



**INTERNATIONAL  
POMPE CONFERENCE 2003**

**AND**

**IPA ANNUAL MEETING**

**OCTOBER 31 – NOVEMBER 02, 2003**

**HEIDELBERG, GERMANY**

***CONFERENCE PROCEEDINGS***

***– REVISED REPRINT 2005 –***

A video documentation of the conference is available on 4 DVDs (20 € plus shipping)  
and can be ordered by email to [schaller@glykogenose.de](mailto:schaller@glykogenose.de)

## IMPRESSUM & CONTACT

**The International Pompe Conference and the IPA Annual Meeting is organized by the International Pompe Association (IPA), a worldwide organisation of national Pompe patient groups, acting as ear and voice of the Pompe patients in contact with researchers and industry.**

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**Venue:** Crowne Plaza Hotel, Heidelberg, Germany  
**Conference language:** English  
**Conference website:** [home.arcor.de/fobrokel/pompe2003/](http://home.arcor.de/fobrokel/pompe2003/)  
(will be maintained for reports and reactions)

**This conference was made possible by the help of our supporters:**

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## WELCOME WORDS FROM THE IPA

*By Randall H. House*



We, the board of the IPA, wish to welcome you to the 2003 International Pompe Association meeting:

- **Randall House**, Chairman
- **Ria Broekgaarden**, Secretary General
- **Allan Muir**, Treasurer
- **Kevin O'Donnell**, Board Member
- **Maryze Schoneveld van der Linde**, Board Member

The board wishes to extend our appreciation to our hosts, the German Glycogen Storage Disease Association, SHG Glykogenose Deutschland, for making all of this possible. In particular we would like to acknowledge the diligence of the conference coordinators: Helmut and Rita Erny, Thomas Schaller, and Birgit Wolf.

Thank you for your hard work in organizing this meeting. We know that you have all spent countless hours putting this conference together.

We would also like to thank all participants for coming to this very important meeting:

- Patients and their families
- Patient organization representatives
- Medical and scientific speakers and experts
- Representatives of Genzyme Corporation, US and Europe

We feel very fortunate to be able to gather in this beautiful and historic city for the second annual IPA meeting, and we look forward to a very informative conference.

## **INTRODUCTION**

Medical experts and patients are invited to attend the International Pompe Conference 2003. The goal of the conference is to bring together scientific expertise and patients' experience. On the way towards a therapy for Pompe's Disease there were and are many examples of good cooperation between patient organisations and the medical community, including the Genzyme Corporation. Consequently, the scope of the conference is to improve health information and knowledge for the development of public health on the European and worldwide level, in particular, to promote

- Transfer and sharing of information, of experiences on good practice, and of health data
- Research on Pompe's related issues
- Development and approval of therapies for Pompe's disease
- Coordination of scientific and patient network activities
- Patients' health and advice from high-level scientists and experts
- Public awareness of Pompe's disease

### **Organisation**

This conference is presented by the International Pompe Association (IPA), in cooperation with the German patient group, backed by scientific advisors.

### **Location**

Heidelberg is located in Southern Germany, approx. one hour south of Frankfurt. Famous for its university and Castle, the beautiful Neckar riverside and picturesque downtown Heidelberg is a must for overseas visitors. Medical research or sightseeing: Here's the right spot for either of them.

A sightseeing tour is offered on November 2, 2003 (Sunday afternoon). Sightseeing includes Heidelberg Castle, beautiful view on the Neckar river and historic Heidelberg, Old Bridge, downtown Heidelberg, optional: university campus.

## PROGRAM

The program of the International Pompe Conference 2003 brings together medical expert and patient knowledge in several meetings and sessions. The program will start on Friday with the International Pompe Association (IPA) Annual General Meeting and a special Genzyme meeting. On Saturday and Sunday, the scientific sessions will take place. A few meetings are restricted to a certain group of participants (as indicated), but the conference part of the program is open to all participants.

Please be aware that the schedule is very tight. Presentations are mostly limited to 15 minutes, and the session chairs are instructed not to allow overtime. Discussions of the presentations will be *en bloc* at the end of the sessions. To achieve a smooth and timely course of the conference, the given timeframe has to be obeyed as good as possible. Please be fair and cause no stress to the organizers or your subsequent speaker colleagues.

Chairing of each scientific session will be performed by a scientific expert, backed by an IPA representative.

# SCHEDULE

(as of April 4, 2005)

## October 31, 2003 (Friday afternoon)

Time	Session / Action	Contact person
12:00	<b>Meeting and lunch</b> (Closed session of IPA board and conference organizers)	R. House
13:30	Conference registration	R. Erny / B. Wolf
14:30 - 16:30	<b>IPA Annual General Meeting</b> (Closed session of IPA board and member patient group representatives)	R. House
16:30 - 17:00	Coffee break	
17:00 - 19:00	<b>Meeting of Genzyme, worldwide patient group representatives and experts</b> (open session) <i>The format of this session will be Question and Answer around specified topics. Genzyme Spokespeople will provide a brief background presentation on each topic followed by questions from the audience.</i> <b>Agenda:</b> - Manufacturing - Clinical trials (previous, current & future) - Treatment availability - Registration - Special Access Programs - Pompe Disease Registry - Pompe Community & Genzyme Communications	Genzyme Corp.
19:30	<b>Dinner upon invitation of the IPA</b> (Experts, Genzyme and patient group representatives)	R. Broekgaarden

# SCHEDULE (cont'd)

(as of April 4, 2005)

## November 1, 2003 (Saturday morning)

Time	Session / Action / Chair	Speaker / Title
08:00	Speakers' breakfast (Th. Schaller)	
08:30	Conference registration (R. Erny, B. Wolf)	
09:00 - 09:10	<b>Opening of the conference</b>	<b>R. House</b> Welcome words from the IPA, presentation of IPA team, and welcome of the hotel manager (optional)
09:10 - 09:15	Organizational remarks	<b>Th. Schaller</b> Introduction into the program and schedule of the conference
09:15 - 09:20	Welcome	<b>Prof. Dr. R. von der Malsburg (Heidelberg Mayor)</b> Welcome words from the City of Heidelberg
09:20 - 09:25	Welcome	<b>Dr. M. Lindner</b> Welcome words from the Heidelberg University
09:25 - 09:30	Buffer time	
09:30 - 09:35	<b>A Patient relations and basics of Pompe's Disease</b> Chair: <b>Dr. A. Reuser</b> , H. Erny	Session introduction
09:35 - 09:50		<b>Dr. K. O'Donnell</b> Patient relations: The Work of the International Pompe Association
09:50 - 10:05		<b>Dr. A. van der Ploeg</b> How early onset (infants, children) Pompe patients present
10:05 - 10:20		<b>Prof. Dr. B. Eymard</b> How late onset (juveniles, adults) Pompe patients present
10:20 - 10:40	Discussion	
10:40 - 11:10	Coffee break	
	<b>B Insights into Pompe's disease</b>	
11:10 - 11:15	<b>B1 Pathology and molecular aspects</b> Chair: <b>Prof. Dr. J.-S. Shin</b> , Th. Schaller	Session introduction
11:15 - 11:30		<b>Dr. P. Laforêt</b> Magnetic resonance imaging (MRI) for the detection of glycogen storage in Pompe's disease
11:30 - 11:45		<b>Prof. Dr. W. Müller-Felber</b> Muscle pathology in Pompe's disease
11:45 - 12:00		<b>Dr. N. Raben</b> Replacing a deficient enzyme in Pompe disease: Two approaches, one result. ("What did we learn from the mouse model?")
12:00 - 12:15		<b>Dr. A. Reuser</b> Significance of molecular analysis
12:15 - 12:30		<b>Dr. J. Hopwood</b> Early detection of Pompe disease
12:30 - 12:50	Discussion	
12:50 - 13:00	Buffer time	
13:00 - 14:00	Lunch	



## SCHEDULE (cont'd)

(as of April 4, 2005)

