible] daring, and one fami[illegible]

To learn mo[illegible] family and the[illegible] www.cr[illegible]

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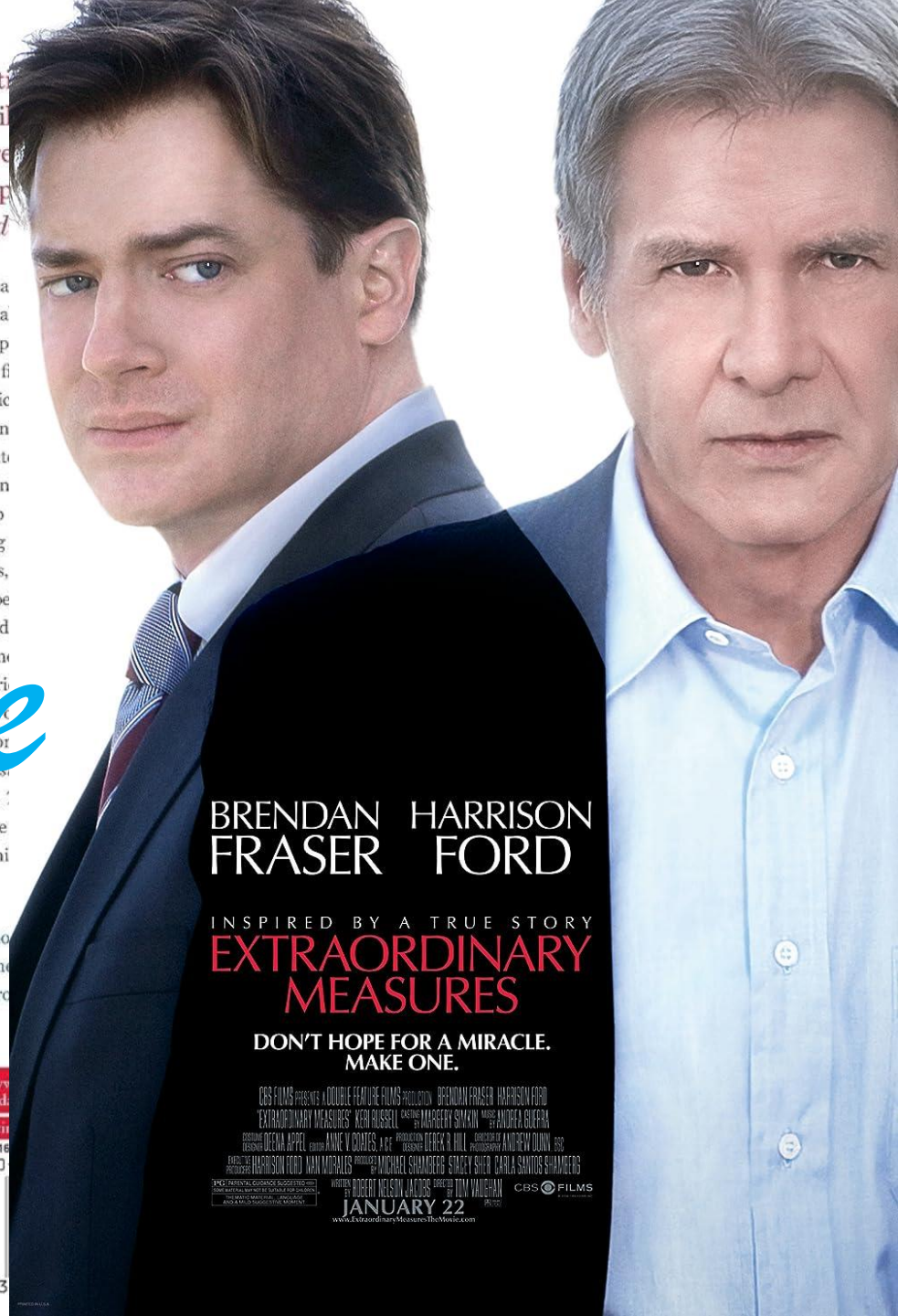
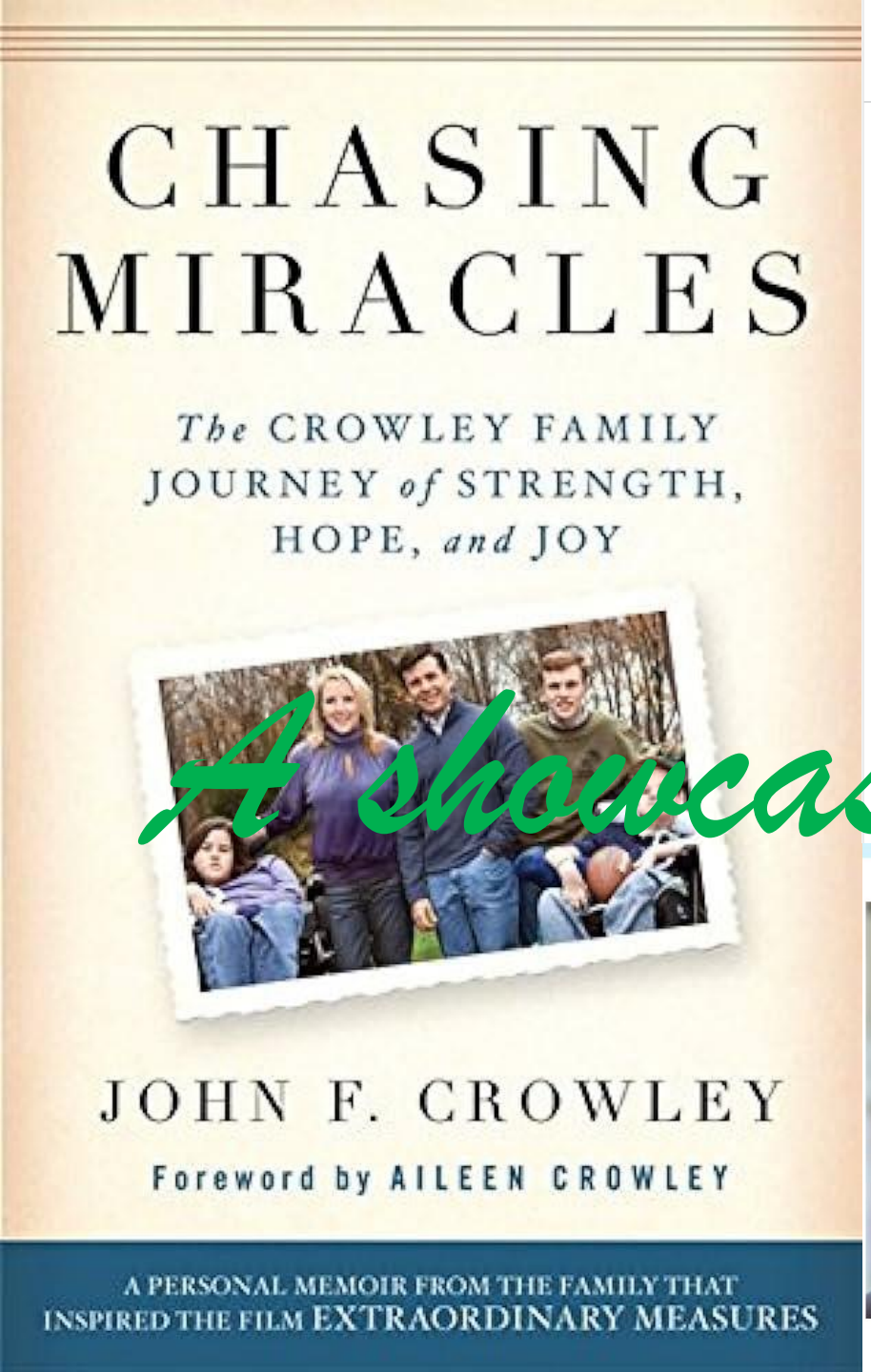


A fairy tale



Harvard Business Publishing Education

Case

MAIN CASE

Father's Love: Novazyme Pharmaceuticals, Inc.

By: Richard Bohmer, Bradley Campbell

John Crowley, CEO of Novazyme Pharmaceuticals, a start-up biotechnology firm developing an orphan drug to treat a rare lysosomal storage disorder from which his children suffer, must choose between a...

Brought to you by: HARVARD BUSINESS SCHOOL

Length: 24 page(s) **Discipline:** Operations Management

Publication Date: Oct 2[illegible] **Product #:** [illegible]-PDF-ENG

A showcase in business study

Mr Crowley resigned from his senior vice president position in Genzyme in 2002 to avoid conflict of interest in getting his children into ERT clinical trials, he later joined Amicus and is now the executive chairman of the company

FIGUUR J.C Pompe (1901-1945). Pompe specialiseerde zich te Amsterdam als patholoog. Bij een meisje van 7 maanden dat was overleden aan hypertrofie van het hart ontdekte hij een sterke stapeling van glycogeen, niet alleen in het hart maar ook in lever, nieren en skeletspieren. Thans is de ziekte van Pompe bekend als glycogeenstapelingsziekte type II. Oorzaak berust op deficiëntie van α-glucosidase. Bij partiële deficiëntie debuteert de ziekte op latere leeftijd, met spierzwakte. Pompe nam in de oorlog deel aan het verzet en werd kort voor de bevrijding terechtgesteld. Foto van onbekende datum.

A national hero

Dr J. C. Pompe, a Dutch pathologist, first described in 1932 in his article *Over idiopathische hypertrophie van het hart* a 7 month girl died with severe muscle weakness and hypertrophic cardiomyopathy, the critical observation from autopsy was the glycogen accumulations in tissue throughout the body. He called this disease *Cardiomegalia Glycogenica* in his thesis finished in 1936.

During WWII when Netherland was conquered by Germany, Dr Pompe joined the Dutch Resistance and use his laboratory to shelter the tele transmitters, he was arrested and later executed on 15 April 1945 by Nazi army

A B

CARDIOMEGALIA GLYCOGENICA

ACADEMISCH PROEFSCHRIFT TER VERKRIJGING VAN DEN GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE UNIVERSITEIT VAN AMSTERDAM, OP GEZAG VAN DEN RECTOR-MAGNIFICUS, DR. W. P. C. ZEEMAN, HOOGLEERAAR IN DE FACULTEIT DER GENEESKUNDE, IN HET OPENBAAR TE VERDEDIGEN IN DE AULA DER UNIVERSITEIT, OP VRIJDAG 15 MEI 1936, DES NAMIDDAGS TE 4½ UUR,

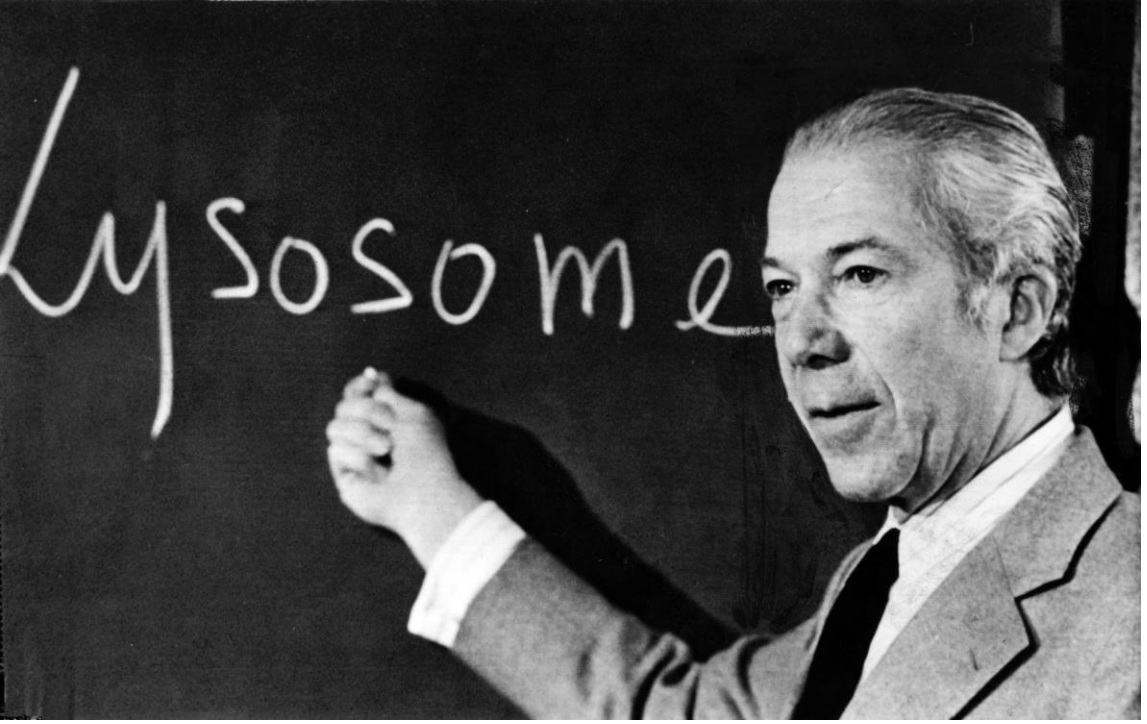
DOOR

JOANNES CASSIANUS POMPE

GEBOREN TE UTRECHT

http://pompestory.blogspot.com/2009/04/joannes-cassianus-pompe-1901-1945.html

Arch Neurol 2000;57:134-135



In 1955, Prof Christian de Duve and his team found that there was some intracellular particles with digestive properties while investigating insulin on liver cells, de Duve named these particles lysozomes. This is an important discovery to realise that our cells have internal compartments (organelles) with different functions. Prof de Duve was awarded the Nobel Prize for his discoveries in 1974.

