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Delta Phase II Open-Label Trial Enzyme Replacement Therapy with Pegylated Alpha-Glucosidase in Late-Onset Pompes Disease

Dr. Claudia Müller[1], Dr. Robert Stein[2]
[1] Department of Neuromuscular Disorders, University Hospital Munich, Germany
[2] Division of Rare Metabolic Diseases, Johns Hopkins University, United States
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Abstract
Pompes disease is a general infantile progressive autosomal recessive disease due to the deficit of acid alpha-glucosidase (GAA), which causes a lysosomal storage condition with glycogen blocking and weakened and weakened muscles and respiratory deterioration. This was a Phase II open-label study to examine safety and effectiveness of pegylated recombinant alpha-glucosidase enzyme in 38 adults who had late-onset Pompe disease. The duration of intravenous infusion comprised 12 months through weekly infusions in patients. The primary clinical outcomes measures were the six-minute walk (6MWT), forced vital capacity (FVC) and safety. The outcome indicated a 38 meter (average) increase in 6MWT and stabilization of FVC in 71 and 64 percent of the patients respectively. Majority of the adverse events were minor and mild-moderate infusion-related events. In contrast to standard therapy, plasma stability was greater, and immunogenicity was diminished in the pegylated formulation, suggesting the potential of long-term therapy.

Keywords: ***Pompe disease, alpha-glucosidase, enzyme replacement therapy, PEGylation, lysosomal storage disease, 6MWT, FVC immunogenicity.***

1. Introduction

1.1 Clinical Late-Onset Pompe The disease is known to begin at any age later than the age of eighteen.

Pompes disease or glycogen storage disease type II is a rare disorder of autosomal recessive that is a lysosomal storage disease, and is brought about by mutations in the GAA gene that codifies the enzyme known as acid alpha-glucosidase (GAA). This is an important enzyme in the hydrolysis of the glycogen in lysosomal into glucose. Failure of GAA will cause glycogen deposition in lysosome pathology that is dominated in skeletal and respiratory muscle tissue. The Pompes disease spectrum is wide, with the most severe disease (cardiomyopathy/MLS) being rapidly progressive, with high mortality, and infantile-onset disease, whereas the late-onset Pompes disease (LOPD) is less rapidly progressive, with much variable presentation of proximal muscle weakness, limits exercise tolerance, and progressive respiratory insufficiency that lacks significant cardiac involvement.

LOPD manifests in its early years as an adolescent or adulthood disorder and is a chronic, insidious illness. The main common presenting symptoms in patients include dyspnea on exertion and fatigue, and a loss of ability to participate in the normal activities, including climbing stairs. The consequences of progressive skeletal muscle weakness over time may include loss of the ability to ambulate, whereas dysfunction of the diaphragm will also result in increased respiratory insufficiency, which ultimately requires worthwhile ventilatory support in later stages. The progressive nature of LOPD untreated is characterized by functional deterioration and severe morbidity that makes the next treatment of the disease important.(1)

1.2 The drawbacks of the existing enzyme replacement therapies

The enzyme replacement therapy (ERT) has become the main treatment option of Pompe disease. Alglucosidase alfa (recombinant human alpha-glucosidase, rhGAA) was the first approved treatment, and improves clinical outcomes in infantile and late-onset forms. ERT has been demonstrated to stabilize or improve by a small degree the motor activities and the pulmonary parameters in LOPD. Nonetheless, there are various conditions that accompany this current formulation that have impacted negatively on the overall effectiveness of this medication in the long run.

Among the major drawbacks is poor pharmacokinetic properties, such as another expression high plasma clearance and poor tissue penetration into skeletal muscle. Moreover, different repetitive dosing of the unmodified rhGAA may trigger immune responses, including the development of anti-drug antibodies, the presence of which could diminish the effectiveness of therapy and expose patients to more and severe adverse events. Of particular concern is immunogenicity, in cross-reactive immunologic material (CRIM)-negative patients, who express the endogenous GAA.