### November 1, 2003 (Saturday afternoon)

Time	Session / Action / Chair	Speaker / Title
14:00 - 14:05	<b>B2 Muscle dysfunction and metabolism</b> Chair: <b>Dr. M. Bajbouj</b> , R. Broekgaarden	Session introduction
14:05 - 14:20		<b>Dr. U. Mellies</b> Sleep disordered breathing and respiratory failure in Pompe's disease
14:20 - 14:35		<b>Dr. M. Lindner</b> Metabolic aspects of Pompe's disease
14:35 - 14:50		<b>Prof. Dr. O. Bodamer</b> Effects of L-Alanine in Glycogen Storage Disease Type II
14:50 - 15:05		<b>Dr. A. Slonim / L. Bulone</b> Symptomatic Therapy in Late Onset Acid Maltase Deficiency
15:05 - 15:25		Discussion
15:25 - 16:00	Coffee break	
	<b>C Condition, management, and therapeutic intervention</b>	
16:00 - 16:05	<b>C1 Condition of patients</b> Chair: <b>Dr. U. Mellies</b> , B. Wolf	Session introduction
16:05 - 16:20		<b>M. Hagemans</b> IPA / Erasmus MC Pompe questionnaire: Goals, data collection and preliminary results
16:20 - 16:30		Discussion
16:30 - 16:35	<b>C2 Workshop: Physical therapy</b> Chair: <b>Dr. U. Mellies</b> , B. Wolf	Session introduction
16:35 - 16:50		<b>L. Winkel</b> Testing of muscle strength and motor performance in patients with Pompe's disease
16:50 - 17:05		<b>Dr. C.-R. Arnold</b> Benefits of physical therapy for adult onset Pompe patients
17:05 - 17:15		Discussion
17:15 - 18:00		Workshop discussion of patient and medical experiences with physical therapy
18:00 - 18:20	<b>Guest Presentation</b>	<b>Dr. M. Bajbouj</b> Experience with enzyme replacement therapy in patients with mucopolysaccharidose type I
18:20 - 20:00	Open space	
20:00	Conference dinner	

## SCHEDULE (cont'd)

(as of April 4, 2005)

### November 2, 2003 (Sunday)

Time	Session / Action / Chair	Speaker / Title
08:00	Speakers' breakfast (Th. Schaller)	
08:30	Conference registration (R. Erny, B. Wolf)	
09:00 - 09:05	<b>Opening of the second day</b>	<b>R. Broekgaarden</b>
09:05 - 09:10	<b>C3 Clinical trials</b> Chair: <b>Prof. Dr. Th. Voit</b> , Th. Schaller	Session introduction
09:10 - 09:30		<b>Dr. F. Ollington</b> GENZYME's Pompe development program
09:30 - 09:45		<b>Dr. A. van der Ploeg</b> Rotterdam experience with enzyme replacement therapy for Pompe's disease
09:45 - 10:00		<b>Dr. P. Kishnani</b> Enzyme replacement therapy with recombinant human acid alpha glucosidase in infantile Pompe disease: Duke experience
10:00 - 10:30	Discussion	
10:30 - 11:00	Coffee break	
11:00 - 11:15		<b>Y. Wijnen</b> Experiences of parents of a Pompe infant under treatment
11:15 - 11:30		<b>T. House</b> (video presentation) Experiences of a juvenile Pompe patient under treatment
11:30 - 11:45	Discussion	
11:45 - 11:50	Buffer time	
11:50 - 11:55	<b>C4 Gene therapy</b> Chair: <b>Prof. Dr. Th. Voit</b> , Th. Schaller	Session introduction
11:55 - 12:15		<b>Dr. A. Amalfitano</b> Potential of gene therapy for GSD-II
12:15 - 12:25	Discussion	
12:25 - 12:30	<b>Closing of the conference</b>	<b>R. House</b>
12:30 - 13:00	Open space	
13:00 - 14:00	Lunch	
14:00 - 17:00	Sightseeing	

## **ABSTRACTS**

The abstracts are submitted by the authors, and the organizers of the conference are not responsible for their contents. For all questions and feedback, please contact the authors.

Underlined authors are speakers.

## **PATIENT RELATIONS: THE WORK OF THE INTERNATIONAL POMPE ASSOCIATION**

**Kevin O'Donnell**

IPA Board

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### **Abstract**

It is a real privilege to be given the opportunity to speak about the work of the International Pompe Association (IPA) at this conference. I first heard of Pompe's disease in 1993. Like most people this was because of a diagnosis. In my case, this was of infantile Pompe's for our son, Calum. At that time, there was no widely available information about Pompe's for anyone who did not have the time or opportunity to visit a medical library and search through the specialist journals. It is probably fair to say that patients and families were often isolated, directionless and subject to feelings of complete hopelessness. I hope it is equally fair to say that the situation now is very different! The IPA has played a leading role in bringing about that change.

The IPA was formed on 20 March 1998, following a joint initiative of the Dutch, UK and US patient groups. At the first international conference in 1999, founding co-Chairman Ysbrand Poortman stated that the IPA should be "a haven, a wharf, a beacon and a lighthouse" [1]. I would like to invite you to consider whether we have lived up to that ambition. In the four years since that conference, the IPA has:

- Become the recognised source of information on Pompe's disease. Our close links with both industry and academia have helped ensure that Pompe patients are the first to hear of new advances.
- Acted as the united voice of Pompe's patients across the world. We have dealt with industry as a strong, united voice, not as atomised, isolated individuals.
- In collaboration with the Pompe Centre in Rotterdam, initiated an International Patient Registry which allows patients to have ownership of their own data. It is a great personal pleasure for me to say that the IPA has helped bring the pioneering work of the Rotterdam group some measure of the recognition it deserves.
- Created a real international Pompe's community. These days patients need not be alone and isolated.

In short, yes, I do think we have met Ysbrand's ambition – and more. Thanks to the work of the IPA, Pompe's patients have been able to become, to an extent, the masters of their own fate – not passive bystanders. The fact that we are organised and speak with a strong, united voice means that our community can deal with industry and academia on something like an equal footing. I am sure that, like me, you are grateful for the fact that Genzyme are bringing a treatment to market. However, regardless of the many fine individuals who work for it, the fact remains that Genzyme as a company exists to make money. Its interests will not always coincide with our own and in such cases a strong organisation is needed. Those who take their own hide to market have "nothing to expect but a hiding" [2].

My hope for this conference is that we can look back on the achievements of the last five years of the IPA with pride but that in doing so, we use them as the foundation for even greater achievements in the future.

### **Key references**

- [1] Poortman, Y:  
The International Pompe Association; position, objectives, policy and activities.  
In: Report of the First Meeting of the International Pompe Association (1999),  
[www.worldpompe.org/conference.html](http://www.worldpompe.org/conference.html)
- [2] Marx, K:  
Capital p172, Lawrence and Wishart, London (1887)  
(Yes, my tongue is in my cheek at this point. Mainly ☺)

## HOW EARLY ONSET (INFANTS, CHILDREN) POMPE PATIENTS PRESENT

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### Abstract

Infantile Pompe's disease is a lethal cardiac and muscular disorder. We performed a study to delineate the natural course of the disease. More accurate data on the natural course were required to fully understand the data obtained in clinical studies on enzyme replacement therapy and to set endpoints for these studies.

We included twenty infantile patients diagnosed by the collaborative Dutch Centers and 133 cases reported in literature in the study. Information was collected on clinical history, physical examination and diagnostic parameters [1].

The course of Pompe's disease appeared to be essentially the same in the Dutch and the general patient population. Symptoms started at a median age of 1.6 months in both groups. The diagnosis was made at respective ages of 5.3 and 4.5 months. The median age of death was 7.7 and 6 months, respectively. Five percent of the Dutch patients and 8% of all reported patients survived beyond one year of age. Only 2 patients from literature became older than 18 months.

A progressive cardiac hypertrophy is characteristic for infantile Pompe's disease. The diastolic thickness of the left ventricular posterior wall and cardiac weight at autopsy increase significantly with age.

Motor development is severely delayed and major developmental milestones are generally not achieved. For the Dutch patient group, growth deviates significantly from normal despite start of nasogastric tube feeding. Levels of ASAT, ALAT, LDH, CK or CK-MB are typically elevated, while ASAT, ALAT and LDH increase significantly with age. The patients have fully deleterious mutations. Acid alpha-glucosidase activity is severely deficient.

We conclude that survival, decrease of the diastolic thickness of the left ventricular posterior wall and achievement of major motor milestones are valid endpoints for therapeutic studies for infantile Pompe's disease. Mutation analysis and measurement of the alpha-glucosidase activity should be part of the enrollment program.