Biochem. J. (1963) **86**, 11

α-Glucosidase Deficiency in Generalized Glycogen-Storage Disease (Pompe's Disease)

By H. G. HERS
Laboratory of Physiological Chemistry, University of Louvain, Belgium

(*Received* 16 *July* 1962)

Prof Henri-Gery Hers, a co-worker of de Duve, did not further the research in lysosomes, but established his own research team to continue his interest in carbohydrates. In testing an enzyme he thought for GSD3, he found the enzyme level was normal in GSD3 but generalized deficient in Pompe disease samples. He also found that the enzyme worked best under acidic medium. With this clue he went on to prove that the enzyme was located in lysosome which has acidic environment, this enzyme was responsible to decompose glycogen inside lysosome, and without the enzyme glycogen accumulates as they were isolated from the normal enzymes for glycogen metabolism in the rest of the cell. This was the discovery of acid α-Glucosidase in 1963.

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PROGRESS IN GASTROENTEROLOGY

INBORN LYSOSOMAL DISEASES

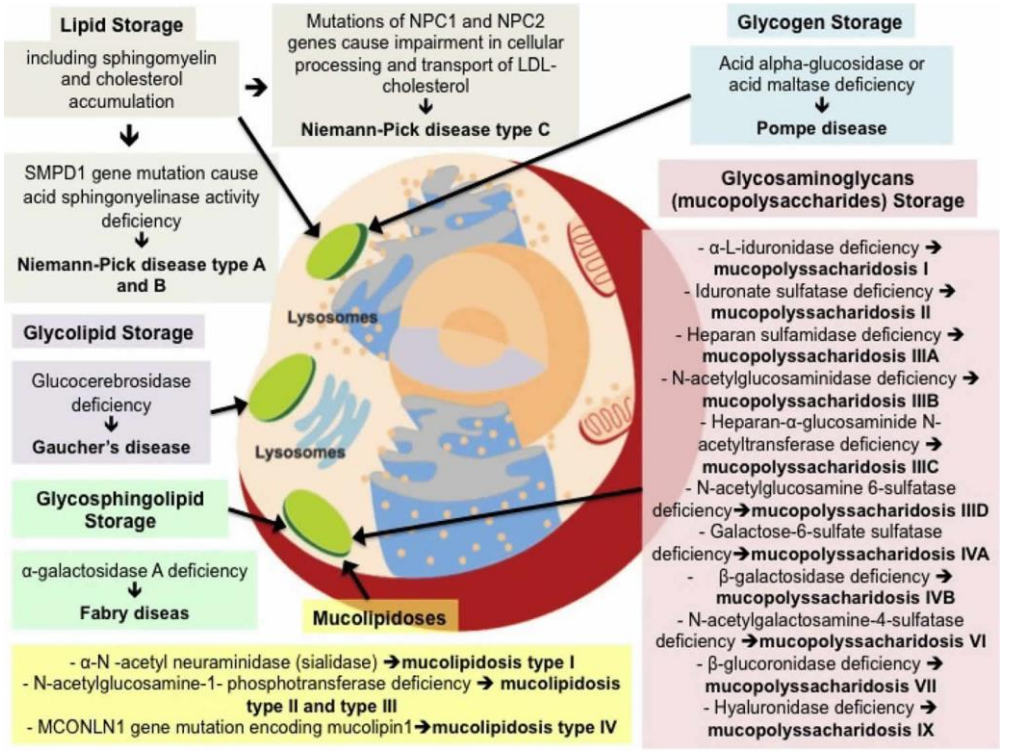
H. G. HERS, M.D.

Laboratory of Physiological Chemistry, University of Louvain, Louvain, Belgium

The recent discovery that type II glycogenosis is due to the defect of an α-1,4-glucosidase[1] normally present in lysosomes[2] has rapidly been followed by the demonstration that, in the same disease, glycogen accumulates within vacuoles which are presumably derived from the lysosomal system.[3] This congenital disorder has been called a "lysosomal disease,"[4] and the possibility that other analogous situations may exist in human pathology has been suggested.[1, 4]

by their behavior in a number of centrifugal systems. They have been isolated in a relatively pure form and identified with the so called "dense bodies" that are encountered in the liver in the vicinity of the bile canaliculi.

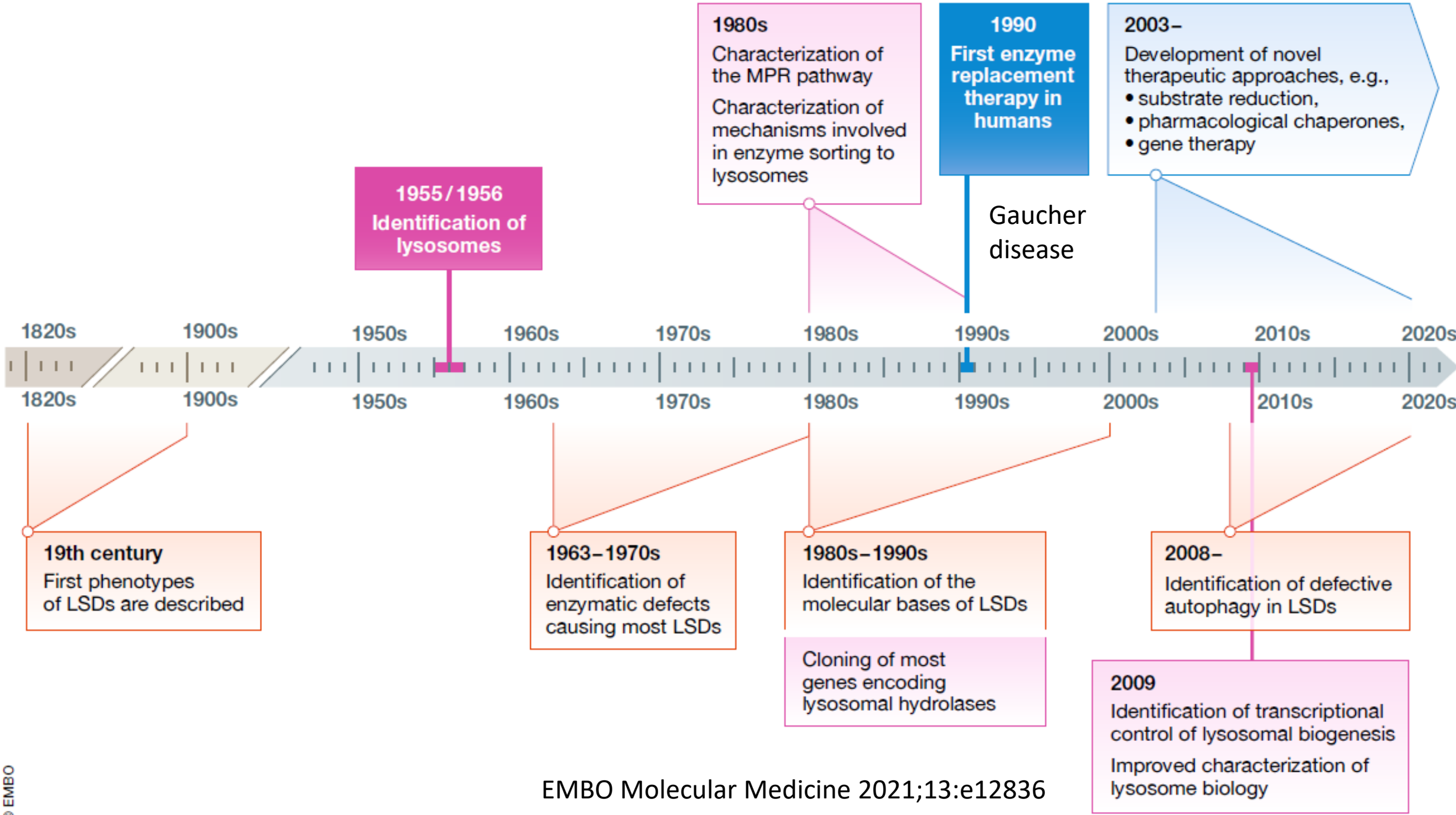
Although the basic work of the Louvain group has mostly been done on rat liver lysosomes, there is little doubt that similar particles exist in most cell types throughout the animal kingdom. However, the lysosomal enzymes show individual



There are > 70 LSDs identified with a collective birth incidence of 1:5,000

Hers then described the concept lysosomal storage disease based on the discovery of lysosomal enzyme acid α-Glucosidase deficiency in Pompe disease, Pompe disease is the first LSD being recognized.

Lysosomal storage disease types, list, causes, symptoms & treatment (healthjade.net)



EMBO Molecular Medicine 2021;13:e12836

Enzyme replacement therapy is particularly appealing in LSD since there is a natural mechanism for enzyme to enter the cell and concentrate in lysosome, this was where the story of Crowley family began

Intravenous Administration of Phosphorylated Acid α-Glucosidase Leads to Uptake of Enzyme in Heart and Skeletal Muscle of Mice

A. T. Van der Ploeg,*‡ M. A. Kroos,* R. Willemsen,* N. H. C. Brons,§ and A. J. J. Reuser*
**Department of Cell Biology and Genetics, Erasmus University, Rotterdam, The Netherlands; ‡Sophia Children's Hospital, Rotterdam; and §Department of Clinical Immunology, University of Groningen, Groningen, The Netherlands*

The initial attempts of enzyme replacement therapy in Pompe disease has been disappointing, the first success came with Erasmus University group Prof Arnold Reuser and his then PhD student Van der Ploeg, they make use of the recently found enzyme trafficking into lysosome though a receptor for sugar mannose-6-phosphate, and inject the phosphorylated enzyme produced from bovine testes into mice, and demonstrated successful uptake of the exogenous enzyme in muscle and heart. Their result was published in 1991.

Clin Invest. 1991;87(2):513-518

Research letters

Recombinant human α-glucosidase from rabbit milk in Pompe patients

Hanneke Van den Hout, Arnold J J Reuser, Arnold G Vulto, M Christa B Loonen, Adri Oomme-Dijkhuis, Ans T Van der Ploeg

Pompe's disease is a fatal muscular disorder caused by lysosomal α-glucosidase deficiency. In an open-label study, four babies with characteristic cardiomyopathy were treated with recombinant human α-glucosidase (rhGAA) from rabbit milk at starting doses of 15 mg/kg or 20 mg/kg, and later 40 mg/kg. The enzyme was generally well tolerated. Activity of α-glucosidase normalised in muscle. Tissue morphology and motor and cardiac function improved. The left-ventricular-mass index decreased significantly. We recommend early treatment. Long-term effects are being studied.

Infantile Pompe's disease is a metabolic myopathy with a rapidly progressive course, and is commonly fatal in the first year of life. The disease presents in the first few months after birth with respiratory and feeding difficulties and hypotonia, and hypertrophic cardiomyopathy is characteristic. Major developmental milestones, such as rolling over, sitting, and standing are not achieved.[1] The late-onset form presents as a slowly progressive proximal myopathy. The disease is caused by lysosomal α-glucosidase deficiency and concomitant storage of lysosomal glycogen.[2]

In the development of enzyme therapy for Pompe's disease, production of rhGAA was tested in genetically modified Chinese hamster ovary cells[3,4] and milk of transgenic animals.[5] The two sources seemed suitable, but the high yield in milk and efficacy of the enzyme seen in mice led to large-scale production of rhGAA in transgenic rabbits being chosen.[6] A phase I study of healthy volunteers showed no major side-effects. We report on the first 36 weeks of treatment in patients, during which safety and efficacy data were gathered.

We did a single-centre, open-label pilot study, approved by the institutional review board. Four patients were included with typical symptoms of infantile Pompe's disease (table) and virtual absence of α-glucosidase. We obtained written informed consent from the parents.

RhGAA was administered intravenously once weekly, at starting doses of 20 mg/kg in babies lighter than 6·5 kg (patients 1 and 2) and 15 mg/kg in babies weighing 6·5 kg or more (patients 3 and 4). Doses were increased to 40 mg/kg for all patients. These doses are generally well tolerated without premedication. Adverse events reported were fever, malaise, erythematous rash, sweating, hypoxia, flushing, and tachycardia. The role of IgE-type antibodies in these responses was not evident, but IgG-type antibodies may be relevant. Adverse events were transient and manageable by adaptation of the infusion rate.