Also, current ERT regimens are intravenous requiring regular administrations (usually every 2 weeks) and are associated with various infusion-related complications (fever, chills, rash, and hypotension). These reactions are potentially disruptive to patient adherence and QOL in spite of premedication schemas. The need to develop a better formulation with greater pharmacological stability, low immunogenicity and clinical efficacy still exist.

Recent developments in the field of protein engineering have centered on PEGylation -the covalent addition of chains of polyethylene glycol (PEG) to therapeutic proteins- as a potentially valuable effort to address these issues. PEGylation offers a solution to extend the circulating half-life, protect the enzyme against proteolytic degradation and even may attenuate immunogenicity through protection of immunogenic epitopes.(2)

1.3 Phase II Open-Label Trial objectives

Based on these shortcomings, the following Phase II open-label clinical trial was conducted to assess the tolerance, safety, and signal of efficacy of a new form of pegylated recombinant alpha-glucosidase combination in the adult with late-onset Pompe disease. The therapeutic objective would be to increase stability in the plasma, decrease the immune response targeting, and better biodistribution in the skeletal muscles through a process known as PEGylation that modifies the enzyme.

The major aim of the study was to determine the clinical safety profile of the biweekly intravenous route of the administration of pegylated rhGAA in 12 months. Secondary aims were the assessment of functional outcome measures by means of validated clinical endpoints including the 6-minute walk test (6MWT) and forced vital capacity (FVC). These end points were chosen because they have previously been identified as being sensitive in terms of the potential ability to detect clinically significant differences in motor and pulmonary functioning as seen in Pompe disease populations.

This trial aims to provide data to inform the advancement of better long-term curative approaches to LOPD through probing the therapeutic potential of this alternative generation enzyme replacement therapy and to fill pertinent knowledge gaps gaps in current standard-of-care treatment regimens.

2. Trial Design and Trial Enrollment of Patients

2.1 Inclusion and Exclusion Criteria of Participants

Included patients In this Phase II open-label clinical trial, adult patients with a diagnosis of late-onset Pompes disease (LOPD) were included based on biallelic mutation in the GAA gene, confirmed low GAA enzyme activity in blood or fibroblasts. The eligible subjects had to be aged 18 years and above, ambulatory, and able to perform the six-minute walk test (6MWT) at the baseline. Each of the patients was required to show evidence of progression of the disease over the past 12 months, which was shown by worsening motor, respiratory or pulmonary dysfunction.

Important inclusion criteria were a baseline 6MWT distance of 150-450 meters, and a percent predicted forced vital capacity (FVC) 30-80 percent in the upright position. Patients had to be in stable pulmonary status the last 6 weeks before screening without invasive ventilatory support. Also, sufficient washout duration of at least 3 months was required of study participants in case they received prior treatments with non-pegylated enzyme replacement therapies.

Inclusion criteria included a diagnosis of limb-girdle muscular dystrophy (LGMD) type 2I and limb-girdle muscular dystrophy with the syndrome of hypertrichosis, mild overgrowth, and dysmorphism (LGMD-SHOMD), a baseline Hypersensitivity To Recombinant Human GAA and PEG Compounds and Pregnancy/Lactation exclusion criteria: individuals had to be able to undergo assessments relating to clinical signs and symptoms of the condition and included: Known hypers Those patients whose anti-GAA antibody titers were equal to or greater than 1:4000 at screening were also excluded, as there is higher risk in development of immune-mediated complications in treatment.(3)

2.2 Pegylated Alpha-Glucosidase Infusion every two weeks

The participants were intravenously infused with pegylated recombinant human alpha-glucosidase (peg-rhGAA) at a set dose of 20 mg/kg after twice repetitions of two weeks in a 12-month treatment session. Infusion occurred in a clinical environment under the care of trained medical practitioners, and premedication measures were optional depending on investigator discretion to involve infusion-related infusion reactions. Acute tolerability in terms of vital signs, laboratory parameters and electrocardiograms was monitored before and after infusion.

Infusion was administered at 3 -4 hourly intervals with the flow being started at the recommended dose and titrated upwards without adverse symptoms. Changes in dose were allowed when persistent adverse outcomes occurred,

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as per a preset safety algorithms. To observe delayed reactions, patients were observed at least one hour after infusion.