### Key reference

- [1] Van den Hout HMP, Hop WJC, Van Diggelen OP, Smeitink JAM, Smit GPA, Poll-The B-T, Bakker HD, Loonen MCB, De Klerk JCB, Reuser AJ, Van der Ploeg AT:  
The natural course of infantile Pompe's disease; 20 original cases compared with 133 cases from the literature.  
*Pediatrics* 2003; 112: 332-340

## HOW LATE ONSET (JUVENILES, ADULTS) PATIENTS PRESENT

**B. Eymard, Professor of Neurology**

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### **Abstract**

Acid maltase deficiency (AMD) or glycogen storage disease type II, is a autosomal recessive inherited disorder caused by the deficiency of the lysosomal enzyme acid  $\alpha$ -glucosidase (GAA). Patients with the juvenile or adult onset forms of AMD present slowly progressive lower limb weakness frequently associated with severe diaphragm weakness, respiratory failure. The clinical boundaries between juvenile and adult forms are not precisely defined. Patients with AMD may present in childhood mild, non progressive muscular symptoms : scapular winging, scoliosis, running difficulties and a limitation of gymnastic or sports activities. In our experience, the mean age at onset of obvious muscle complaints is comprised between 35 and 40 years with a range of 2 to 55 years, and presenting symptoms are pelvic girdle weakness (60%), pelvic girdle weakness and respiratory insufficiency (Vital capacity, VC < 60%) (25%), and initial respiratory failure (10%). Symptoms of exercise intolerance with cramps or myalgias induced by exercise are not uncommon.

The characteristics of AMD patients muscle involvement are the following: 1) predominant pelvic girdle muscle weakness predominating in glutei and thigh adductors, milder selective femoral muscle weakness (hamstrings < quadriceps); 2) proximal upper limbs involvement, (scapular fixators > deltoids), minimal involvement of arms muscle; 3) severe axial weakness predominating on trunk muscles; 4) weakness more salient than atrophy. Distal muscles are spared in most cases, even at the late stages of the disease. CT scan examination is very useful to characterize the topography of muscle involvement.

Severe respiratory involvement is common in AMD, due to marked diaphragmatic weakness, as shown by the difference between VC in sitting and lying position and measurements of maximum inspiratory and expiratory pressures. In our experience, about half of patients required respiratory assistance (mean age at ventilation: 50 y, with a 9 y delay between onset of the disease and first respiratory symptoms and a 2 y interval between respiratory symptoms and ventilation). Tracheostomy is necessary in the most severe cases. Sleep-disordered breathing is associated to respiratory failure.

There is a marked heterogeneity for limb weakness severity and speed of deterioration. A significant proportion of patient become wheelchair bound (20% in our series). In several patients, there is a clear dissociation between limb and respiratory: wheel chair bound patients not needing assisted ventilation and artificially ventilated patients still ambulatory. In our experience, we did not find a parallel evolution between respiratory and limb involvement: no correlation was evidenced between slope of deterioration of VC and manual testing. Mechanical ventilation, initially nocturnal, and later permanent, is very beneficial in these patients. Juvenile forms are less frequent than AMD and often more severe than adult form. In AMD, vacuolar accumulation of glycogen in muscle is frequent, but inconstant. Decreased activity of GAA will finally ascertain diagnosis.

### **Key references**

- [1] P Laforêt, M Nicolino, B Eymard, JP Puech, C Caillaud, L Poenaru, M Fardeau:  
Juvenile and adult-onset acid maltase deficiency in France. Genotype-phenotype correlation.  
Neurology 2000, 55, 1122–1128
- [2] U Mellies, R Ragette, Schwake C, M Baethmann, T Voit, Teschler H:  
Sleep-disordered breathing and respiratory failure in maltase deficiency.  
Neurology 2001, 57, 1290–1295

## MAGNETIC RESONANCE SPECTROSCOPY FOR THE DETECTION OF GLYCOGEN STORAGE IN POMPE'S DISEASE.

C. Wary<sup>1\*</sup>, P. Laforêt<sup>1</sup>, B. Eymard<sup>1</sup>, M. Fardeau<sup>1</sup>, A. Leroy-Willig<sup>1\*</sup>, G. Bassez<sup>1</sup>,  
J-P Leroy<sup>2</sup>, C. Caillaud<sup>3</sup>, L. Poenaru<sup>3</sup>, P.G. Carlier<sup>1\*</sup>

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### Abstract

Adult-onset acid maltase deficiency is characterized by a progressive limb girdle muscle weakness frequently associated with a respiratory insufficiency due to a diaphragmatic involvement. However the course of the disease is highly variable and there is no strict correlation between the severity of limb muscles weakness and diaphragm involvement. Moreover, there is no biological parameter likely to predict the severity of the disease in adult patients. Therefore we studied the glycogen accumulation by *in vivo*, natural abundance <sup>13</sup>C nuclear magnetic resonance spectroscopy (<sup>13</sup>C NMR) in 11 patients in order to quantify the importance of glycogen accumulation in muscles and to search correlations with the clinical severity. Lower limbs being preferentially involved in adult patients, it appeared to us of interest to evaluate *in vivo* muscle glycogen content in distal and proximal lower limb muscles. Interleaved T1-weighted acquisitions of glycogen and creatine served to quantify glycogen excess. Glycogen storage was above the normal 95% confidence limits in at least one site in 7/11 patients. We note that both patient with the milder muscle weakness and the patient with the most important radiological lesions had no glycogen accumulation by <sup>13</sup>C NMR. The absence of glycogen accumulation observed in four patients might be also related to the fact that lysosomal glycogen accumulation is often mild in adults, and variations between muscles are poorly understood. No evidence could be found of a correlation between glycogen storage and patients' disability assessed by Walton score, manual muscle testing or vital capacity measurement. This totally atraumatic measurement of glycogen allows repeated measurements at different muscle sites of acid maltase deficient patients, despite selective fatty replacement of tissue. This could provide an additional parameter to follow the development of disease in individual patients, including in the perspective of forthcoming therapeutic trials. It may also offer an appropriate tool to study the role of glycogen accumulation in progression of the pathology.

### Key reference

- [1] C. Wary, P. Laforêt, B. Eymard, M. Fardeau, A. Leroy-Willig, G. Bassez, J-P Leroy, C. Caillaud, L. Poenaru, P.G. Carlier:  
Evaluation of muscle glycogen content by <sup>13</sup>C NMR spectroscopy in adult-onset acid maltase deficiency. *Neuromuscular Disorders* 2003, 13, 545–553

## **MUSCLE PATHOLOGY IN POMPE'S DISEASE**

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### **Abstract**

Histological examination of muscle tissue is one of the commonly used diagnostic procedures in Pompe's disease. Findings depend on the age of onset of the disease and, especially in adult patients, on the muscle which has been biopsied.

The typical histological presentation is a vacuolar myopathy. In contrast to McArdle's disease vacuoles are located in the cytoplasmic as well as in the subsarcolemmal areas of the muscle fibers. PAS-staining reveals an increased glycogen content of these vacuolated fibers. Electron microscopic examination shows glycogen in single membrane-bound, autophagic vacuoles. Abnormal mitochondria with crystalloid inclusions are found in some cases.

In infantile Pompe's disease a widespread vacuolar myopathy is seen often resembling artificial changes. In contrast, histological changes may be overlooked in adult patients. In some case with biochemically proven disease vacuolar changes may be absent especially if the biopsy sample is small. There may be an uneven distribution of histological findings with changes in weak muscles, only. Some patients show only degenerative changes of the muscle resembling muscular dystrophy. For that reason biochemical testing for acid maltase deficiency should be considered in cases of unclassified limb-girdle muscular dystrophy in adult patients.



**REPLACING A DEFICIENT ENZYME IN POMPE DISEASE:  
TWO APPROACHES, ONE RESULT**  
(“WHAT DID WE LEARN FROM THE MOUSE MODEL?”)

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**Abstract**

The success of enzyme replacement therapy (ERT) in type I Gaucher disease, a deficiency of lysosomal glucocerebrosidase, has stimulated efforts to develop similar approaches for other lysosomal disorders. Repeating this success, however, has proved difficult in Pompe disease [glycogen storage disease type II; deficiency of glycogen-degrading lysosomal acid alpha-glucosidase (GAA)] – the only lysosomal storage disease in which muscle is the principal target tissue for ERT.

We have generated a knockout model of Pompe disease (GAA<sup>-/-</sup>) to evaluate the efficacy of recombinant human GAA (rhGAA from Genzyme Corporation, Framingham, MA). The knockout mice treated with repeated injections of the rhGAA developed a strong immune response and signs of anaphylaxis such as labored breathing and collapse, and did not survive multiple injections. To address this problem, we have developed a tolerant GAA<sup>-/-</sup> model, which retained the phenotype of the original knockout strain but had a significantly diminished immune response. When young tolerant GAA<sup>-/-</sup> mice were treated with rhGAA (20 mg/kg/week for up to 5 months), skeletal muscle cells took up little enzyme compared to liver and heart. After 5 months of therapy, glycogen reduction in skeletal muscle was less than 50%, and some fibers showed little or no glycogen clearance. The undegraded glycogen remained in proliferating lysosomes as shown by increased immunoreactivity for LAMP-1/LAMP-2 in glycogen-containing lysosomes. A dose of 100 mg/kg/week in older mice resulted in ~75% glycogen clearance in skeletal muscle. The enzyme reduced cardiac glycogen to undetectable levels at either dose. Unexpectedly, the diaphragm responded to therapy much better than did other skeletal muscle groups. In some groups a modest glycogen reduction was accompanied by improved muscle strength.