α-glucosidase activity in muscle on the starting doses showed a ten-fold increase at 12 weeks of treatment (from 0·15–0·37 nmol/mg per h to 2·1–4·9 nmol/mg per h), but was still lower than normal (8–40 nmol/mg per h). 12 weeks later, with 40 mg/kg RhGAA, α-glucosidase activity was in the normal range for all four patients. On histological assessment, lysosomal glycogen storage was lowered and tissue morphology improved. The total tissue glycogen content did not change significantly.

Skeletal muscle function and strength improved in all patients, most significantly for patient 1, who had the least severe disease at start of treatment. This infant reached milestones that are beyond realistic expectations for a patient with the disease. At 12 months, he could crawl in a four-point position and stand with the support of one arm. Patient 3, who had more severe disease, learned to touch her feet in play. Her improvement has continued, despite producing no endogenous acid α-glucosidase (cross-reactive-immunological-material [CRIM] negative). Patients 2 and 4 also gained strength, most notably in the arms. At start of treatment these two patients (ages 7 months and 8 months) had end-stage disease and muscle function was almost lost. Patient 2 became dependent on a respirator during the inclusion period, as did patient 4, after 10 weeks of treatment, during a bout of pneumonia. The two patients, included before age 3 months, developed normal respiration and became outpatients. All patients showed progress in mental development.

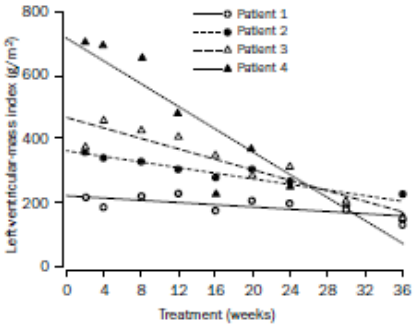
The most prominent effect was on the heart. Left-ventricular posterior-wall thickness and left-ventricular-mass index (figure) decreased in all patients from the start of treatment. Patient 4 responded best. Her left-ventricular-mass index at 36 weeks of treatment was less than 30% of baseline. Symptoms of cardiac instability disappeared in all patients, which was life-saving for patient 4. All patients passed the critical age of 1 year.

RhGAA resulted in uptake of α-glucosidase in skeletal

Patient	Onset of symptoms	Head-lag/axial hypotonia*	Cardiac hypertrophy/ECG abnormality	Oxygen need*	Age at diagnosis	Date at inclusion
1	At birth	+	+	−	1 month	3 months
2	3 months	+	+	+	4 months	7 months
3	At birth	+	+	−	14 days	2·5 months
4	3 months	+	+	+	6 months	8 months

ECG=electrocardiography. *During inclusion period.

Patients' characteristics



Linear-regression analyses of left-ventricular-mass index

r=–0·74, r=–0·93, r=–0·93, and r=–0·93 for patients 1, 2, 3, and 4, respectively; each $p<0·05$.

Lancet 2000;356:297-8

Recombinant human acid α-glucosidase enzyme therapy for infantile glycogen storage disease type II: Results of a phase I/II clinical trial

Andrea Amalfitano, DO, PhD[1], A. Resai Bengur, MD[1], Richard P. Morse, MD[1], Joseph M. Majure, MD[1], Laura E. Case, PT, MS[2], Deborah L. Veerling, PT, MS[2], Joanne Mackey, CPNP[1], Priya Kishnani, MD[1], Wendy Smith, MD[1], Alison McVie-Wylie, PhD[1], Jennifer A. Sullivan, MS[1], George E. Hoganson, MD[4], John A. Phillips III, MD[5], G. Bradley Schaefer, MD[6], Joel Charrow, MD[7], Russell E. Ware, MD, PhD[1], Edward H. Bossen, MD[3], and Yuan-Tsong Chen, MD, PhD[1]

Genetics in edicine,2001:3(2):132-8

Two methods for recombinant acid α-Glucosidase was developed, one from transgenic rabbit milk and one from Chinese hamster ovary (CHO) cell lines.

The Dutch group published a first open label study on 4 IOPD patients using ERT from transgenic rabbit milk demonstrated positive results. In the later development production from transgenic rabbit milk was discontinued since it is easier for large scale production using CHO cell lines.

Prof Yuan-Tsong Chen (陳垣崇)
Duke University

Recombinant human acid α-glucosidase

Major clinical benefits in infantile-onset Pompe disease

P.S. Kishnani, MD*; D. Corzo, MD*; M. Nicolino, MD, PhD; B. Byrne, MD, PhD; H. Mandel, MD; W.L. Hwu, MD, PhD; N. Leslie, MD; J. Levine, MD; C. Spencer, MD; M. McDonald, MD; J. Li, MD; J. Dumontier, MD; M. Halberthal, MD; Y.H. Chien, MD; R. Hopkin, MD; S. Vijayaraghavan, MD; D. Gruskin, MD, PhD; D. Bartholomew, MD; A. van der Ploeg, MD, PhD; J.P. Clancy, MD; R. Parini, MD; G. Morin, MD; M. Beck, MD, PhD; G.S. De la Gastine, MD; M. Jokic, MD; B. Thurberg, MD, PhD; S. Richards, PhD; D. Bali, PhD; M. Davison, MD; M.A. Worden, BS; Y.T. Chen, MD, PhD; and J.E. Wraith, MD

- The Duke university group then published the first comparative study on 18 IOPD patients treated with aglucosidase alfa at 20mg/kg EOW and 40mg/kg EOW
- All survived at 18m age
- ERT reduced risk of death by 99%, risk of death or invasive ventilation by 92%, and risk of death or any type of ventilation by 88%, LV mass dropped by half

LV mass

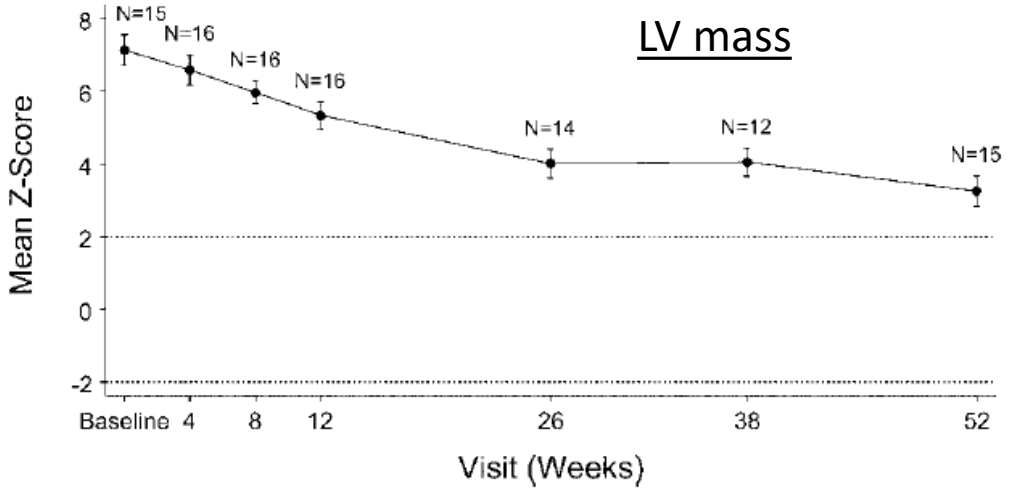
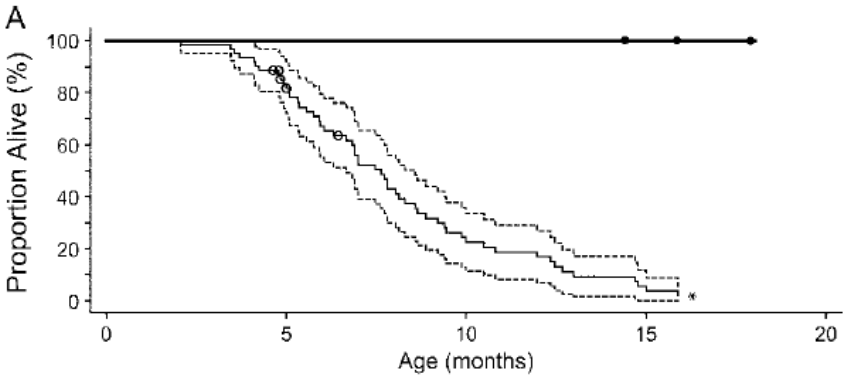


Figure 3. Mean left ventricular mass Z scores of treated patients from baseline to week 52; vertical bars represent standard error.

Survival



Neurology 2007;68(2):99–109

Alglucosidase alfa was approved by FDA & EMA in 2006 for Pompe disease

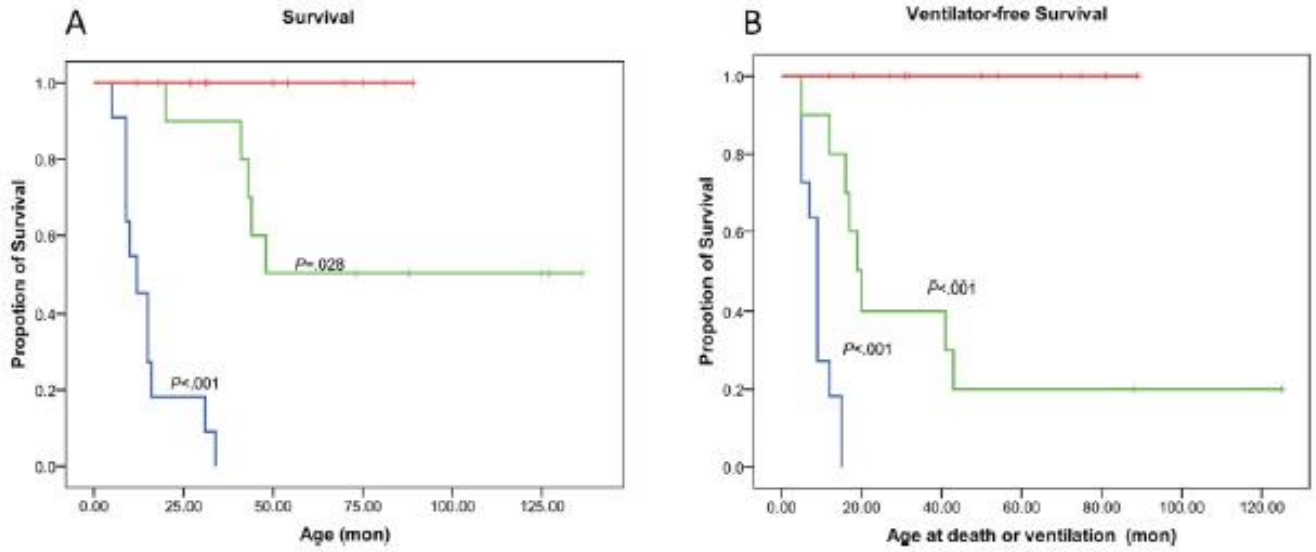
J Pediatr 2015;166:985-91

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Long-Term Prognosis of Patients with Infantile-Onset Pompe Disease Diagnosed by Newborn Screening and Treated since Birth

Yin-Hsiu Chien, MD, PhD[1,2], Ni-Chung Lee, MD, PhD[1,2], Chun-An Chen, MD[2], Fuu-Jen Tsai, MD, PhD[3], Wen-Hui Tsai, MD, PhD[4], Jeng-Yi Shieh, MD, PhD[5], Hsiang-Ju Huang, MS[6], Wei-Chung Hsu, MD, PhD[7], Tzu-Hsun Tsai, MD, PhD[8], and Wuh-Liang Hwu, MD, PhD[1,2]



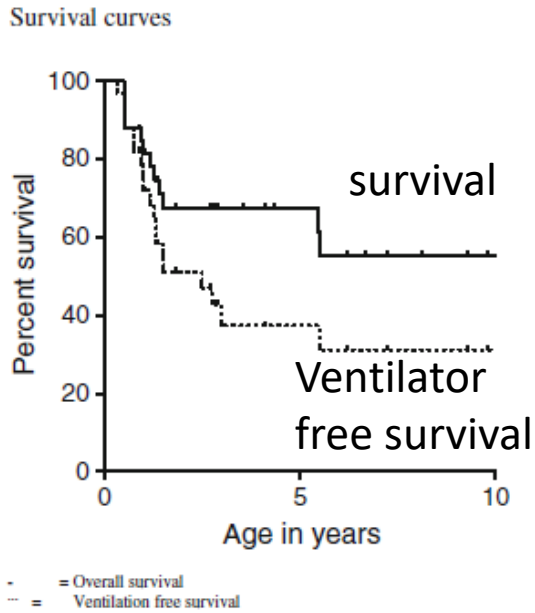


Fig. 1 Survival curves

J Inherit Metab Dis (2016) 39:261–271
DOI 10.1007/s10545-015-9898-5

ORIGINAL ARTICLE

Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy

Impact of high & sustained anti-drug antibody titre (HSAT) on disease outcome in IOPD