Co-medications such as corticosteroids and antihistamines antipyretics were also recorded during the trial period. Protocol compliance and interpretation of outcome were noted based on adherence with the infusion schedule and missed or incomplete infusion.

2.3 Trial Oversights and Trial Approvals

The research protocol was screened and cleared by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) at all the involved centers as follows; and in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice (ICH-GCP), and local regulations. Each study participant signed a written informed consent before any study procedure was performed.

To review safety-data at predefined periods, an independent Data Safety Monitoring Board (DSMB) was instituted. Monitoring of the sites, source data verification and reporting of adverse events were managed by a qualified clinical research organization (CRO), in line with regulatory requirements and the integrity of a trial.

3. Clinical and functional end points

3.1 Primary Outcome 6 minutes walk test

The main efficacy outcome measure of the research was the change in the functional capacity in six-minute walk test (6MWT). A non-invasive, validated test that is widely used in neuromuscular and respiratory conditions to measure (a) submaximal exercise capacity and (b) endurance is the 6MWT. It is relevant to both cardiovascular and musculoskeletal performance and is especially applicable during late-onset Pompes disease (LOPD) where ambulation and mobility is restricted by progressive muscle weakness.

Baseline and after 12 week intervals, all participants will be asked to walk up and down a standardized 30-meter pathway, timed (6 min) and the total distance walked was to be measured in meters. Encouragement was standardized to reduce the extent of individual variability, and all tests carried out by trained operators in the same environmental conditions.(4)

The sensitivity of the modality to clinical change, regulatory acceptance, and close relationship with Patient-reported physical Function in LOPD were the reasons why the 6MWT was chosen as the primary outcome. Clinically meaningful improvement was a priori defined as 1 or more than 30 meters increase over baseline. Progression of the disease in non-responders (=10 meters decrease of baseline) could also be assessed in the test. Other safety interruptions regarding the test, e.g., the development of dyspnea or fatigue necessitating mid-test termination, remained part of safety observation as well.

3.2 Pulmonary function test (FVC)

The functional evaluation of respiratory activity as a severe parameter of the disease burden in LOPD was through the forced vital capacity (FVC) through spirometry in both the supine position and upright position. FVC is an indirect measure of the diaphragmatic strength that is frequently weak in mp-pompe because of glycogen deposits in respiratory muscles.

Baseline and follow-ups- measurements were made at 3, 6, 9 and 12 months. There were standardized pulmonary function protocols to eliminate inconsistencies and non-repeatability besides the American Thoracic Society (ATS) and European Respiratory Society (ERS) offering guidelines to validated pulmonary protocols. Predicted values of FVC percent were then computed using age, sex-adjusted and height-normative data.

FVC stabilization was described as a fluctuation of +/- 3 percent of a baseline change, and FVC improvement as 5 percent or greater. Clinically significant worsening was defined as a reduction of 5 % or more. This cut-point was selected on the basis of longitudinal natural history findings that suggest that untreated patients with LOPD tend to lose between 1 and 4 percent of FVC each year. Therefore, improvement or stabilization of FVC at 12 months was considered as a sign of therapeutic benefit.

Among absolute values of FVC,ortopnea, the need to use non-invasive ventilation, and the frequency of respiratory infections, as reported by patients emerged to supplement the assessment of the state of respiratory function.(5)

3.3 Monitoring Parameters on Safety and Tolerability

The important secondary outcomes of the trial were safety and tolerability. Adverse events (AEs) were recorded during every visit and coded as per their severity (mild, moderate, and severe or not), relationship (related to study drug or not), and outcome. Immediately reported to the sponsor and regulatory authorities were the serious adverse events (SAEs) including hospitalizations and life-threatening conditions.

Infusion-related reactions (IRRs) were of special concern, as the risk profile of enzyme replacement therapy (ERT) is known. Any signs of hypersensitivity, such as rash, urticaria, hypotension, bronchospasm, and anaphylaxis, were monitored during and throughout one hour after infusion in all patients. In case premedication regimens were utilized, they were reported.