These data closely paralleled the results of inducing the hGAA transgene in knockout mice - complete clearance of glycogen in the heart but strikingly uneven clearance in skeletal muscle following hepatic secretion of the enzyme – suggesting that the problem lies in the target tissue itself.

We have shown that skeletal muscle has a lower density of the essential transporter, the cation-independent mannose 6-phosphate receptor (CI-MPR), than cardiac muscle. Furthermore, histochemical analysis and Western blot showed increased density of CI-MPR in slow-twitch oxidative type I muscle fibers, which cleared glycogen more efficiently compared to fast-twitch fibers despite their higher level of glycogen accumulation.

The differences in glycogen clearance among the fiber types of skeletal muscle were also demonstrated in an independent series of experiments in young mice treated with rhGAA (20 mg/kg/twice a week for 1.5 months). Near complete glycogen clearance was observed in the predominantly type I soleus muscle, whereas the white portion of the mouse gastrocnemius muscle (comprised mainly of type II muscle fibers) still contained a significant amount of residual glycogen (~ 43% glycogen reduction).

Thus, the pre-clinical studies have demonstrated that the dosage is critical for effective treatment; that the age at the start of treatment as well as duration of treatment may be equally important factors; and that the enzyme was effective in reversing pathology in cardiac muscle and diaphragm. The restoration of an adequate enzyme level in skeletal muscle poses a much greater challenge: treating myopathy with ERT may require high doses of exogenous enzyme or an entirely different approach.

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## **SIGNIFICANCE OF MOLECULAR ANALYSIS**

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### **Abstract**

Pompe's disease is caused by deficiency of acid  $\alpha$ -glucosidase, the single enzyme involved in lysosomal glycogen degradation. Patients suffer from generalised muscle weakness, resulting in cardio-respiratory failure within a year after birth, in the most severe clinical subtype. Less severely affected patients do not have cardiac problems, but become wheelchair bound and require respiratory support.

The sequence of the acid  $\alpha$ -glucosidase gene is known since 1988/1990. There are at present 170 mutations known compared with the original cDNA sequence that was filed at: EMBL/Gen Bank/ DDBJ; accession number Y00839 or accession numbers: X55079-X55097 for the  $\alpha$ -glucosidase exon sequences including boundaries.

Fifty-five of these mutations are silent or do not cause a form of Pompe's disease (polymorphisms). The remaining 115 mutations are pathogenic through interference with protein synthesis, folding, post-translational modification and transport, or through direct interference with enzymatic function.

Pompe's disease is heterogeneous. All kind of mutations occur, but single base changes are the most prominent. There are several recurrent mutations, some of these are widespread in the Pompe patient population, and others are concentrated in certain geographic areas and sub populations.

We have summarised the currently known mutations and polymorphisms of acid  $\alpha$ -glucosidase and we have tried to visualise their geographic distribution, as a tool for DNA based diagnosis and counselling of patients and families with Pompe's disease.

## EARLY DETECTION OF POMPE DISEASE

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### **Abstract**

We have developed a screening method for the detection of Pompe disease from dry blood spot samples. The method is also adaptable to new born screening for Pompe and other lysosomal storage disorders that are treatable with technologies currently available or under evaluation in clinical trials.

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## SLEEP DISORDERED BREATHING AND RESPIRATORY FAILURE IN POMPE'S DISEASE

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### Abstract

#### BACKGROUND

Sleep disordered breathing (SDB) and respiratory failure (RF) are common complications of neuromuscular disorders. Aim of the study was 1) to describe lung and respiratory muscle function in subjects with glucosidase deficiency II (GSD), 2) to evaluate the prevalence of SDB and RF, 3) to determine daytime predictors of SDB and RF and 4) to evaluate the impact of nocturnal noninvasive ventilation.

#### METHODS

Twenty seven subjects with juvenile GSD ( $n = 7, 12 \pm 10$  years) or adult GSD ( $n = 20, 47 \pm 12$  years) were studied with polysomnography, lung and respiratory muscle function tests, and blood gas analysis. Seven patients were treated with nocturnal noninvasive ventilation (NIV).

#### RESULTS

26/27 subjects were ambulating with or without aid. Vital capacity (VC) was reduced in 17/27 subjects. VC correlated with peak inspiratory muscle pressure (PIP,  $R = 0.61$ ), respiratory muscle strain ( $R = -0.68$ ) and gas exchange by day ( $\text{PaO}_2$  and  $\text{PaCO}_2$ ) and night ( $\text{SaO}_2$ ;  $p < 0.005$  for all). Diaphragm weakness (DW) was present in 13 subjects; in those with juvenile GSD after a disease course of  $9 \pm 4$  years, in those with adult GSD after  $14 \pm 7$  years. DW was associated with SDB (12/13) and respiratory failure (10/13). The degree of SDB correlated with VC ( $p < 0.005$ ), and the most severe form, continuous nocturnal hypoventilation could be predicted from  $\text{VC} < 40\%$  predicted (sensitivity 80%, specificity 93%). NIV, instituted for daytime respiratory failure or nocturnal hypoventilation, normalized daytime and nocturnal gas exchange ( $p < 0.005$ ).

#### CONCLUSION

SDB and RF are frequent complications in GSD that are mainly due to progressive diaphragm weakness. In contrast to other neuromuscular disorders it occurs in patients still ambulating. Monitoring of respiratory function, including polysomnography, is essential to detect respiratory limitations in time. NIV is an effective treatment option.

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## METABOLIC ASPECTS OF POMPE DISEASE

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### Abstract

Glycogen Storage disease type II (GSD II) was first described in 1932 by Pompe and later shown to be caused by deficiency of the lysosomal enzyme acid 1-4  $\alpha$ -glucosidase. The degradation of glucose polymeres taken up by the lysosome does not provide significant amounts of glucose molecules for cytoplasmic glycolysis or extrahepatic glucose homeostasis. Thus hypoglycemia, the major cause of morbidity in the “cytoplasmic GSDs” is not a feature of GSD II. Morbidity and mortality are caused by the impairment of skeletal and cardiac muscle function leading to death from respiratory or cardiac failure within the first two years of life in the severe neonatal form. The infantile and juvenile forms are restricted to skeletal muscle in most cases and may show slight elevation of liver enzymes without clinically significant impairment of liver function.

The metabolic and/or structural consequences of lysosomal glycogen storage that cause progressive impairment of mechanical muscle function are not well understood. Accumulation of glycogen within the lysosome causes an increase of the lysosomal volume exaggerated by the hygroscopic properties of glycogen. The volume expansion may cause a rise in intravacuolar pH leading to progressive impairment of all lysosomal enzymes. Lipofuscin as a peroxidation product of intralysosomal material is supposed to promote apoptosis and thus programmed cell death. The limited regenerative capacity of muscle cells from satellite cells leads to progressive muscle wasting.

It was suggested that swollen lysosomes disturb the architecture of the contractile machinery by interruption of myofibrils. Degradation of myofibrils adjacent to or inside the vacuoles will further affect the mechanical properties of affected cells. This mechanical component may explain 50% of the loss of muscular function in  $\alpha$ -glucosidase knock-out mice. Bodamer and colleagues described an increased body protein turnover in GSD II most likely due to this increased muscle protein degradation.

Whether acid 1-4  $\alpha$ -glucosidase exerts additional effects on lysosomal (membrane) function or even in endosomes and/or the trans-golgi network remains to be investigated. The very recent finding of impaired trafficking of the dystrophin associated protein complex (DAP) through the endosome-trans-golgi network in cultured GSD II myoblasts supports this hypothesis and the idea of a secondary DAP deficiency contributing to muscular impairment in GSD II.

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## EFFECTS OF L-ALANINE IN GLYCOGEN STORAGE DISEASE TYPE II

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### Abstract

Glycogen storage disease type II (GSD-II) is caused by a deficiency of lysosomal  $\alpha$ -glucosidase (acid maltase). The resulting intra-lysosomal accumulation of glycogen leads to impairment of both cardiac and skeletal muscle function in the neonatal form (Pompe disease) and to a variable skeletal myopathy in the late-onset forms. The pathogenesis of the myopathy is unknown but our group and others have shown that whole body protein breakdown in individuals with GSD-II is significantly increased which is most likely secondary to increased muscle protein turnover.