CRIM status

- Presence of endogenous GAA detected on Western blot-> CRIM+ve
- No detectable GAA on Western blot-> CRIM-ve

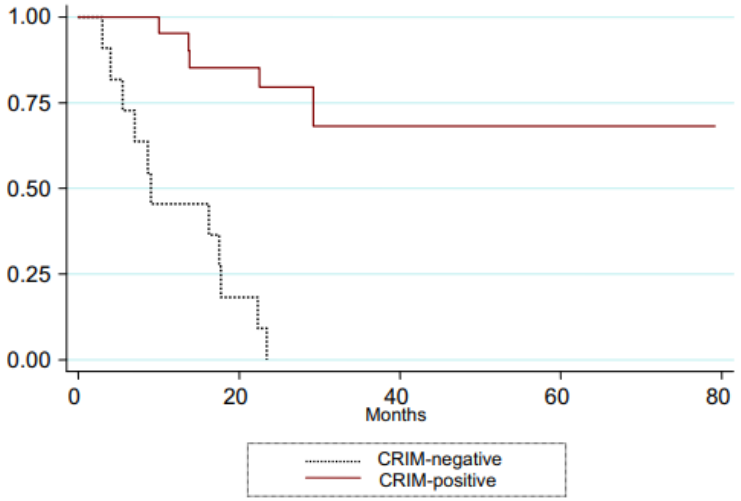
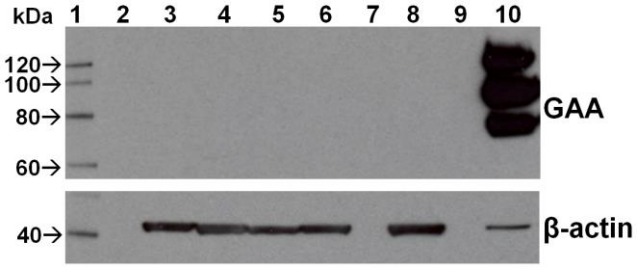


Fig. 2. Kaplan–Meier curve of ventilator-free survival of the CRIM-negative ($n = 11$) and CRIM-positive ($n = 21$) patients.

Mol Genet Metab 2010;9:26-33

With ERT, CRIM+ve patients had much better survival than CRIM-ve patients

CRIM+ve patients who developed HSAT had poor survival, similar to CRIM-ve patients



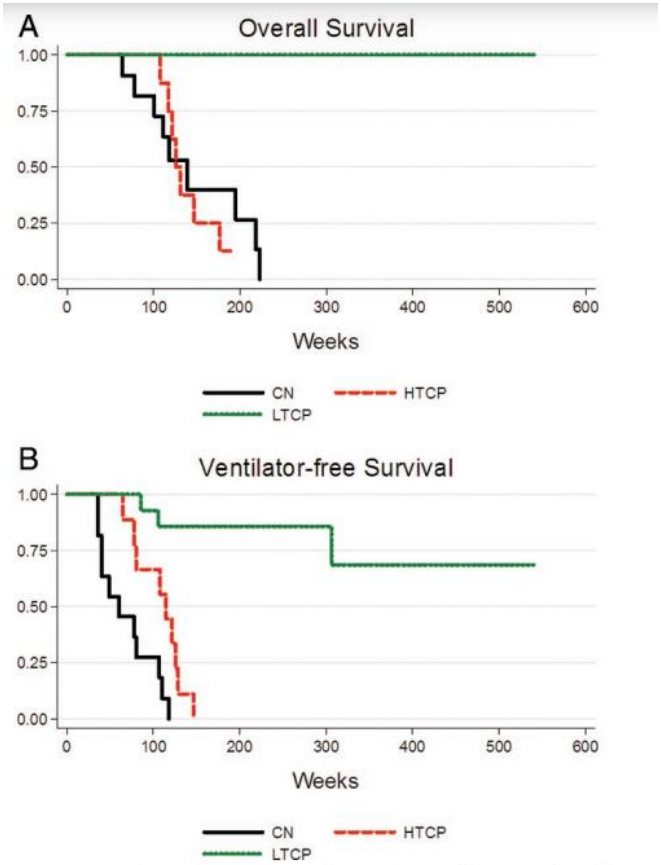


Fig. 2. Kaplan-Meier curves for (A) overall survival and (B) ventilator-free survival for CN (black), HTCP (red), and LTCP (green). CN, CRIM negative; HTCP, high-titer CRIM positive; LTCP, low-titer CRIM positive.

Genet Med 2011;13:729-736

Molecular Genetics and Metabolism Reports 23 (2020) 100591

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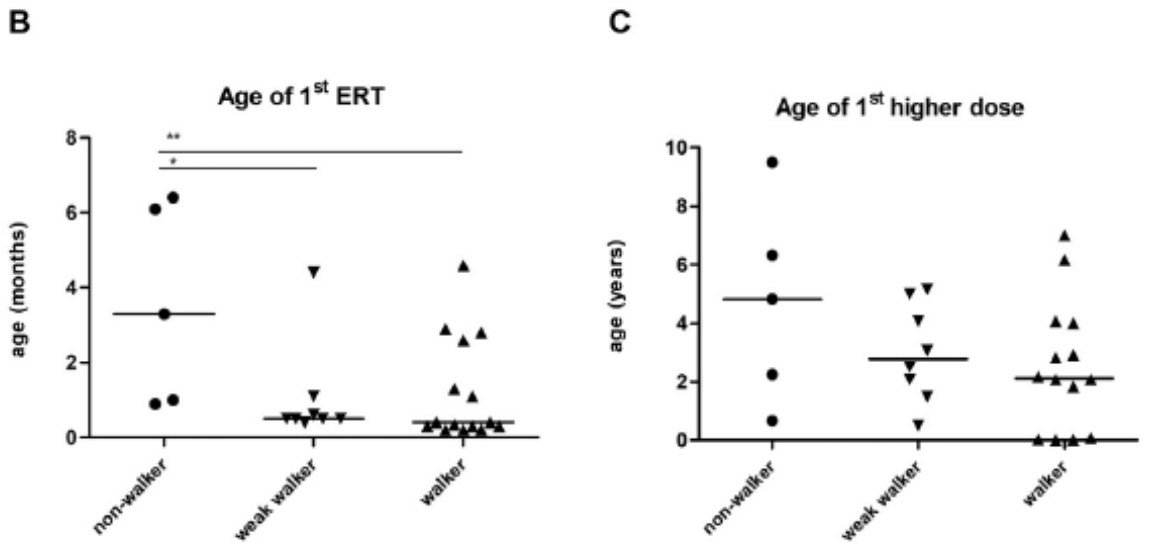
journal homepage: www.elsevier.com/locate/ymgmr

Earlier and higher dosing of alglucosidase alfa improve outcomes in patients with infantile-onset Pompe disease: Evidence from real-world experiences

Yin-Hsiu Chien[a,b], Wen-Hui Tsai[c], Chaw-Liang Chang[d,e], Pao-Chin Chiu[f], Yen-Yin Chou[g], Fuu-Jen Tsai[h,i], Siew-Lee Wong[j], Ni-Chung Lee[a,b], Wuh-Liang Hwu[a,b,*]



Higher dosing of alglucosidase alfa improves outcomes in children with Pompe disease: a clinical study and review of the literature

Aleena A. Khan, MBBS[1], Laura E. Case, PT, DPT[2], Mrudu Herbert, MD, MPH[1], Stephanie DeArmey, MHS, PA-C[1], Harrison Jones, PhD[3,4], Kelly Crisp, CCC-SLP, MA[3], cia Zimmerman, MD[5], Mai K. ElMallah, MD[6], Sarah P. Young, PhD[1] and Priya S. Kishnani, MD[1]

se: Enzyme replacement therapy (ERT) with recombinant n acid-α glucosidase (rhGAA) at standard dose of 20 mg/kg other week is insufficient to halt the long-term progression of thy in Pompe disease.

ods: We conducted a retrospective study on infantile-onset e disease (IPD) and late-onset Pompe disease (LOPD) ts with onset before age 5 years, ≥12 months of treatment tandard dose ERT, and rhGAA immunogenic tolerance prior e escalation. Long-term follow-up of up to 18 years was ed. We obtained physical therapy, lingual strength, biochem- nd pulmonary assessments as dose was escalated.

ts: Eleven patients with IPD ($n = 7$) or LOPD ($n = 4$) were treated with higher doses of up to 40 mg/kg weekly. There were improvements in gross motor function measure in 9/10 patients, in lingual strength in 6/6 patients, and in pulmonary function in 4/11. Significant reductions in urinary glucose tetrasaccharide, creatine kinase, aspartate aminotransferase, and alanine aminotransferase were observed at 40 mg/kg weekly compared with lower doses ($p < 0.05$). No safety or immunogenicity concerns were observed at higher doses.

Conclusion: Higher rhGAA doses are safe, improve gross motor outcomes, lingual strength, pulmonary function measures, and biochemical markers in early-onset Pompe disease, and should be considered in patients with clinical and functional decline.

Genetics in Medicine (2020) 22:898–907; https://doi.org/10.1038/s41436-019-0738-0

Keywords: alglucosidase alfa; Pompe disease; enzyme replacement therapy; high dose; recombinant human GAA

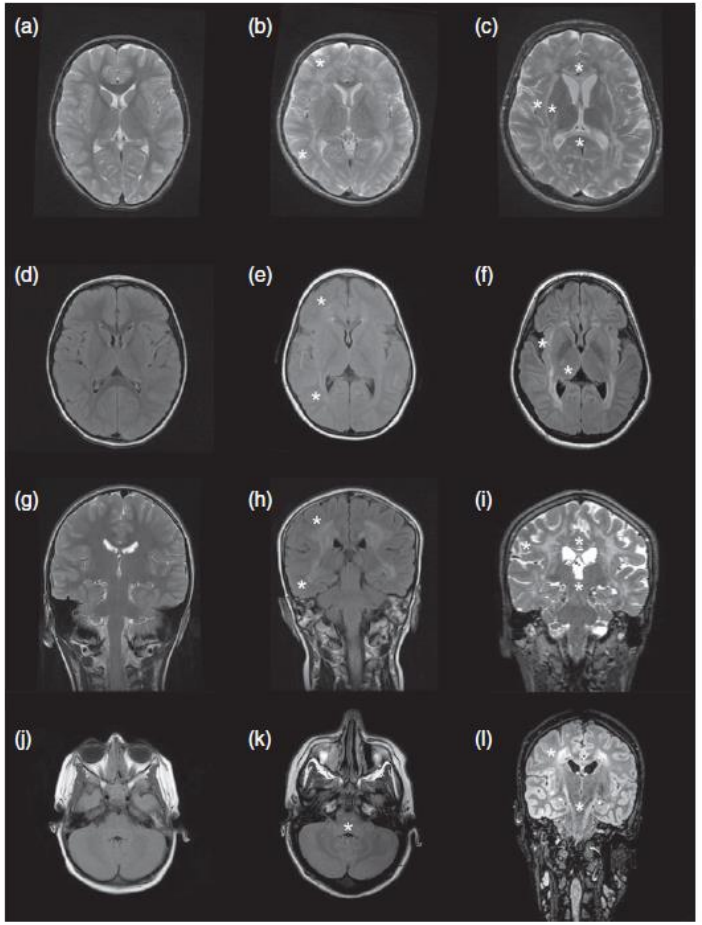
DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Classic infantile Pompe patients approaching adulthood: a cohort study on consequences for the brain

BERENDINE J EBBINK[1] | ESTHER POELMAN[1] | FEMKE K AARSEN[1] | IRIS PLUG[1] | LUC RÉGAL[2] | CARSTEN MUENTJES[3] | NADINE A M E VAN DER BEEK[4] | MAARTEN H LEQUIN[5] | ANS T VAN DER PLOEG[1] | JOHANNA M P VAN DEN HOUT[1]

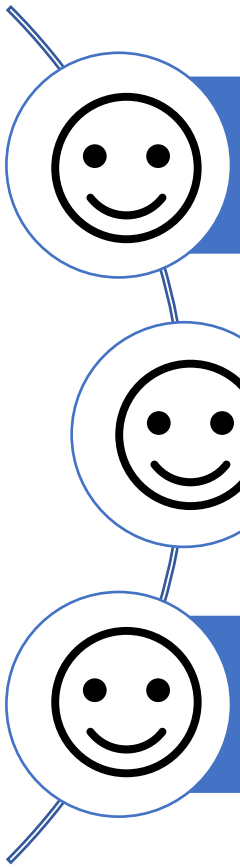
Evolvement of cerebral white matter change occurred in three-stage pattern:

- Stage 1: around 2y, periventricular white matter involvement at centrum semiovale
- Stage 2: from 8y onwards, white matter abnormalities expanded to subcortical areas and internal / external capsule
- Stage 3: from 11y onwards: infratentorial white matter being involved



Dev Med Child Neurol 2018;60:579-586

ERT experience in IOPD



Survival

Ventilator free survival

Mobility

- Age of ERT
- Immunogenicity
- ERT dosage

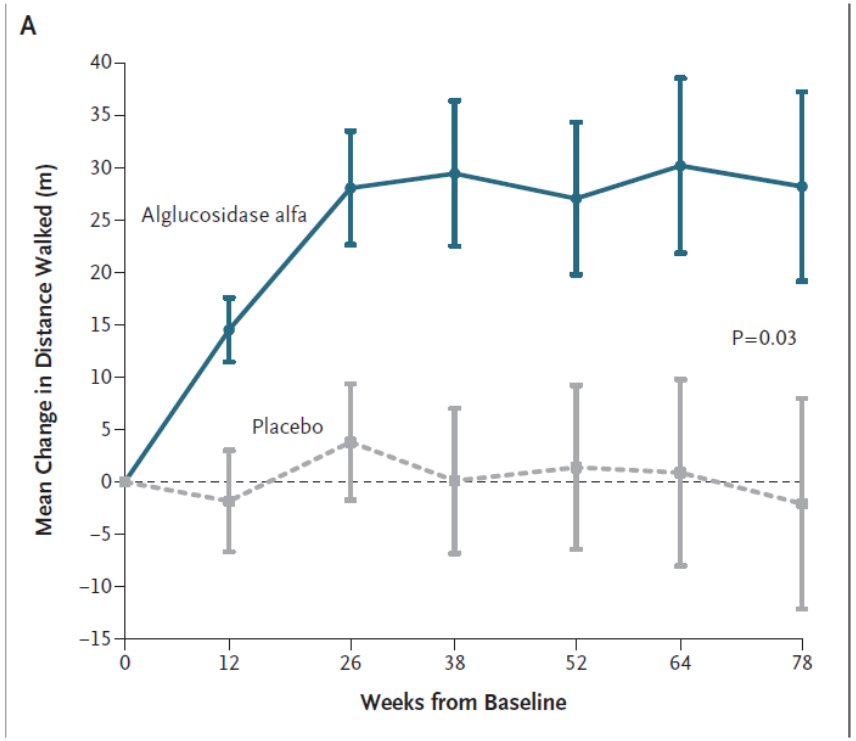
The NEW ENGLAND JOURNAL of MEDICINE

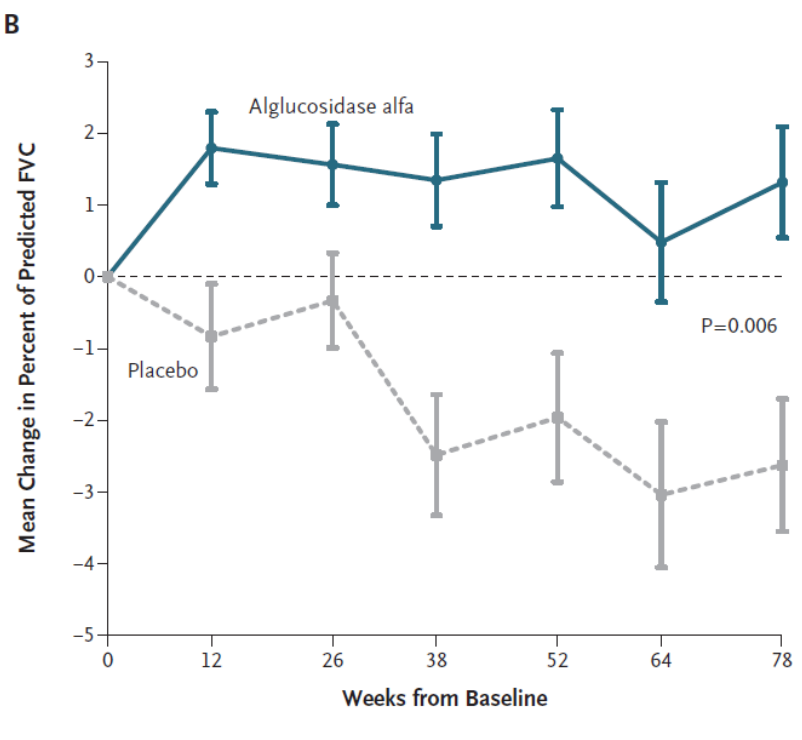
N Engl J Med 2010;362:1396-406

ORIGINAL ARTICLE

A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease

Improvement in ambulation, 6min walking distance improved by 25m or 7.5%





Stabilization of respiratory function

Long-term benefit of enzyme replacement therapy in Pompe disease

A 5-year prospective study

Neurology 2017;89:2365–2373

Dutch national cohort involving 102 adult Pompe patients

Table 3 Effect of ERT at 5 years compared to baseline value

	Effect of ERT compared to baseline values			At 5 y of ERT		
	At 5 y of ERT					
	Difference	p Value	Improved/stable compared to baseline, %[a]	Difference	p Value	Better than expected if untreated, %[a]
MRC sum score	+0.7	0.25	59	+6.6	<0.0001	87
HHD sum score	+8.4	<0.0001	89	+9.6	<0.0001	89
FVC upright	−0.1	0.84	48	+7.3	0.0006	73
FVC supine	−2.9	0.005	37	+7.6	0.0003	75
MIP	−0.5	0.81		+20.8	<0.0001	
MEP	+2.6	0.18		+17.3	<0.0001	
QMFT sum score	−0.2	0.87		+1.5	0.47	
R-PAct	+3.6	0.004	59	+10.8	0.002	80
6MWT	+40.9	0.03	69	NA	NA	NA

Received: 5 March 2020 | Revised: 24 May 2020 | Accepted: 5 June 2020
DOI: 10.1002/jimd.12272

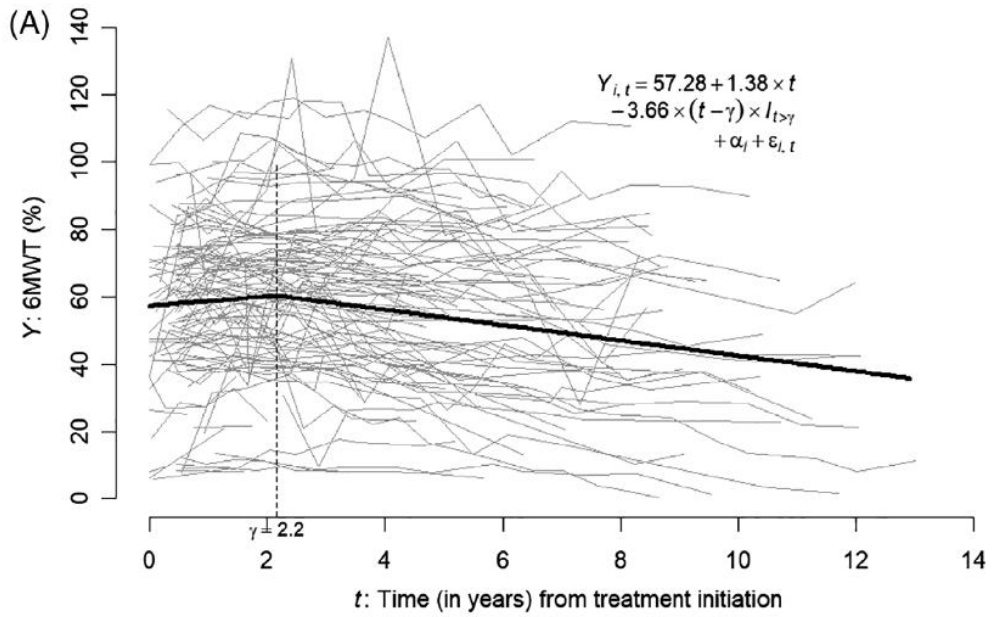
ORIGINAL ARTICLE

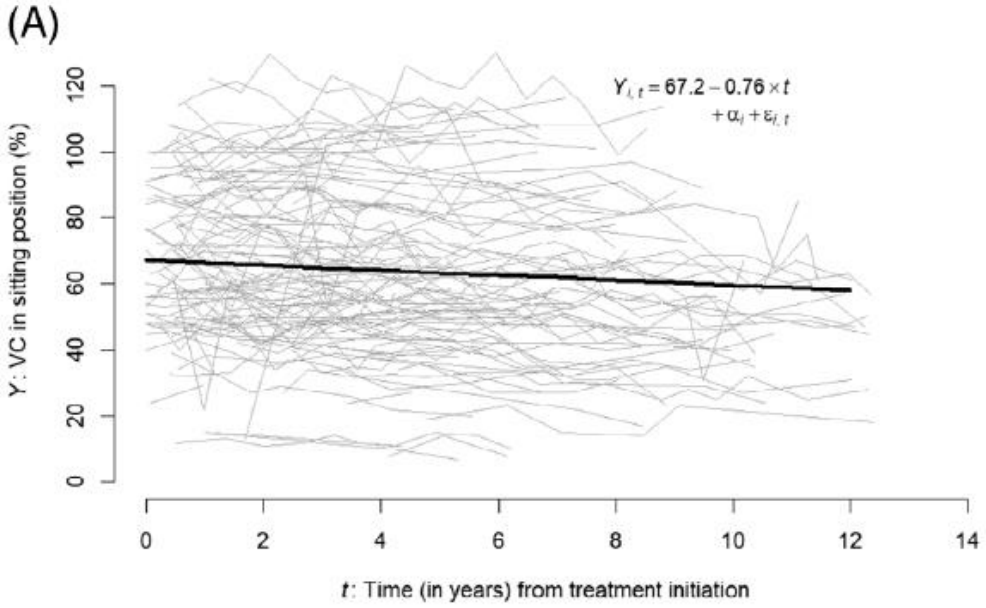
JIMD SSIEM WILEY

Long-term benefit of enzyme replacement therapy with alglucosidase alfa in adults with Pompe disease: Prospective analysis from the French Pompe Registry

J Inherit Metab Dis. 2020;43:1219–1231

This registry included 158 adult Pompe patients after ERT, a two-model effect was observed in 6MWD with initial improvement in the first 2y followed by a gradual decline of 2.3%/y while the FVC showed a single slop -0.9%/y, a ceiling effect is seen at 2-3y after ERT





Güngör et al. Orphanet Journal of Rare Diseases 2013, 8:49
http://www.ojrd.com/content/8/1/49

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study

Deniz Güngör[1,2], Michelle E Kruijshaar[1,2], Iris Plug[1,2], Ralph B D'Agostino Sr[3], Marloes LC Hagemans[1,2], Pieter A van Doorn[1,4], Arnold JJ Reuser[1,5] and Ans T van der Ploeg[1,2,6*]

Abstract

Background: Pompe disease is a rare metabolic myopathy for which disease-specific enzyme replacement therapy (ERT) has been available since 2006. ERT has shown efficacy concerning muscle strength and pulmonary function in adult patients. However, no data on the effect of ERT on the survival of adult patients are currently available. The aim of this study was to assess the effect of ERT on survival in adult patients with Pompe disease.

Methods: Data were collected as part of an international observational study conducted between 2002 and 2011, in which patients were followed on an annual basis. Time-dependent Cox's proportional hazards models were used for univariable and multivariable analyses.

Results: Overall, 283 adult patients with a median age of 48 years (range, 19 to 81 years) were included in the study. Seventy-two percent of patients started ERT at some time during follow-up, and 28% never received ERT. During follow-up (median, 6 years; range, 0.04 to 9 years), 46 patients died, 28 (61%) of whom had never received ERT. After adjustment for age, sex, country of residence, and disease severity (based on wheelchair and ventilator use), ERT was positively associated with survival (hazard ratio, 0.41; 95% CI, 0.19 to 0.87).

Conclusion: This prospective study was the first to demonstrate the positive effect of ERT on survival in adults with Pompe disease. Given the relatively recent registration of ERT for Pompe disease, these findings further support its beneficial impact in adult patients.