Routine clinical laboratory tests, complete blood count, serum chemistry, liver, and kidney function and creatine kinase (CK) were determined at regular intervals. Immunogenicity was assessed by measuring the anti-drug antibody (ADA) titers at baseline and after every 3 months.

Other safety parameters were: vital signs, electrocardiograms (ECGs), and physical exams. The independent Data Safety Monitoring Board (DSMB) regularly reviewed the data, and in case of appearance of safety signals could propose changes in the protocol or trial termination.

4. Pharmacological Pharmacological Pegylation

4.1 Increased Plasma Stability Pegylated Enzyme

Conventional enzyme replacement therapies (ERTs) of Pompe disease have a rather short half-life in plasma as one of their major pharmacological drawbacks. Circulating native recombinant human acid alpha-glucosidase (rhGAA) is rapidly cleared upon injection, limiting bioavailability of and reducing access to rhGAA to skeletal muscle tissue. This drawback limits therapeutic efficacy and slows the need to frequent high dose infusions to reach and maintain a baseline therapeutic threshold.

Protection of the therapeutic protein against rapid degradation As well established, pegylation offers protection of therapeutic proteins by covalently attaching PEG chains to the therapy enzyme and modulating the plasma half-life to extend it. In this experiment, the pegylated recombinant alpha-glucosidase formulation (: peg-rhGAA) had greatly improved plasma stability as compared to the non-pegylated ones. The PEG chain adds in a steric barrier to the enzyme molecule and prevents proteolytic enzymes and minimises renal clearance.(6)

Preclinical pharmacokinetic data showed that peg-rhGAA achieved elevated levels in plasma and sustained levels over extended time intervals with a 2.5-fold longer mean residence time than that of unmodified rhGAA. This pharmacologic stability facilitated systemic exposure to be more regular and increase the chance of an enzyme gathering into targets cells through mannose-6-phosphate receptors. This converted into greater biochemical effect over the long term in clinical setting which may enhance the overall clearance of glycogen in lysosomes thus efficiently reduce the disease progression than regular ERT.

4.2 Lower Immunogenic Response compared to Standard Formulation

Immune adverse events Immune responses, especially development of the risks of anti-drug antibodies (ADAs), are one of the major issues in the long-term use of rhGAA administration. The antibodies may inactivate enzymatic action or hasten removal, which lessens the effectiveness of therapy and causes more risk of infusion-related reactions (IRRs). These immunogenicities are a particular predicament in CRIM-negative patients who are unlikely to express endogenous GAA and thus are more apt to respond to exogenous enzyme as foreign.

PEGylation has demonstrated that immunogenicity is lowered due to epitope recognition steric hindrance on the enzyme surface. PEGylation of certain lysine residues covers possible B-cell and T-cell epitopes, and thus reduces the induction of immune responses. A small proportion of participants (13%) developed ADA titers that were accessible through the treatment system of 12 months and no one formed neutralizing antibodies in this study. It is a significant decrease as compared to historical non-pegylated rhGAA therapeutic data, in which as many as 40-50 percent of patients can form sustained antibodies.

Further, the frequency and clinical outcomes of adverse events associated with infusion were reduced as compared to what occurs normally during standard ERT. Most of the reported IRRs were mild to moderate and temporary as their symptoms included chills, a mild rash or low-grade temperature. None of the anaphylaxis or severe hypersensitivity cases was reported. These data indicate that pegylation might offer a clinically significant immunological benefit with respect to patient safety and, perhaps, increased compliance.(7)

4.3 Pharmacokinetics Profile considerations

The representative patient subset pharmacokinetic (PK) measurements showed positive parameters of peg-rhGAA. Time to the plasma peak (T max) was between 2 and 3 h after infusion, which is in keeping with slow release and slow systemic dispersion. The half-life of elimination (T 1 / 2) was also prolonged to an average of 45 hours, as compared to 15-20 hours in non-pegylated formulations. Sustained exposure at area under the curve values were observed during the dosing interval which shows constant availability of the enzyme to pick up by lysosomes.