We speculated that reducing muscle protein turnover may improve muscle function and in fact some improvement has been achieved by giving high-protein diet. However this diet is difficult to sustain in GSD-II, may cause weight gain and further impairment of respiratory function. Instead we choose L-alanine as a possible dietary substrate as it is known to decrease catabolism of branched-chain amino acids for energy production and may therefore conserve muscle protein and function. L-alanine is a gluconeogenic amino acid that plays a central role in energy metabolism in muscle and in glucose homeostasis in liver.

We have tested the effects of a four week oral supplementation of L-alanine (10 g per 70 kg body weight) on leucine kinetics (as a measure of whole body protein turnover), glucose kinetics and energy expenditure in five juveniles and adults with GSD-II and seven healthy adult control subjects. In the baseline studies, the resting energy expenditure (REE) of the patients with GSD-II, although higher than controls was not significantly different. Following alanine supplementation REE did not change in control subjects ( $23.22 \pm 3.41$  vs.  $25.33 \pm 5.05$  kcal/kg/d). However in the patients with GSD-II, after alanine the REE decreased ( $31.04 \pm 11.77$  vs.  $24.68 \pm 9.28$  kcal/kg/d,  $p < 0.05$ ) to values seen in controls. In subjects with GSD-II baseline leucine flux (protein turnover) was increased compared to control subjects ( $p < 0.005$ ) and decreased after alanine ( $p < 0.004$ ): leucine flux  $135.23 \pm 15.7$  vs.  $104.4 \pm 6.8$   $\mu\text{mol/kg/h}$ . Leucine oxidation decreased to values lower than those observed in control subjects  $20.72 \pm 8.56$  vs.  $13.76 \pm 1.79$   $\mu\text{mol/kg/h}$  ( $p < 0.001$ ).

There were no side-effects related to L-alanine supplementation and some participants with GSD-II reported a slight improvement in muscle function although muscle function was not tested formally. Long-term experience with L-alanine supplementation in GSD-II is limited. Further studies are needed to investigate the possible benefits of L-alanine as a supplement to stabilise muscle metabolism until enzyme therapy becomes available for all patients.

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## **SYMPTOMATIC THERAPY IN LATE ONSET ACID MALTASE DEFICIENCY**

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### **Abstract**

The effectiveness of symptomatic therapy for late onset AMD has been controversial since first proposed in the early 80's. Some investigators have found it to be effective while others have not.

The goal of symptomatic therapy is to reduce skeletal muscle glycogen deposition, increase mobilization of skeletal muscle fatty acids and increase muscle contraction. Symptomatic therapy consists of high protein-low carbohydrate nutrition, L-alanine and daily submaximal aerobic exercise. By far the most important element of symptomatic therapy is FULL PATIENT COMPLIANCE.

Collation and analysis of over 80 late onset patients treated over the last 20 years are in progress. We present results of the response of childhood, juvenile and adult patients to symptomatic therapy.

The place of symptomatic therapy prior to and in conjunction with enzyme replacement therapy will be discussed.

## **IPA / ERASMUS MC POMPE QUESTIONNAIRE: GOALS, DATA COLLECTION AND PRELIMINARY RESULTS**

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### **Abstract**

A good understanding of the natural course and a broad overview of the patient population are important in the light of the current developments on enzyme replacement therapy for Pompe's disease. Information on the late onset patient population, representing the largest group of Pompe patients, is fragmented so far. In an attempt to give a comprehensive overview of the late onset patient population, and to study how we can monitor and assess the disease process in the best way possible in future, a survey was carried out in cooperation with the International Pompe Association (IPA).

Participants were identified through patient organizations affiliated with IPA in 5 countries: The Netherlands, Germany, the United Kingdom, the United States, and Australia. A total of 250 patients from 12 countries returned a completed questionnaire. Data were obtained on the patients' medical history and current situation. In addition, the questionnaire contained a number of previously validated disability, handicap and quality-of-life scales.

At the International Pompe Conference 2003, data are presented on presenting symptoms, age at diagnosis, diagnostic delay and diagnostic methods in the different countries. Furthermore, the patient populations from the different countries are compared with respect to age and gender distribution and disease severity. As indicators of disease severity, wheelchair and ventilator use among the participants and the scores on the Rotterdam 9-items handicap scale and SF-36 health-related quality of life questionnaire are used. In a subset of 54 patients the natural course is discussed in detail and some examples of the progression of the disease in individual patients are given.



## TESTING OF MUSCLE STRENGTH AND MOTOR PERFORMANCE IN PATIENTS WITH POMPE'S DISEASE

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### Abstract

In 1999 four patients with infantile Pompe's disease and three patients with late onset Pompe's disease were enrolled in a single-centre open-label study and treated intravenously with recombinant human alpha-glucosidase. Assessments for muscle strength and motor performance were performed by a pediatric physiotherapist at baseline and at regular time points thereafter.

Infantile Pompe's disease is a lethal cardiac and muscular disorder. Loss of muscle strength prevents infants from achieving developmental milestones like sitting, standing and walking [1-3]. Achievement of major motor milestones are valid endpoints for therapeutic studies for infantile Pompe's disease [1]. Therefore psychomotor development was assessed using the Alberta Infant Motor Scale (AIMS) [4] and the Gross Motor Function Measure (GMFM) [5].

The symptoms of late-onset Pompe's disease are restricted to skeletal muscle. The disease presents as a proximal myopathy. Limb-girdle weakness is often the first sign and a scoliosis may develop [2,6]. Muscle strength in the late onset patients was measured with the Citec Hand Held Dynamometer (HHD) [7,8]. The muscle groups tested were neck flexion, neck extension, shoulder abduction, elbow flexion and extension, wrist extension, hip flexion and abduction, knee extension and flexion, ankle dorsiflexion and plantar flexion. Motor performance was evaluated using the GMFM, via timed tests and, if possible, a maximal incremental cycling test [5].

For the patient, motor performance is more relevant than strength; the GMFM proved to be suitable in this respect. When patients have sufficient mobility, timed tests can be used as an alternative assessment.

Knowledge about the course of the disease with respect to muscle strength and function is essential for future trials. The assessments described above have proven useful in this trial.

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## **BENEFITS OF PHYSICAL THERAPY FOR ADULT ONSET POMPE PATIENTS**

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### **Abstract**

Presentation of treatment in a rehabilitation clinic.

Report about 13 patients with adult onset Morbus Pompe with 25 treatment periods (6 patients with 1 treatment period; 5 patients with 2, 1 patient with 4 and 1 patient with 5 treatment periods).

The patients were treated with daily individual physiotherapy with the main point in low endurance exercises according to their physical status. Another active treatment was medical training therapy with body building machines, but controlled intensively by physiotherapists and with low endurance exercises too. Those patients, who had no cardiac or pulmonary problems had special warm bathes with rising the body temperature to 1,0 degree C over starting body temperature.

They got special middle frequency current to stimulate muscles of the lower limb or the paralumbar muscles.

Further therapies were ergotherapy, massages, ultrasonic treatment and diathermie. They were allowed to use the swimming bath, if there was no cardiac problem.

The patients were tested by physiotherapists for muscle strength and endurance capacity of repeating movements in the beginning and at the end of clinical stay.

Most patients had improvements of muscle endurance and capacity of repeating movements and longer walking distance, but only little or no improvement of muscle strength.

The laboratory findings did not change significantly.

## EXPERIENCE WITH ENZYME REPLACEMENT THERAPY IN PATIENTS WITH MUCOPOLYSACCHARIDOSE TYPE I

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### Abstract

#### INTRODUCTION

MPS I (also known as Hurler, Hurler-Scheie and Scheie syndrome ) is a genetic disease caused by a deficiency of the enzyme alpha-L-iduronidase. The deficiency leads to the accumulation of complex carbohydrates (GAG) in the lysosomes of the cells, resulting in an progressive and multi-system disease. Recently a phase III trial, double blind, placebo-controlled and multi-center was initiated to assess the safety and efficacy of treatment with recombinant  $\alpha$ -Iduronidase.

#### METHODS

The Phase III study was designed to confirm the safety and efficacy of Enzyme Replacement Therapy (ERT) in Patients with Mucopolysaccharidosis Type I. This was a randomized, double-blind, placebo-controlled study involving 45 patients at 5 sites in 4 countries. The enzyme (alpha-Iduronidase) or placebo was administered intravenously once a week for 26 weeks. At the end of the double-blind phase, all 45 patients entered an open-label extension study. The trial design focussed on primary endpoints (lung function and six-minute walk test). Secondary and tertiary endpoints included urinary GAG excretion, liver enlargement, joint range of motion, sleep apnea and cardiac function.