Keywords: Pompe disease, Survival, Acid maltase deficiency, Lysosomal storage disease, Glycogen storage disease type II, Enzyme replacement therapy, Alglucosidase alfa

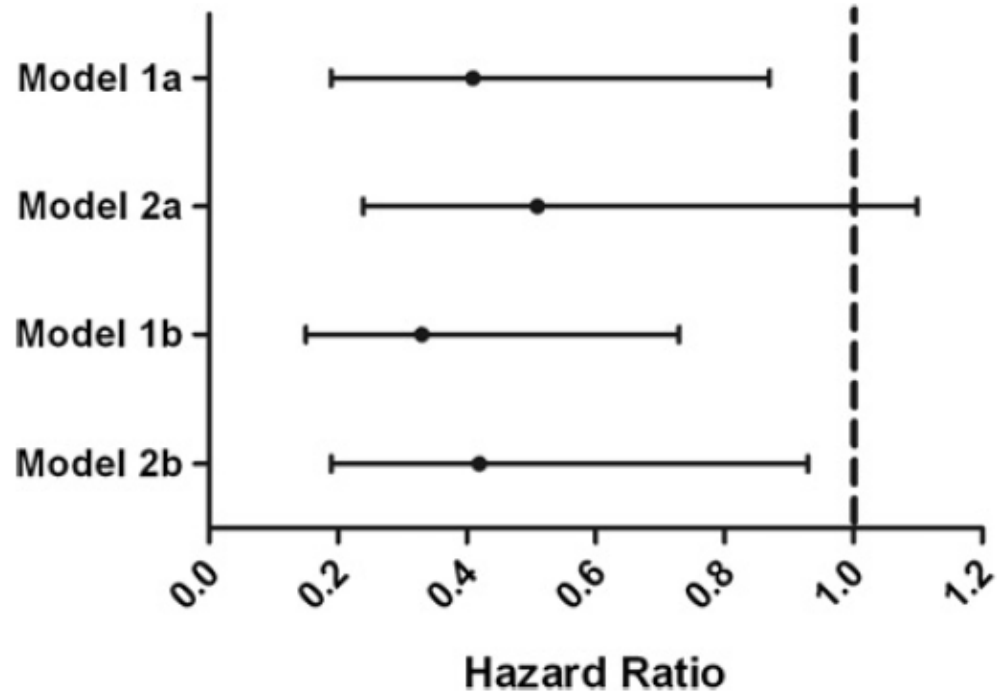
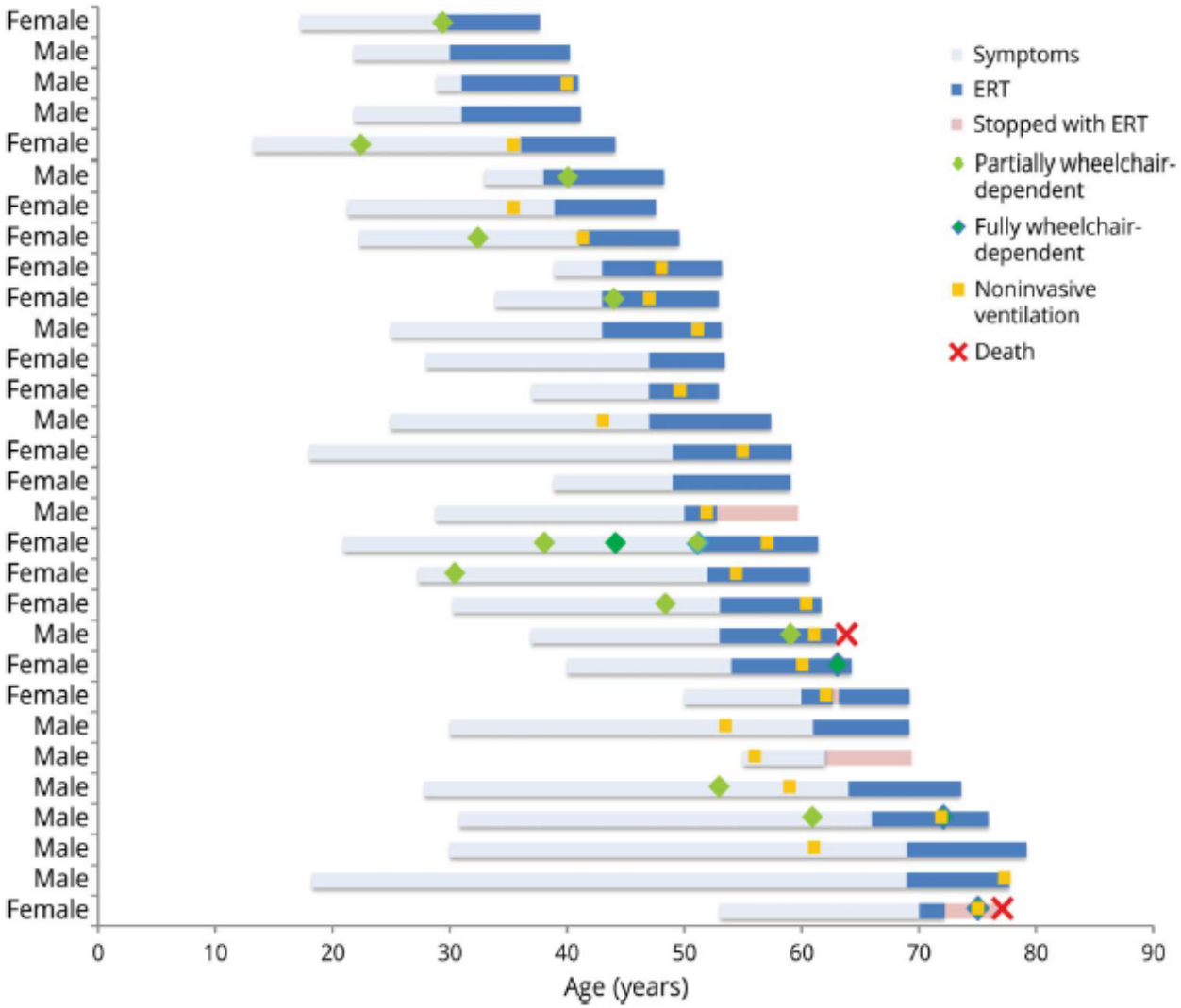


Figure 1 Adjusted Hazard Ratios of the Different Models Describing the Relationship Between ERT and Survival. Model 1a: Intent-to-treat approach with enzyme replacement therapy (ERT), age categories, and disease severity as time-dependent covariates. Model 2a: Intent-to-treat approach with only ERT as time-dependent covariate. Model 1b: Analysis excluding person-time after discontinuation of treatment with ERT, age categories, and disease severity as time-dependent covariates. Model 2b: Analysis excluding person-time after discontinuation of treatment with only ERT as time-dependent covariate.

Figure 2 Disease course of the individual patients over time (n = 30)



Each bar represents 1 individual patient. The length of each bar represents the symptom duration before the start of enzyme replacement therapy (ERT) (light blue), follow-up period during ERT (dark blue), and follow-up duration after stopping ERT (red). The age at the start of using a wheelchair (green diamond), ventilation (yellow square), or death (red cross) is indicated.

10y Fu in 30 patients initially recruited in LOTS (Late Onset Treatment Study), majority of patients had decline in 6MWT and FVC after initial improvement or stabilization, large variation in individual response was seen in long term Fu

Neurology 2019;93:e1756-e1767

Experience of ERT in LOPD

Although there is gradual deterioration over time, ERT in LOPD still brings about

- Improvement or stabilization of muscle strength and respiratory function
- Improvement of QoL
- Possible better survival

Unmet needs in the treatment of Pompe disease

- Although as a group both IOPD and LOPD responds to ERT, individual patient response highly variable
- Gradual deterioration of strength and respiratory function over years
- Lysosomal glycogen storage and autophagic buildup are the two main pathological findings in Pompe disease, autophagic buildup interrupts the trafficking of rhGAA to the target lysosome, and with accumulation of acid-phosphatase +ve inclusions (lipofuscin inclusions) further disrupt the myofibril architecture and muscle damage, disruption of enlarged lysosomes with accumulation of cytoplastic glycogen accumulation, autophagic buildup is more prominent in type II (fast fibre, glycolytic)
- ERT cannot reverse the autophagic buildup or clear the cytoplastic glycogen accumulation
- Lack of abundant M6P receptor in skeletal muscle cell and the low M6P content in aglucosidase alfa results in suboptimal targeting of ERT to its target tissue

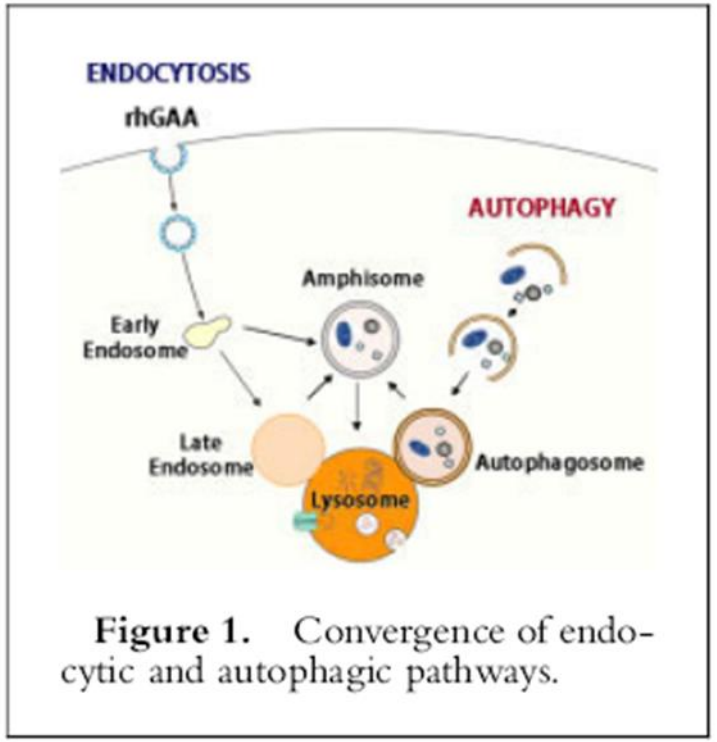


Figure 1. Convergence of endocytic and autophagic pathways.

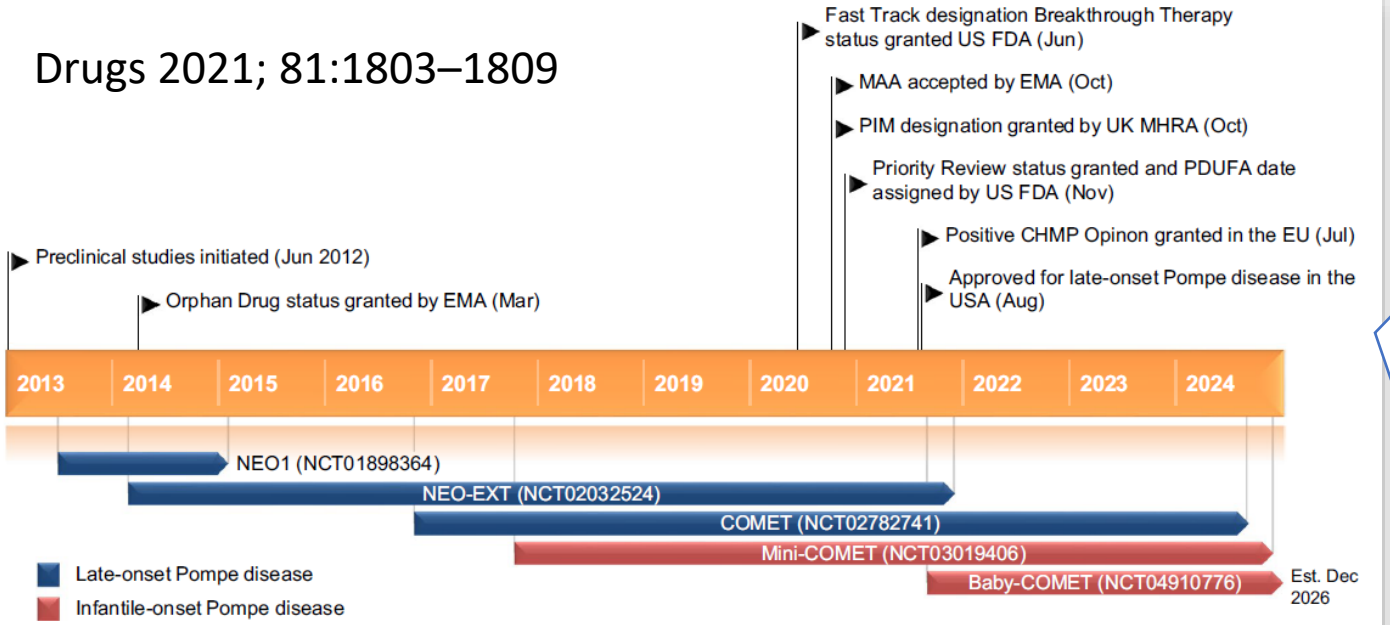
Acta Neuropathol Commun 2014;2:2

Aims at better target tissue delivery through modification of M6P moiety in rhGAA