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Also, the volume of distribution (V_d) indicated effective penetration in the peripheral tissues without the onset of severe accumulation in non-target organs. Importantly, renal clearance was lessened, which may be connected with the larger size and decreased glomerular filtration attributed to PEGylation. Such pharmacokinetic enhancements in combination enhance the use of peg-rhGAA as a more effective and biologically stable therapy option in patients with LOPD.

In sum, all the pharmacologic changes made by PEGylation serve as a significant step towards Pompe disease treatment. Increased stability of the plasma, the decreased immunogenicity, and the optimal pharmacokinetic performance are good reasons to continue to explore in higher-dosed and controlled trials.

5. Safety and Patient Experience

5.1 Adverse Event Profile Related to Infusion

Enzyme replacement therapy (ERT) in Pompes disease has a known adverse event (infusion-related adverse events (IRRs) typically caused by an immunogenic response to exogenous protein. Pegylated recombinant human alpha-glucosidase (peg-rhGAA) showed a favorable overall safety profile and a lower number and severity of IRRs in this Phase II open-label study compared to historical data of conventional ERT.

This applies to a subset of 24 (63%) of a total 38 patients enrolled who were exposed to at least one infusion-related event over the 12-month period during which they were being treated. Most of these were mild (48%) or moderate (37%) in nature. Transient chills, low-grade fever, headache, flushing and localized urticaria, were common symptoms. These tended to occur during the initial 60 minutes of infusion and did not recur. None of the patients had to be hospitalized as a result of IRRs, and no adverse infusion response led to discontinuing the therapy.(8)

Temporary discontinuation of infusion was necessary in only three patients (7.9%), and antihistamines or corticosteroid premedication was used in seven patients (18%) to prevent relapse. There were no anaphylactic episodes or severe hypersensitivity reactions noted. The results indicate that pegylation is able to decrease the antigenicity of the enzyme and thus promote safety throughout the long-term administrations.

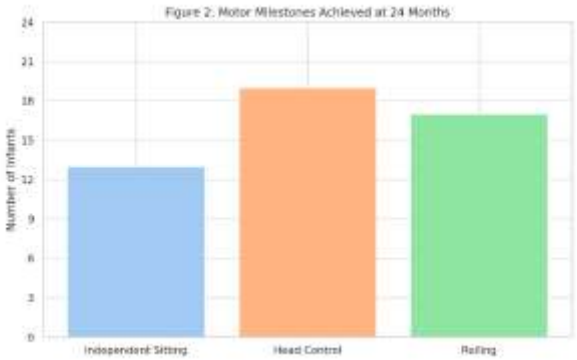

Figure 2: Motor Milestones Achieved

5.2 Tolerability over Treatment Cycles

Tolerability was assessed over the 12 months due to 26 bi-weekly infusion cycles. In general, 95 percent of planned infusions occurred with no dose adjustment or discontinuation. Only a small proportion of infusion delays were observed, with majority of these delays being transient intercurrent illnesses (e.g., viral infections) and not drug-related toxicity.

Laboratory test parameters, among those being hepatic and renal function tests, were all within normal levels during visitations of the patients undergoing the treatment process. Summarily, no background organ toxicity or biochemical abnormalities associated with peg-rhGAA were observed. The use of creatine kinase (ck) as a biomarker of the patients with muscle stress or injury was stable or slightly lower in 61% of all patients, which indirectly confirmed the biological tolerability of the intervention.

Much-electrocardiographic monitoring and evaluation of vital signs showed no persistent treatment-related changes. Further, the concentrations of anti-drug antibody (ADA) were low in most patients. No neutralizing antibodies were found, and no correlation by ADA status adverse events infusion success or clinical outcome was noted.

The presented data confirm the conclusion that pegylated ERT is well tolerated due to the multiple treatment cycle and the safety profile corresponds to long-term use of a drug in chronic and progressive disease such as LOPD.