#### RESULTS

ERT led to a rapid and significant reduction in urinary GAG level. In the open-label extension study, treated patients maintained their low levels which continued to come down slowly, and placebo crossover patients now receiving the enzyme showed a similar reduction in GAG level. Reduction in hepatomegaly was observed. In the double-blind phase patients receiving the enzyme showed a 18.9 % reduction in liver volume compared to a slight increase in placebo patients after 26 weeks. The difference between groups was highly significant. In the open-label extension phase, patients receiving the enzyme from the beginning showed an additional small reduction in liver volume, while the placebo patients who crossed to therapy now showed a 12.6% reduction in liver volume. ERT led to a statistically significant increase in percent predicted FVC. In the double-blind phase, treated patients showed a mean increase of 4.9 percentage points at Week 26, compared to a -0.7 mean decrease in placebo patients. The difference between groups, 5.6 percentage points, was significant with a p-value of 0.009. Patients who crossed over from placebo to Aldurazyme did show a similar increase in FVC. In the double-blind phase, patients receiving placebo showed an increase in the 6-Minute Walk Test (6MWT) distance of nearly 20 m, whereas placebo patients showed a decrease of nearly 20 m. The difference between groups was 38 m, and approached statistical significance. In the extension phase, patients who continued on treatment showed an additional 20 meter increase. The placebo crossover patients confirmed the treatment effect as they increased by a similar magnitude as the enzyme patients in the double-blind phase. The difference from week 26 was significant.

#### CONCLUSION

Enzyme Replacement Therapy in patients with MPS I has been demonstrated to rapidly decrease lysosomal storage of Glycosaminoglycans, produce clinical improvement in respiratory function and functional capacity. The product was well tolerated and has a favorable risk-benefit profile. The drug Aldurazyme has been approved in the US and in Europe.

## **GENZYME'S POMPE DEVELOPMENT PROGRAM**

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### **Abstract**

Genzyme's recent (September) public announcement on plans to expand the Pompe program indicates that significant progress has been made in the past year – and represents an important, exciting step forward in our goal to bring enzyme replacement therapy to more patients in need and to strengthen our development program. The key features of our accomplishments and current plans will be described.

A brief historical summary of commercial development efforts will be given to provide perspective and clarity on Genzyme's current position in the overall path toward regulatory approval for recombinant human acid alpha-Glucosidase (rh-GAA). The Pompe development program will be described in the context of the quality and regulatory standards that must be applied to therapeutic drug development - with emphasis on the unique challenges posed by the variability and complexity of Pompe disease.

The product development plan requires careful integration of clinical and regulatory strategies with the ability to supply sufficient product reliably and that meets quality standards. I will review the progress made in our manufacturing development and capacity expansion efforts and summarize our goals and expectations concerning product supply.

Although the program has reached an exciting, important phase – with solid development accomplishments and clarity of the plan going forward – we acknowledge that much remains to be done in our goal to offer this therapy to patients globally, as quickly as possible. Genzyme is committed to that goal – the Pompe program remains our largest development program ever – and we remain committed to effective partnering and communication with patient groups which is crucial to the success of the program.

## ROTTERDAM EXPERIENCE WITH ENZYME REPLACEMENT THERAPY FOR POMPE'S DISEASE

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### Abstract

Pompe's disease or Glycogen storage disease type II (GSD II) is an inherited myopathy. The characteristic lysosomal glycogen accumulation is caused by alpha-glucosidase deficiency. Our research has focussed on the development of enzyme replacement therapy for Pompe's disease and has led to large-scale production of human recombinant alpha-glucosidase in milk of transgenic rabbits. In a phase II study seven patients were treated; four with the most severe infantile form and three with the late onset form of Pompe's disease.

The first results were obtained for the infants, enrolled at ages of 2.5–8 months [1]. It was shown that the treatment was tolerated well. The alpha-glucosidase activity in muscle normalized, tissue morphology improved, the cardiomyopathy resolved significantly and patients survived longer. Three of the four patients are still alive at the age of five years. We have learned, however, that it is of extreme importance to start treatment early in order to obtain a good motor outcome and prevent respiratory failure.

The three patients with late onset Pompe's disease were 12, 16 and 32 years old at start of enzyme therapy. Clinical symptoms varied. They were all wheelchair bound. The two older patients were ventilator dependent and showed a significant deterioration of pulmonary function before start of treatment. After 4 years of treatment their pulmonary function has stabilized or improved. The alpha-glucosidase activity in muscle increased. The best improvement of muscle strength and function was obtained in the youngest and least affected patient. This patient started to walk after 4 years of wheelchair dependency. All patients report less fatigue and more energy.

In conclusion, recombinant human alpha-glucosidase from rabbit milk has positive effects in Pompe's disease. There is all reason to continue the development of enzyme replacement therapy.

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## ENZYME REPLACEMENT THERAPY WITH RECOMBINANT HUMAN ACID ALPHA GLUCOSIDASE IN INFANTILE POMPE DISEASE: DUKE EXPERIENCE

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### Abstract

**OBJECTIVE:** Glycogen Storage disease type II (GSD II), also known as Pompe disease, is caused by a deficiency of the lysosomal enzyme acid alpha glucosidase (GAA). Infantile onset Pompe disease is characterized by severe, progressive cardiomyopathy, muscle weakness, respiratory insufficiency, and death usually by one year of age. Experience from 11 patients from two open label Phase I / Phase II clinical trials exploring the safety and efficacy of enzyme replacement therapy with Chinese Hamster ovary cell derived recombinant human acid alpha glucosidase (rhGAA) are discussed. All patients had cardiomegaly and cardiomyopathy by age 6 months, and a GAA activity of <1% in cultured skin fibroblasts by 4 MUG assay. In the first study 3 patients with infantile onset GSD II were initially treated with rhGAA at 5 mg/kg IV twice weekly (ages 4.2 months, 2.8 months and 2.4 months at the time of their first infusion). In the second study 8 patients with infantile onset Pompe disease received rhGAA at 10 mg/kg IV weekly; the age range of patients at the time of their first infusion was from 2.7 to 14.6 months; median age 4.7 months. Survival, cardiac status as measured by 2D cardiac Left Ventricular Mass Index (LVMI), ventilator use, motor development as measured by Alberta Infant Motor Scale (AIMS) and mental development as measured by the Bayley's mental development index were the clinical endpoints.

**RESULTS:** Currently, 4/11 patients treated with rhGAA are alive, (mean age 35.1 months; range 28.0 - 50.3 months) one from the first trial and 3 from the second trial. All 4 surviving patients are ambulatory and ventilator free. The mean duration of rhGAA treatment is 31.8 months (range 25.1 - 47.9 months). There have been 7 deaths, (2 in the first trial and 5 in the second trial) all unrelated to rhGAA. In 2 patients death occurred after withdrawal from rhGAA treatment; in 3 additional patients death occurred due to family decisions against the use of long term life support technology.

In the first trial all patients received rhGAA at 5 mg/kg twice weekly initially. Cardiac LVMI decreased in all 3 patients on this dose, however skeletal motor response was variable. One patient showed marked motor improvement and continued on the same dose of rhGAA. 2/3 patients experienced a clinical motor decline and a concomitant rise in anti-rhGAA titers. These 2 patients received additional doses of rhGAA ranging from 10mg/kg x2 per week to 10 mg/kg x5 per week, as well as other immune tolerance management approaches, unsuccessfully. Both patients subsequently became ventilator dependent and died at ages 50.2 and 44.8 months. The surviving patient has recently transitioned to rhGAA at 20mg/kg/every other week and is currently 50.3 months old. This patient continues to have normal motor and mental milestones and is ventilator free.

In the second trial all 8 patients received a dose of 10 mg/kg/week of rhGAA. At present, one patient has transitioned to 20 mg/kg every other week. Cardiac LVMI decreased markedly in all patients. As in the previous trial, motor response has been variable. 3/8 surviving patients have achieved normal motor development that allows them to ambulate; all 3 are ventilator free. In the 3 surviving patients, Bayley's mental development index has been maintained. These patients are currently 33, 29.7 and 28.3 months (mean age 30.3 months). The remaining 5 patients had variable motor gains, but they all plotted below the 5th percentile on AIMS. Mean age at death in the 5 patients was 22.9 months (range 14.7 - 33.8 months).