Second generation ERT

- Avalglucosidase alfa
- Cipaglucosidase alfa

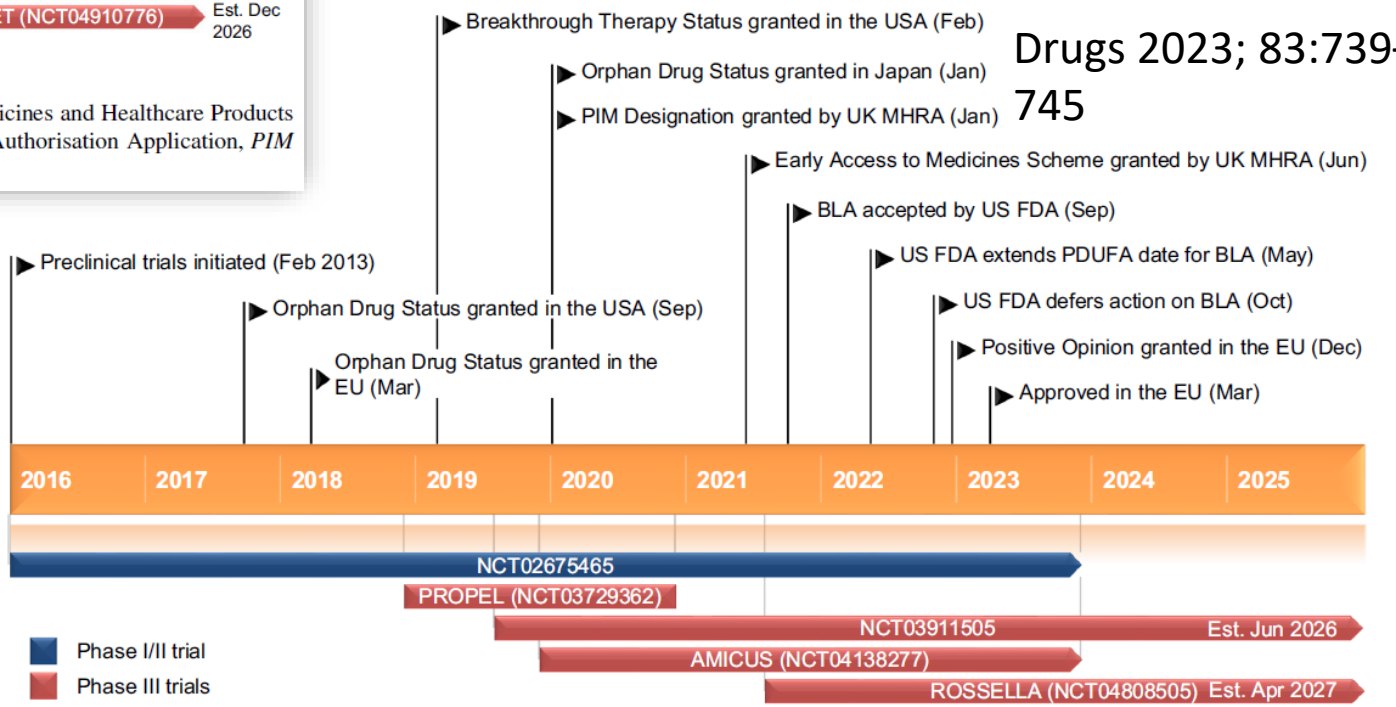
Drugs 2021; 81:1803–1809



Key milestones in the development of avalglucosidase alfa for the treatment of Pompe disease. *CHMP* Committee for Medicinal Products for Human Use, *EMA* European Medicines Agency, *FDA* Food and Drug Administration, *MHRA* Medicines and Healthcare Products Regulatory Agency, *MAA* Marketing Authorisation Application, *PIM* Promising Innovative Medicine

Avalglucosidase alfa is a rhGAA enzyme conjugated with multiple synthetic bis-mannose-6-phosphate (bis-M6P)-tetra-mannose glycans developed by Sanofi, aims to enhance receptor targeting and enzyme uptake. Preclinical studies found that avalglucosidase alfa had increased binding affinity for the M6P receptor compared with alglucosidase alfa (> 95% vs 15–30%), and it achieved 5x more glycogen clearance in muscle cells

Drugs 2023; 83:739–745



Key milestones in the development of cipaglucosidase alfa (co-administered with miglustat) for the treatment of Pompe disease. *BLA* Biologic License Application, *FDA* Food and Drug Administration, *MHRA* Medicines and Healthcare Products Regulatory Agency, *PDUFA* Prescription Drug User Fee Act, *PIM* Promising Innovative Medicine

Cipaglucosidase alfa + miglustat as two component study developed by Amicus. Cipaglucosidase alfa is a rhGAA enriched with bis-phosphorylated (bis-M6P) N-glycans for high affinity mannose-6-phosphate receptor binding. Co-administraton of miglustat increases the GAA area under concentration-time curve by 35%. The drug manufacturer is WuXi biologics 药明生物, a Chinese biologics company listed in HKEX.

Table 3 PROPEL and COMET Clinical Trials

	PROPEL[55]	COMET[54]
Clinical trial	Phase III	Phase III
Study design	Randomized, double blind, parallel group	Randomized, double blind, parallel group
# of patients	Total n= 123 (28 ERT naive and 95 ERT experienced) • CPA + MG n=85 (ERT naïve n=20) • RhGAA + placebo n=38 (ERT naive n=8)	Total n= 100 (all ERT naive) • Avalglucosidase alfa n=51 ○ RhGAA n=49
Mean age (+-SD)	CPA + MG: 47.6 yo (13.3) rhGAA + placebo: 45.1 yo (13.3)	Avalglucosidase alfa: 46 yo (14.5) RhGAA: 50.3 yo (13.7)
Drugs tested	Cipaglucosidase alfa plus Miglustat vs rhGAA plus placebo	Avalglucosidase alfa vs rhGAA
Administration route	Intravenous (CPA) Oral (MG)	Intravenous
Follow-up duration	52 weeks.	49 weeks.
Inclusion criteria	• Age ≥18 yo. • Weight ≥40 kg. • Diagnosis of LOPD based on genetics or enzyme activity measures. • Had either received rhGAA for at least 2 years at a dose of 20 mg/k eow OR were treatment naive. • FVC ≥30%. • 6MWT ≥75m AND 80–90%.	• Age ≥3 yo. • Diagnosis of LOPD based on 2 confirmed pathogenic variants and/or low enzyme activity. • Naive to Pompe specific treatment. • FVC 30–85%. • 6MWT ≥40m without stopping or using an ambulation assistance device.
Results primary endpoint	Changes in 6MWT: 20.8m (CPA+MG) vs 7.2m (rhGAA), p=0.07.	Changes in FVC%: 2.89% (AvA) vs 0.46% (rhGAA). Statistically non-inferior (p=0.007) but not statistically superior (p=0.06).
Results secondary endpoints	• Change FVC%: −0.9% (CPA+MG), −4% (rhGAA), p=0.02. • Change in GSGC score: −0.5 (CPA+MG), 0.8 (rhGAA), p<0.05. • Changes in MMT score in LL and PROMIS score: differences not statistically significant.	• Changes in 6MWT (m): 32.2m (AvA) vs 2.2 m (rhGAA), p=0.04. • Changes in QMFT: dbg 2.08 (p<0.05). • Changes in MIP, MEP, HHD LL and SF-12: differences not statistically significant.
Safety	Similar safety profiles between both groups.	Avalglucosidase had a more favourable safety profile. Avalglucosidase is not more immunogenic than rhGAA.

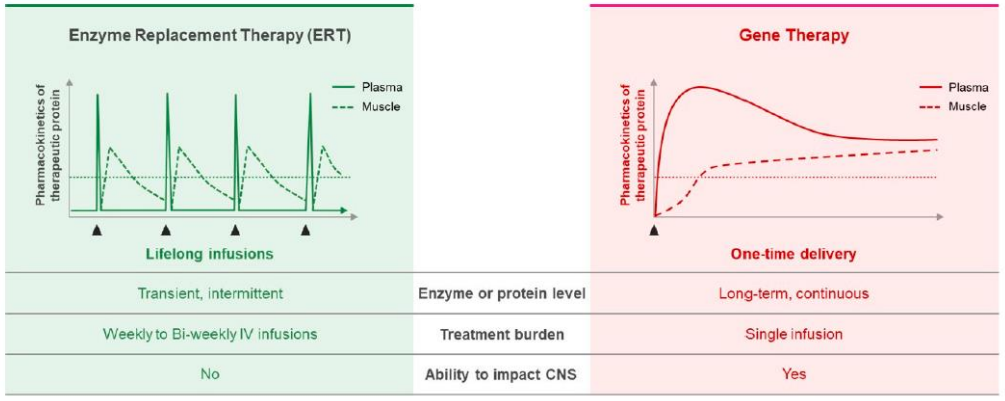
Abbreviations: 6MWT, 6 minute walking test; AvA, Avalglucosidase alfa; CPA, Cipaglucosidase alfa; dbg, difference between groups; eow, every other week; FVC, forced vital capacity; GSGC, Gait; Stairs; Gower's maneuver; Chair; HHD, Hand help dynamometer; LL, lower limbs; LOPD, late onset Pompe disease; m, meters; MEP, mean expiratory pressure; MG, Miglustat; MIP, mean inspiratory pressure; MMT, manual muscle testing; PROMIS, Patient-Reported Outcomes Measurement Information System; QMFT, quick motor function test; rhGAA, recombinant human alpha-glucosidase; SD, standard deviation; SF-12, 12-item short form; yo, years old.

Both products demonstrated better patient outcome in phase III trials over a wide range of different parameters and biomarkers

Therapeutics and Clinical Risk Management 2022:18 1099–1115

Gene therapy in Pompe disease: the future is approaching

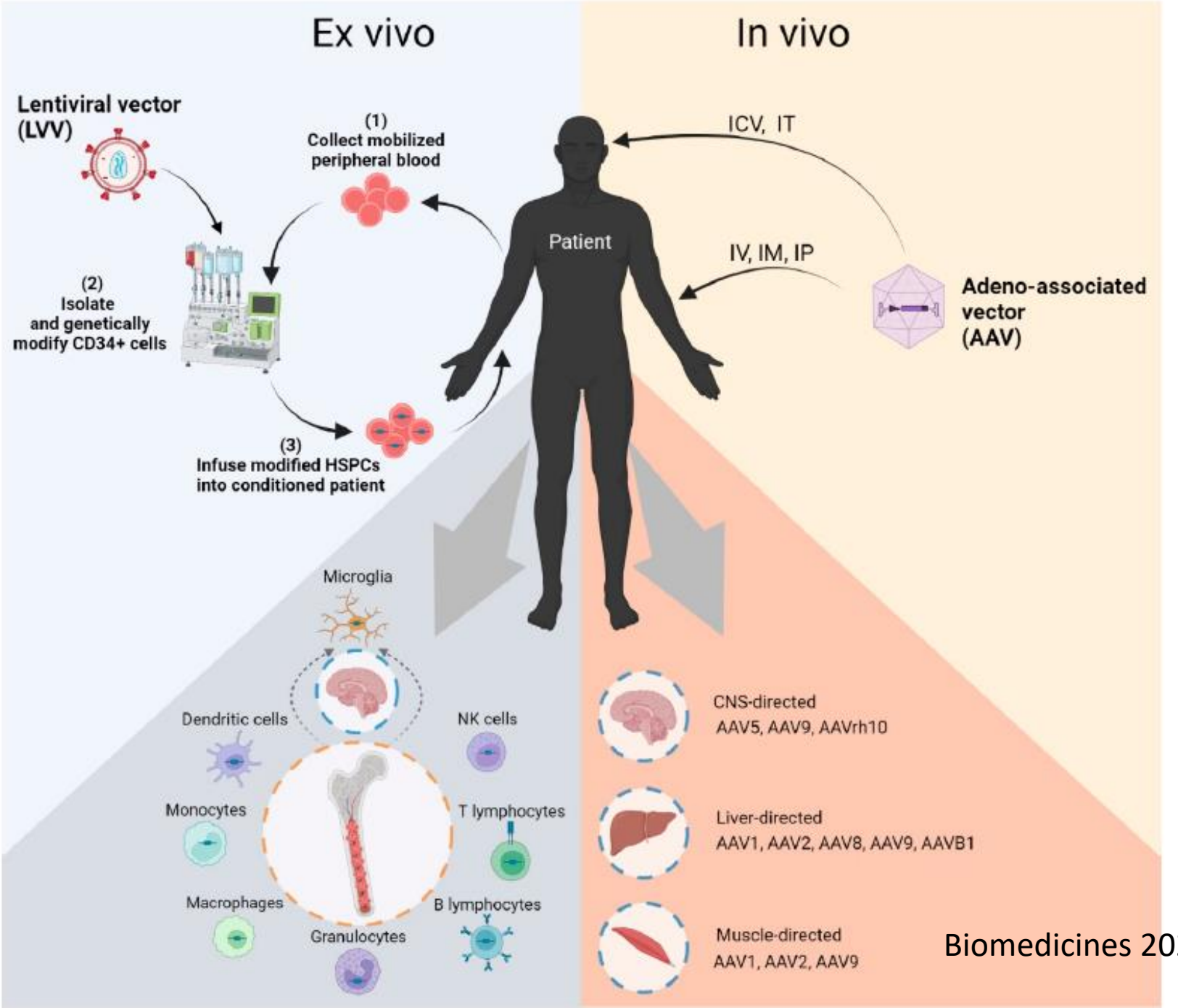
- Gene therapy is frequently quoted as the ultimate cure in hereditary disease
- Gene therapy has many therapeutical advantages over ERT
  - One-off treatment, avoid the need for life-long regular enzyme infusion
  - No immunogenicity
  - CNS correctable
- Muscle-directed, liver-directed
- In vivo vs ex-vivo