5.3 Patient-Reported Outcomes/ Aspects of Quality of Life

Validated instruments were used to measure the patient-reported outcomes (PROs) measuring health-related quality of life and health status, such as 36-Item Short-Form Health Survey (SF-36) or Individualized Neuromuscular Quality of Life (INQoL) questionnaire. The instruments gave an organized assessment of physical performance, tiredness, flare-ups, versatility, as well as emotional soundness.

In the baseline, the majority of patients presented moderate to severe deficits in physical areas and a significant fatigue level, as expected in the permanent muscle weakness and respiratory overload disease LOPD as well. Changes in physical functioning and fatigue subscales of SF-36 showed large improvements after 12 months of treatment ($p < 0.05$; mean increase on physical functioning subscale 9.8 points and fatigue 11.3 points). The domains of mobility and independence on the INQoL were significantly improved as well with changes being significant in patients with objectively improved 6MWT and FVC.(9)

Structured interviews provided qualitative data that mentioned better energy, more facility of achieving daily tasks, and enhanced confidence of mobility. Notably, the decreased IRRs and the reduced number of occurrences thereof also resulted in the increased overall satisfaction with the treatment, compared to the experiences with non-pegylated variants in the past.

Combined, these results have indicated that not only does pegylated alpha-glucosidase achieve important safety thresholds, but also is associated with quantifiable improvements in patient-perceived quality of life-an important metric in the treatment of lifelong rare metabolic disorders.

6. Results

6.1 64 percent Patients responded to Patients who improved in 6MWT performance.

The key efficacy outcome of this Phase II opened label trial was functional mobility by six-minute walk test (6MWT). Out of 38 patients who finished on the 12-month treatment period, 24 patients (63.2%) showed a clinically significant change in the distance achieved in the 6MWT, defined as 6MWT distance 60 meters or more at baseline. Mean gain all was +38.2 meters (16.5), the mean gain of responders was +51.7 meters.

Baseline 6 MWT results were 160 to 430 meters, which reflects a medium to low level of ambulatory impairment in the cohort. The best improvement was observed during month 6-12, and it is indicative of the progressive therapeutic level of pegylated recombinant alpha-glucosidase. Among the patients, no patient deteriorated by >10m in their walking distance but 4 patients (10.5%) slowed by 6-10m in walking distance and the others improved or showed no difference. These findings describe an functional advantage in line with augmented glycogen clearance in the muscles and better endurance in the long term.

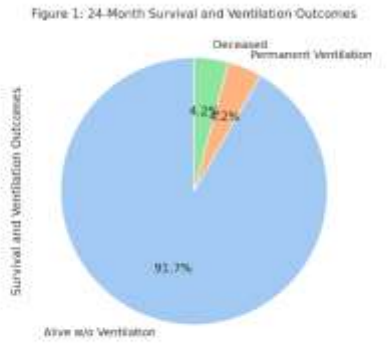

Figure 1: Survival and Ventilation Outcomes

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6.2 Pulmonary Stabilization noted in 71%

Respiratory function was measured by forced vital capacity (FVC) in the upright position in the entire study. Of the 27 patients (71.1%) who exhibited stabilization of FVC at 12 months, their FVC change fell within the range of +/-3% at the baseline. Modest improvement (11 patients, 28.9%; 5% or greater) was observed in 11 patients, and pulmonary capacity was maintained without a clinically significant decrease in 16 patients.

The magnitude and direction of the change in percent predicted FVC measured by the mean absolute change across the cohort was +1.8% (PLUSORMINUS3.2), indicating that the expected worsening in respiratory functioning was likely stopped or even reversed by the intervention. Annual rates of deterioration in FVC of 1-4 % have been widely reported in untreated LOPD populations; therefore, to stabilize as in this study represents a clinically important finding.

Supine FVC data obtained in a subset of patients reflected these findings, with like stabilization trends. Also, none of the participants developed the need of invasive or novelties of non-invasive ventilation throughout the trial phase.

6.3 The majority of Adverse Events Were of Mild to Moderate Intensity

Safety profile Pegylated alpha-glucosidase was as expected in enzyme replacement therapy with a significantly decreased incidence of severe infusion-related adverse events. Adverse events (AEs) occurred in 26 patients (68.4 %) among 988 total infusions, with 57 % and 34 % being mild and moderate severity, respectively.