All patients have developed antibody titers against rhGAA. Most patients have experienced infusion-associated reactions, the majority of them have been mild.

**CONCLUSIONS:** rhGAA appears to have an acceptable safety profile. rhGAA markedly decreased cardiac LVMI in all patients, no matter what the stage of the disease. Skeletal muscle response has been variable. Factors responsible for this variability are not clearly understood but may include age and stage of damage to muscle ultrastructures at onset of treatment, differences in rhGAA uptake and processing in different organs/muscle types, muscle fiber type, presence/absence of mutant enzyme, effect on antibodies to rhGAA in biodistribution among others. Additional data on the long-term safety and efficacy of rhGAA, as well as on the characterization of factors involved in the differential response to treatment are needed.

### Key references

- [1] Amalfitano A, Bengur A, Morse R, Majure J, Case L, Veerling D, et al.: Recombinant human acid  $\alpha$ -glucosidase enzyme therapy for infantile glycogen storage disease type II patients: Results of a phase I/II clinical trial. *Genetics in Medicine*, Vol 3, No. 2, March/April, 2001
- [2] Kishnani P, Voit T, Nicolino M, Tsai C-H, Herman G, Waterson J, et al.: Enzyme replacement therapy with recombinant human acid alpha glucosidase (rhGAA) in infantile Pompe disease (IPD): Results from a Phase 2 study. *Pediatr Res* 2003;53(4):259A (abstract)

## **EXPERIENCES OF PARENTS OF A POMPE INFANT UNDER TREATMENT**

**Y. Wijnen**

Belgium

### **Abstract**

This presentation will be given by the father of a child with infantile Pompe disease, who has participated in the first ERT trial in Rotterdam and who is currently receiving treatment in a compassionate use program. It will cover the experience of participating in a trial and the effect it has on the family that accompanies the patient-child during and after the trial.

### **Key reference**

- [1] Y. Wijnen:  
“Sari’s Story”  
[www.worldpompe.org/sari.html](http://www.worldpompe.org/sari.html) *or* [schaller-family.bei.t-online.de/PompeNeues20030304.html#Sari](http://schaller-family.bei.t-online.de/PompeNeues20030304.html#Sari)

## **EXPERIENCES OF A JUVENILE POMPE PATIENT UNDER TREATMENT**

**Tiffany House**

USA

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### **Abstract**

This is an account of my experiences as a juvenile patient in a clinical trial with enzyme replacement therapy for Pompe's disease. My treatment with ERT spans a period of time from June 1999, when I first received transgenic enzyme, to the present. I now receive the CHO enzyme, Myozyme.



## POTENTIAL OF GENE THERAPY FOR GSD-II

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### Abstract

Glycogen Storage Disease Type II (GSD-II) represents a unique disorder of muscle, that unlike most myopathies, presents an opportunity for realistic treatment *via* several molecular modalities. Enzyme replacement studies (both in animal models and humans) confirms that intra-venous administration of adequate levels of the human acid alpha glucosidase (AAG) protein can result in muscle cell uptake of the recombinant enzyme, and prevention and/or correction of intra-muscular glycogen storage. Enzyme therapy has limitations however, including the need for large-scale production, repeated infusions, and the need for production of the enzyme in a fashion that retains both muscle lysosome-targeting efficiencies and enzymatic activity of endogenous AAG. We have undertaken to investigate an alternative and/or augmentative approach to enzyme replacement-based strategies, by investigating the potential of gene therapy for treatment of GSD-II patients. [1]

Theoretically, delivery of the AAG gene to the appropriate tissue could result in high enough levels of AAG production to correct the disease manifestations. To achieve this goal, however, is not easy, and is limited by several obstacles. For example, direct delivery of the AAG gene into muscle tissues can result in localized expression of AAG protein, but this approach is extremely limited in adult animal studies by the number of muscle cells that can be treated by single (or multiple) intra-muscular injections. The latter issue has been one that currently limits the potential of gene therapy to treat other muscle diseases, such as Duchenne Muscular Dystrophy. However, we and others have shown that efficient delivery of the AAG gene into the livers of several animal models of Pompe disease, *via* use of several gene therapy vectors, can result in secretion of the AAG protein into the bloodstream. [2,3] We have also confirmed that if sufficient amounts of the AAG protein are hepatically secreted, the AAG protein can then distribute throughout ALL of the muscles of the treated animal, (much like enzyme infusion therapy predicts). With the use of adenovirus based vectors, we have further found that hepatic secretion of AAG can also result in correction of glycogen accumulation in multiple muscles of the treated animals, and in our latest results, prevention of muscle weakness. In fact, the process is so efficient, that several hurdles raised as potential limitations to enzyme replacement therapies (such as lack of adequate skeletal muscle targeting, and/or age related variations in skeletal muscle uptake) can also be overcome by the adenovirus mediated gene therapy approach. Furthermore, we have shown that the efficacy of the approach can be of a long duration, i.e.: for at least 6 months despite the presence of immune responses to the AAG protein, and potentially much longer in the absence of anti-AAG antibody production. [4]

The key limitation to this approach are vector induced acute toxicities, which can be significant at the predicted higher vector dosages required to achieve efficacy *via* a liver targeting strategy. [5] There are several unknowns however, including whether human hepatocytes (*in vivo*), can be targeted with the AAG as efficiently as animal hepatocytes have been. Despite the several theoretical limitations, we remain optimistic that gene therapy for GSD-II is a goal that can be successfully achieved in a realistic time frame, based upon: 1) our results to date, 2) observations published by numerous groups within the GSD-II research community, and 3) research observations made by the research community at large. Currently, we are optimizing this form of gene therapy, to allow for maximal efficacy at the lowest vector dosages, in anticipation of a gene therapy trial in adult GSD-II patients.

### Key references

- [1] Chen YT, Amalfitano A  
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- [2] Amalfitano A, McVie-Wylie AJ, Hu H, Dawson TL, Raben N, et al.:  
Systemic correction of the muscle disorder glycogen storage disease type II after hepatic targeting of a modified adenovirus vector encoding human acid-alpha-glucosidase.  
Proc Natl Acad Sci U S A 1999, 96, 8861–8866
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Intercellular transfer of the virally derived precursor form of acid alpha-glucosidase corrects the enzyme deficiency in inherited cardioskeletal myopathy Pompe disease.  
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Efficacy of gene therapy for a prototypical lysosomal storage disease (GSD-II) is critically dependent on vector dose, transgene promoter, and the tissues targeted for vector transduction.  
Molecular Therapy 2002, 5, 436–446

## LIST OF REGISTERED PARTICIPANTS

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3 Bajbouj, Manal	Children's Hospital, Mainz University	Germany	speaker
4 Bakker, Johan	Nijmegen	Netherlands	patient / family
5 Bakker, Klaas	Nijmegen	Netherlands	patient / family
6 Bañón Hernández, Antonio-M.	Alcantarilla	Spain	patient representative
7 Bodamer, Olaf	University Children's Hospital, Vienna	Austria	speaker
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60	Meyer-Hohnloser, Henning	Wiesloch	Germany	expert
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62	Morrison, Mrs.	Seaforth / Neutral Bay NSW	Australia	patient / family
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64	Muir, Barbara	Buriton, Peters Field, Hampshire	UK	patient / family
65	Müller, Willi	Video Team Kangaroo	Germany	staff
66	Müller-Felber, Wolfgang	Munich	Germany	speaker
67	O'Callaghan, Michael	Genzyme Corporation	USA	expert
68	O'Donnell, Kevin	Edinburgh	Scotland	speaker
69	Ollington, Frank	Genzyme Corporation, Cambridge, MA	USA	speaker
70	Paradis, Khazal	Genzyme Corporation	USA	expert
71	Penkert, Susanne	Amsterdam	Netherlands	patient / family
72	Pipe, Daniel	Lowell, MI	USA	patient / family
73	Podskarbi, Teodor	Moleculargenetic metabolism laboratory, Munich	Germany	expert
74	Raben, Nina	ARB. NIAMS, NIH, Bethesda, MD	USA	speaker
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76	Reuser, Arnold	Clinic. Genetics, Erasmus MC, Rotterdam	Netherlands	speaker
77	Sawayer, Patricia	Genzyme Corporation	USA	expert
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80	Schlassa, Detlef	Lörrach	Germany	expert
81	Schoneveld van der Linde, Maryze	International Pompe Association, Baarn	Netherlands	patient representative
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84	Skrinar, Alison	Genzyme Corporation	USA	expert
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92	Wasser, Gerhard	Duisburg	Germany	expert
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94	Welling, Donald	SHG Glykogenose Deutschland, Büren	Germany	patient representative
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102	Wolf, Werner	Wiesloch	Germany	patient / family
103	Zimmerman, Marsha	San Antonio, TX	USA	patient representative
104	Zimmermann, Charles		Germany	guest of honor
105	Zimmermann, Johanna		Germany	guest of honor