Preclinical Program	Clinical Stage
AAV2/8 Gene Therapy delivered Ab-GAA (Regeneron)	AAV2/8 LSPhGAA liver-directed Gene Therapy (LOPD, Phase 1) Bayer/Actus/AskBIO (Actus-101) (NCT03533673)
AAV/Proprietary capsid Gene Therapy (Amicus)	AAV9 muscle-directed Gene Therapy w/immune modulation (LOPD, Phase 1) University of Florida (NCT02240407)
AAV Gene Therapy (Sarepta-licensed from Lacerta)	AAV1/CMV-hGAA muscle-directed Gene Therapy (LOPD, Phase 1/2) University of Florida (NCT00976352)
AAV/Proprietary capsid Gene Therapy (Abeona)	AAV8 liver-directed Gene Therapy (LOPD, Phase 1/2) Audentes (AT845) (NCT04174105)
HSPC LV Gene Therapy (Erasmus MC)	AAV/Proprietary Rh74-derived capsid, liver-directed Gene Therapy (LOPD, Phase 1/2) Spark/Roche (SPK-3006) (NCT04093349)
HSPC LV Gene Therapy AVR-RD-03 (AVROBIO)	

Biomedicines 2022;10:302

In autologous ex vivo lentiviral gene therapy, CD34+ cells are extracted form the mobilized blood and transduced with the LV vector carrying the functional GAA, and infused back to patient. Patient are conditioned with alkylating agents to assist the engulfment of marrow and repopulation of haematopoietic cells capable to secret GAA, cross correcting the affected tissues



Utilization of different AAV vector capsid proteins and routes of administration are used to target distinct tissue niches. Transduced cells secrete functional enzyme locally, or systemically depending on targeted tissue

Biomedicines 2022;10:302

ClinicalTrials.gov Search Results 09/24/2023

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Evaluation of the Safety and Efficacy of Infantile-onset Pompe Disease Gene Therapy Drug	Recruiting	No Results Available	•Pompe Disease Infantile-Onset	•Genetic: GC301	•Peking Union Medical College, Beijing, China •301 Chinese PLA General Hospital, Beijing, China •Central South University, Xiangya Hospital, Changsha, China •Zhejiang University, School of Medicine, The Children's Hospital, Hangzhou, China •The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
2	Clinical Exploration of Adeno-associated Virus (AAV) Expressing Human Acid Alpha- Glucosidase (GAA) Gene Therapy for Patients With Infantile-onset Pompe Disease	Recruiting	No Results Available	•Infantile-onset Pompe Disease	•Biological: Genetic: GC301	•Bayi Children's Hospital, Seventh Medical Center, PLA general hospital, Beijing, Beijing, China
3	Gene Transfer Study in Patients With Late Onset Pompe Disease	Recruiting	No Results Available	•Pompe Disease (Late-onset)	•Genetic: AT845	•University of California Irvine, Department of Neurology, Orange, California, United States •Stanford University, Palo Alto, California, United States •University of Utah, Division of Medical Genetics, Salt Lake City, Utah, United States •Newcastle Upon Tyne Hospitals Foundation Trust Clinical Research Facility, Newcastle upon Tyne, United Kingdom
4	A Gene Transfer Study for Late-Onset Pompe Disease (RESOLUTE)	Active, not recruiting	No Results Available	•Pompe Disease •Pompe Disease (Late-onset) •Glycogen Storage Disease Type 2 •Glycogen Storage Disease Type II •LOPD •Lysosomal Storage Diseases •Acid Maltase Deficiency	•Genetic: SPK-3006	•Barrow Neurological Institute, Phoenix, Arizona, United States •University of California Irvine Health, Orange, California, United States •Emory University School of Medicine, Atlanta, Georgia, United States •University of Kansas Medical Center Research Institute, Kansas City, Kansas, United States •University of Minnesota, Minneapolis, Minnesota, United States •Oregon Health & Science University, Portland, Oregon, United States •University of Pennsylvania, Philadelphia, Pennsylvania, United States •University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States •University of Utah, Salt Lake City, Utah, United States •Lysosomal and Rare Disorders Research & Treatment Center, Fairfax, Virginia, United States •and 19 more
5	AAV2/8-LSPhGAA (ACTUS-101) in Late-Onset Pompe Disease	Active, not recruiting	No Results Available	•Pompe Disease	•Biological: ACTUS-101	•Duke University, Durham, North Carolina, United States
6	Re-administration of Intramuscular AAV9 in Patients With Late-Onset Pompe Disease	Completed	No Results Available	•Pompe Disease	•Genetic: Recombinant Adeno-Associated Virus Acid Alpha-Glucosidase •Drug: Rapamycin •Other: saline •Drug: Rituxan •Drug: Diphenhydramine •Drug: Acetaminophen •Drug: Lidocaine •Drug: LMX 4 Topical Cream	•Clinical and Translational Research Building (CTRB), University of Florida, Gainesville, Florida, United States
7	Safety Study of Recombinant Adeno-Associated Virus Acid Alpha-Glucosidase to Treat Pompe Disease	Completed	Has Results	•Pompe Disease	•Drug: rAAV1-CMV-GAA (study agent) Administration •Other: RMST	•Shands at the University of Florida, Gainesville, Florida, United States

ClinicalTrials.gov

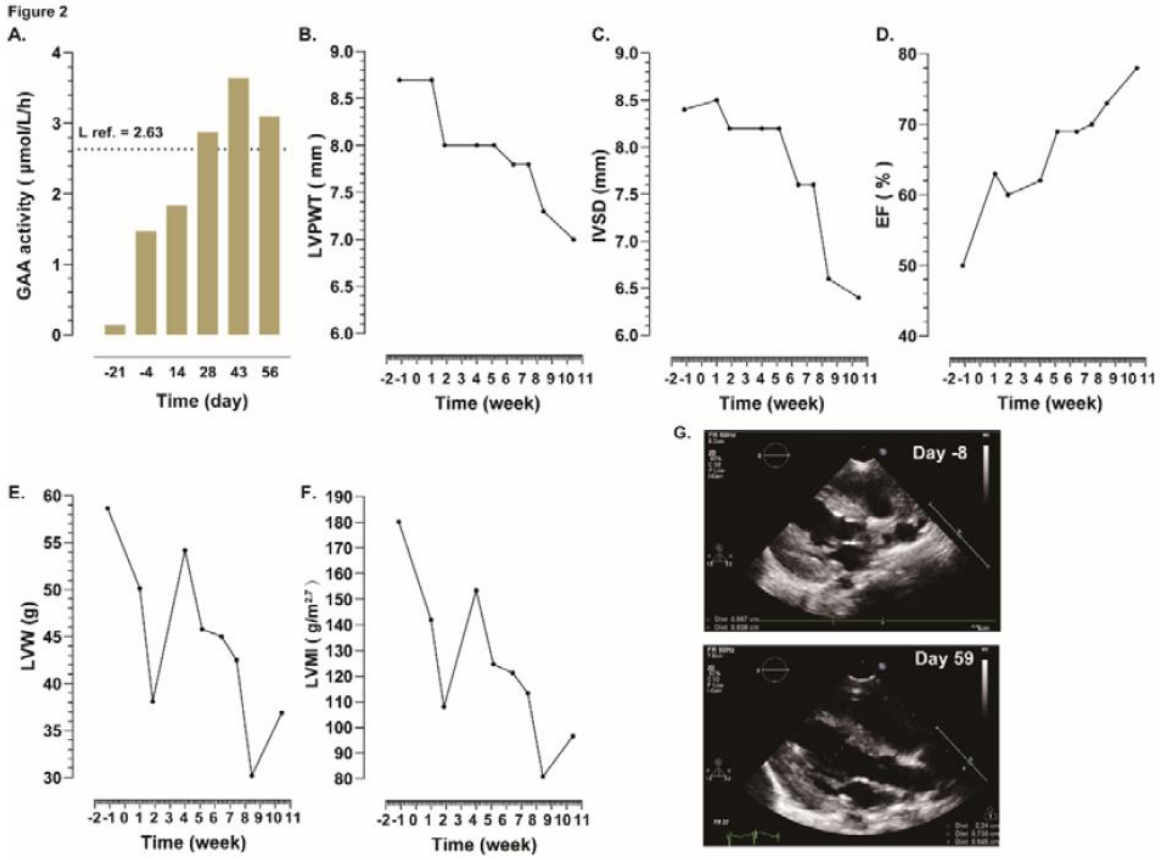
Follow this preprint

First-in-human case report: AAV9-hGAA gene therapy for a patient with infantile-onset Pompe disease

Xiuwei Ma, Jun Li, Xiaodong Wang, Wenhao Ma, Jianhua Wang, Ruijie Gu, Zhiming Zhu, Yongxia Wang, Ying Du, Juan Xu, Fang He, Xiao Yang, Sheng Zhang, Lina Zhu, Qiuping Li, Hui Xiong, Xiaobing Wu, Zhichun Feng

doi: https://doi.org/10.1101/2022.12.22.22283398

This first case in IOPD trial probably received tx in Sep 2023 as reported in the sponsor's homepage



国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA

IND (investigational new drug) approval)

受理号	药品名称	申请人名称	适应症	注册分类
CXSL2300013	GC301腺相关病毒注射液	北京锦篮基因科技有限公司	晚发型庞贝病（LOPD）	1
CXSL2200480	GC301腺相关病毒注射液	北京锦篮基因科技有限公司	早发型庞贝病（IOPD）	1

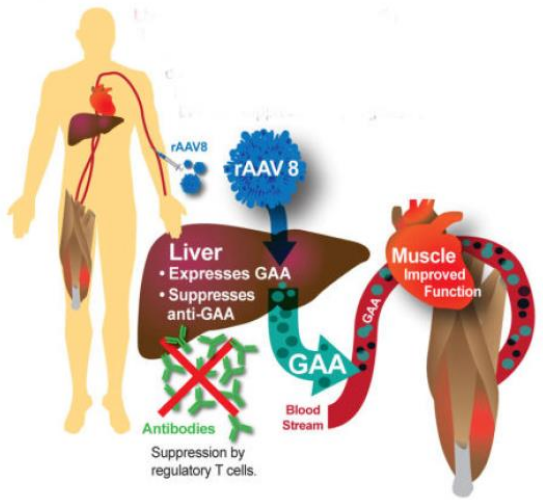
GeneCradle 锦篮基因

Immunomodulation by liver specific gene therapy

Cell Immunol. 2019 August ; 342: 103737. doi:10.1016/j.cellimm.2017.12.011.

Immunomodulatory, Liver Depot Gene Therapy for Pompe Disease

JE Bond[1], PS Kishnani[2], DD Koeberl[2,3,**]



- Liver specific gene therapy could modulate the immune response by stimulating T reg cells
- Adeno associated virus (AAV)8 shows good liver tropism and serves a good vector for liver targeted gene therapy
- Preclinical study on GAA knock-out mice with liver-depot gene therapy using rAAV8 vector showed good liver expression of GAA and trafficking of enzyme to the target tissues without anti-GAA Ab development
- Using subtherapeutic liver-depot gene therapy in GAA knock-out mice so that GAA was expressed only in liver, followed by regular rhGAA challenges, those with gene therapy showed significantly lower antibody titre, proving the immune tolerance effect
- Liver depot gene therapy for Pompe disease is now under phase I trial

- *As human beings we are defined at our core by how we respond to hardship. Good doesn't just happen. If you want good things to happen for yourself, your family and for the world, you have to fight.*

  John F. Crowley

- From being an incurable, devastating and fatal disease to our then focusing on better survival, better strength and better quality of life
- We see lots of love, hope and excitements
- Truely, we still have many unmet needs, many issues inadequately addressed
- Nevertheless, with the courage we saw in the Pompe community, from patients to scientists, we fight, we believe we will make miracle again and again

Thank you