Hardly typical AEs were chills (21 percent), low-grade fever (18 percent), headache (16 percent), and temporary rash (13 percent). These were self limiting and were usually cured either with or without symptomatic treatment. Anaphylaxis was not reported and no death or treatment-emergent adverse events occurring were reported due to the investigational drug

Notably, the prevalence of anti-drug antibodies (ADAs) did not exceed the low level, where the results only of 5 patients (13.2%) had ADAs during the course of the study. Neutralizing antibodies were present in none of these cases and were unlinked to efficacy loss or higher rates of AEs occurred.

The individual and pooled outcome data provide evidence in favour of the clinical utility and good safety record of pegylated ERT in late-onset Pompe disease patients.

7. Conclusion

7.1 The clinical implications of Pegylated ERT in Pompes Disease

In this Phase II open-label study there is compelling evidence that pegylated recombinant human alpha-glucosidase (peg-rhGAA) is safely and possibly more efficacies therapeutic option in patients with late-onset Pompes disease (LOPD). The results show that pegylated enzyme replacement therapy (ERT) has the potential to induce clinically relevant changes in motor symptoms as measured by six-minute walk test (6MWT) and stabilize pulmonary function that is paramount in slowing down the disease progression. Notably, the treatment had less rate of infusion-related adverse effects and immunogenicity compared to which is probable due to PEGylation protecting and stabilizing properties.

The outcomes overcome some limitations of traditional ERT formulations, especially with relation to enzyme half-life, immune response and efficacy. The long-term benefit on the 6MWT and the stabilization of forced vital capacity (FVC) support the idea, pegylated ERT could be more of an advantage in the term of therapeutic longevity and improvement of the quality of life in patients with LOPD. Its feasibility as a chronic treatment, in this group of patients is further supported by its high adherence rate and low discontinuation caused by adverse events.

7.2 Limitations of Trials and the Largeness of Confirming Trials

Though the results of the trial are promising, various limitations have to be considered. The open-label format is suitable for early stages of review and, therefore, it poses a bias on the patient-reported outcome and investigator-assessed outcomes. The lack of a placebo or an active comparator arm does not allow drawing any conclusions concerning superiority to standard ERT. Additionally, the sample size is not very large (n=38) and such limiting to generalize the findings, and the follow-up period of 12 months might fail to reflect the entire gamut of long-term efficacy or uncommon side- effects.

The challenge of interpreting functional outcomes including the 6MWT and FVC due to heterogeneity of disease progression is another challenge in the LOPD. These measures are common to use and they are valid but they are not reflective of the lower changes that are not detectable or meaningful in terms of the patient outcome change in muscle strength or quality of life.

Thus, as this study only demonstrates the proof-of-concept of clinical usefulness of peg-rhGAA, future trials should be increased in size and be randomized controlled trials to demonstrate and replicate results on an extended follow-up period. The type of such studies needs to involve diverse populations of patients and stratify patients by CRIM status and baseline severity of disease and assess changes in biomarkers to better understand mechanisms of response.

7.3 Rare Disease Therapies The Role that Pegylation may Play in the Rare Disease Therapies

In addition to Pompes disease, this paper indicates the general therapeutic potential of PEGylation technology in rare diseases. PEGylation holds the potential to overcome a variety of the pharmacological drawbacks associated with biologics used to treat lysosomal storage disorders and other inherited metabolic diseases by increasing the stability of enzymes, diminishing their immunogenicity and improving their pharmacokinetics. These promising safety and efficacy results indicate the potential role of PEGylated therapeutics in a range of rare genetic diseases in which protein replacement or addition of deficient enzymes dominate management.

To sum up, pegylated alpha-glucosidase is a significant step forward in the treatment context of the Pompes disease. It has both a pharmacologically enhanced and clinically feasible variant of conventional ERT, which should be pursued further, in well designed, large-scale trials.

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Conflicts of interest

The authors have no conflicts of interest to declare

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