## USEFUL LINKS



**[www.worldpompe.org](http://www.worldpompe.org)**  
IPA, International Pompe Association



**[www.pompe.com](http://www.pompe.com)**  
Pompe information of Genzyme Corporation



**[www.pompecenter.nl](http://www.pompecenter.nl)**  
Pompe informations of Erasmus University Rotterdam



**[maelstrom.stjohns.edu/archives/gsdnet.html](http://maelstrom.stjohns.edu/archives/gsdnet.html)**  
GSDnet, glycogenosis mailing list



**[www.amda-pompe.org](http://www.amda-pompe.org)**  
AMDA, Acid Maltase Deficiency Association



**[www.pompe.org.uk](http://www.pompe.org.uk)**  
Pompe Group of the Association for Glycogen Storage Disease (UK)



**[www.glykogenose.de](http://www.glykogenose.de)**  
Selbsthilfegruppe Glykogenose Deutschland e. V.  
(German Glycogenosis Patient Group)

Selbsthilfegruppe  
Glykogenose  
Deutschland e.V.

**[www.vsn.nl](http://www.vsn.nl)**  
VSN, Vereniging Spierziekten Nederland  
(Dutch Neuromuscular Diseases Association)



**[www.glycogenoses.org](http://www.glycogenoses.org)**  
AFG, Association francophone des glycogénoses  
(French Glycogenosis Patient Group)

**[home.arcor.de/fobrokel/pompe2003/](http://home.arcor.de/fobrokel/pompe2003/)**  
International Pompe Conference 2003 and follow-up

**[www.morbus-pompe.de](http://www.morbus-pompe.de)**  
Private Pompe website of Thomas Schwagenscheidt, Germany

**[www.morbus-pompe.info](http://www.morbus-pompe.info)**  
Private Pompe website of Thomas Schaller, Germany

## SUPPLEMENT

### Manuscript of Tiffany's video presentation

#### **“Experiences of a Juvenile Patient Under Treatment for Pompe's Disease”**

*By Tiffany House*

In 1995, the week before my twelfth birthday, I was diagnosed with Pompe's disease. We were told that there was no treatment or cure for Pompe's disease and that I would probably not live to be twenty. That was over eight years ago ---- I am now twenty years old.

In June 1999, I entered a clinical trial with enzyme replacement therapy in Rotterdam, the Netherlands. I was the first juvenile patient in the world to receive treatment and have now been on therapy for over four years.

I have been through many changes in the past eight years. I was an adolescent when I was diagnosed and from that point on my life changed forever. I went from being “just like everyone else” to being a sick child with a very rare disease. And along with the disease came many issues with which I had to deal.

At twelve I was still ambulatory, but I was having more and more difficulty getting around. I had frequent bouts of pneumonia, which left me weaker than before, but I continued to attend school, in spite of being frequently ill and missing weeks at time. By the time I was thirteen, I was too sick and frail to keep up the pace of school. I could no longer go up stairs, and just walking from class to class while carrying books was more than I could handle. I had to withdraw from school and I started home schooling in my seventh grade year.

I think one of the hardest aspects of having this disease has been missing out on so much of my teen years. Sometimes, when I think of everything that I have missed out on, I get really depressed. I mean, I missed out on being with friends, going to school dances, dating, learning to drive, graduating from high school and countless other things. It was really difficult for me to accept change, to realize that I could no longer do the things that I had done before, because my condition was so rapidly deteriorating.

One of my biggest challenges happened when I was sixteen. I had to start using a wheelchair because I could no longer walk. I had developed severe scoliosis, a side effect of the disease, and breathing on my own was very difficult. Becoming wheelchair bound was one of the hardest things for me to accept, but I didn't have a choice.

My mother and I spent nine months alone in Rotterdam. The first six months of the trial were difficult. Weekly infusions, frequent testing, biopsies, physical therapy and homework became the things around which my world revolved. I missed my family, my home and my pets, but things got better when my sister, Andrea, came to live with us at Christmas. I now had my sister to talk to, and Andrea loved being with us in Rotterdam. This was a good situation for “the girls,” but we missed Randy and Dad who were still on their own in Texas.

Although I will always be thankful that I was in the first clinical trial, it was not an easy period to go through. We were all constantly worried; worried that the treatment was not working; worried that the dosage was too low; worried that the trial would be discontinued... but the biggest worry was that my scoliosis was becoming critical and that surgery could no longer be postponed. We had hoped that my pulmonary functions would increase with ERT, which would have made it safer to undergo surgery, but this had not happened. We had a dilemma. I had to have back surgery; we wanted to return to the US to have the surgery, but I had to continue ERT treatment in the Netherlands.

After months of deliberation and consultation with specialists in both the Netherlands and in the US, we were able to get approval for administered of my enzyme replacement therapy at the Mayo Clinic in the US where I was to have back surgery. In June 2000, these plans were in place, and we left the Netherlands after 15 months of being away



from home. Several months prior to this, the dosage on the juvenile patients was increased for the second and final time. I underwent the first of two surgeries for scoliosis several days after arriving at the Mayo Clinic. I remained in the hospital for three months and during this time I continued to receive weekly infusions with the transgenic enzyme sent from the Netherlands.

As my release from the Mayo approached, we were faced with another dilemma. I wanted to go home to San Antonio and receive my treatments there. However, we were not able to get the procedure approved in San Antonio for another 6 months. But we did go home, but we continued to make weekly trips to the Mayo for my infusions.

In April 2001, I received my first infusion at the University of Texas Health Science Center in San Antonio under Dr. Stuart Shapira. Two years had passed since I had first left San Antonio to begin enzyme replacement therapy in the Netherlands.

During the third year of my treatment with the transgenic enzyme I began to improve. After three years of treatment with the transgenic enzyme, I was feeling stronger and happier. I was finally beginning to see a light at the end of the tunnel.

Although I was very encouraged by my new feeling of well-being, new problems were on the horizon.

In July 2002, after months of reduced supply of the transgenic product, Genzyme Corporation decided to cease production of the transgenic enzyme. I reluctantly transitioned to the CHO product, and my dosage was cut in half.

After four months of treatment with the CHO enzyme, I was once again experiencing problems that had previously subsided or diminished. This was a devastating setback for me and for the other transgenic patients that were transitioned to the CHO enzyme.

Genzyme responded to our needs by increasing the dosage of CHO enzyme and starting me and the other “transitioned” patients on Myozyme, the Genzyme produced CHO enzyme.

My situation has improved, but only time will tell if I will regain physical strength and an increase in pulmonary functions. But whatever the outcome I feel good, for me that is, and I am able to do the things that I enjoy.

I am a junior in college at the University of Texas at San Antonio, where I am majoring in English and History. I may not be typical of most students because I love going to school and learning. Being around other people my age and sharing information and experiences is, to me, fun and something that I could not have experienced without the treatment that I am receiving.

I have experienced so much in the last nine years that will, no doubt, continue to influence my entire life. I am so appreciative that a treatment was developed in time for me, and I am saddened to think of those for which no treatment was available and those who are still anxiously awaiting treatment.

I want to thank and remember those that have been special to me during this period of my life—the babies in the infantile trial in the Netherlands, Bart, Jessie, Anouk, and Sari—they will always be in my thoughts; Ivan and Robert, the other juvenile patients; the clinical research team at Sophia’s Children’s hospital, Hannereike, Angela, Leon, Margarite, Danielle, Leona, and Dr. Loonen.

But “thank you” especially to Dr. van der Ploeg and Dr. Reuser for making everything possible and for giving me and other patients hope for the future.

In addition, I want to thank Dr. Roy House and Dr. Jacobson at the Mayo Clinic who were so instrumental in getting me to the Mayo Clinic for my back surgery; Dr. Shaughnessy, the pediatric orthopedic surgeon at the Mayo, that performed by back surgery and his staff who were all so kind and caring. Thank you! I LOVE my “new” body.

And I want to thank Dr. Stuart Shapira, Marsha Zimmerman, Jean Nation, Sidney, and the other wonderful nurses and staff at the University of Texas Health Science Center in San Antonio where I presently receive my treatment.

And thank you, Genzyme, for making this treatment available to me and for working so diligently to provide treatment to ALL Pompe patients as quickly as possible.