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Annual Report 2023

Introduction

Exciting advancements continue to evolve within the Pompe community. The IPA continues to monitor, liaise and develop relationships with all parties involved in the development of treatments or interventions for Pompe. In addition, we work closely with the Medical/Scientific Community to improve our mutual understanding of Pompe disease and the unmet needs of the Pompe Community. As you read the 2023 Annual Report, it is the hope of the IPA Board that the exciting advances that are coming, as well as the IPA's planned collaborations for 2024 (and beyond), will fill you with the same hope for the future that we have.

Chairman's statement 2023

October 22, 2024 will be the 25th Anniversary of the founding of the IPA. As we look forward to that event next year, I would like to focus on where we find ourselves today. As a member of the rare disease community, Pompe is in a very fortunate position. We have not 1, not 2, but now 3 regulatory approved treatments for Pompe. Having a treatment makes us extremely rare within the rare disease community as a whole. According to the National Institute of Health (NIH) in the US, there are approximately 7,000 rare diseases that have been identified, and only around 500 have treatments. And to be able to have a choice in treatment? That is even more rare.

While it is well known that the treatments we do have only help to slow or stop progression, we still have a choice and a chance to stop the natural history of Pompe. But where does that leave us? We are not ready to stop looking for better choices, better treatment management, and a better understanding of Pompe. And we are fortunate to be surrounded with clinicians and researchers who feel the same.

So where does that leave us? It leaves us with a lot of work left to do. We need to better understand how these different treatments work in real-world settings. We need to work with clinicians to develop better ways of tracking treatment effects on a global level so that we can begin to understand which treatments work best for which patients. We need to push for better methods of tracking the progress of Pompe, and evaluating treatment effects by utilizing tools like AI.

We have our work cut out for us—but the Pompe Community has never been afraid of hard work. By working closely with the clinicians and researchers who share our passion for making the future better for all patients, we will be able to overcome any obstacle in our way.

In the rest of this report, you will read about the activities that have occurred over the last year, and activities that we believe will be vital to the future of Pompe treatment, knowledge, and disease management. #Together We Are Strong!

2023 International Pompe Day—Every Move Counts!

April 15, 2023 was our 10th Annual International Pompe Day. As we look forward to new treatments like gene therapy, substrate reduction therapy, and more, it is important for patients to stay as healthy as possible while these treatments are being developed. Therefore, for the 10th International Pompe Day, the IPA Board issued a challenge to the community: show us how "Every Move Counts!"

Regardless of where any individual may live in the world, or where they may be on the Pompe disease spectrum, or the severity of their disease, it is important for all of us to stay moving. But it can be very difficult at times to stay motivated to continue moving forward. Therefore, we are asking our members to encourage individuals in their community to send in videos or pictures to show themselves moving. It can be clips of a person exercising, demonstrating how walking sticks are used, or playing with your kids or pets. We will be collecting these videos to include on the IPA's YouTube channel. We would also encourage people to include a short description of what the video is showing. For more information on where to

send the videos or photos, as well as what to include with them, please visit the IPA website at: https://worldpompe.org/news/2023-every-move-counts/

Patient Affiliates

We currently have 66 contacts with patient organisations and individuals, representing almost 61 countries around the World.

Community Advisory Board

The IPA established its own Community Advisory Board (CAB) for Pompe disease in 2019. The difference between industry-driven advisory boards and the IPA's CAB is that the IPA's is a patient-driven endeavour that is organised and owned by the Pompe patient community. Traditionally, a CAB is a group established and operated by patient advocates to facilitate discussions, in a neutral setting, on the latest developments and challenges related to medical research and procedures with the company or body conducting the research. A CAB is a group of patients or advocates who offer their expertise to sponsors of clinical research, on overall program development, single clinical trials, and other aspects beyond the research program. A CAB helps also ensure that clinical studies are designed to consider the real needs of patients, resulting in higher quality research. The IPA CAB is composed of 23 members from 10 countries spanning across 3 continents and representing the full spectrum of Pompe disease. The original composition of the CAB was 19 members in 2019, and we now have 23 members with new additions to the board from the US, the Netherlands, Hong Kong, Japan and, France in 2022.

The first IPA CAB meeting was held on October 28, 2019 in San Antonio, Texas, and was in the form of a multi-company round-table, with 15 CAB members attending in person and 5 sponsors attending as observers. While the intent was to follow this up with another in-person meeting in 2020, the COVID-19 pandemic made that impossible. Instead, the IPA offered interest parties the opportunity to host online CAB meetings, and has already facilitated many virtual one-on-one CAB meetings with several different industry partners throughout 2020, 2021, 2022, and 2023: AskBio/Bayer (July 2020 and 2022); Sanofi Genzyme (September 2020, June 2021, December 2021, June 2023); Avrobio (2 CAB meetings in September 2021); and Maze Therapeutics (2022); Amicus Therapeutics (expected in late-2023).

Virtual one-on-one CAB meetings have proved to be very effective and have been appreciated by industry partners. Therefore, we are constantly working with all parties to continue this valuable program, and an increasing number of industry partners have expressed their interest in the IPA CAB. Further online CAB meetings are expected in the months to come.

Due to the format of online virtual meetings, with a sub-section of the CAB attending each webinar, the IPA is looking for CAB members, preferably members of an organization, to represent the full spectrum of Pompe disease. Potential CAB members should be 18 years old or older, with good English skills, able to commit to a minimum of 2 meetings a year and sign a non-disclosure/confidentiality agreement. Specific training will be provided.

Application letters stating relevant skills, experience and interest can be sent to fabiodipietro@worldpompe.org.

Research and Drug Development

The Pompe CAB will certainly have its work cut out for it if all of the proposed therapies under development engage with it. At the last estimate there are at least 14 new therapies under development for Pompe disease, with rumours of several more to come.

The IPA always approaches all companies or investigators active in the Pompe field to discuss their drug development programme; many are very willing to meet with us, either by teleconference, or face-to-face when we come together for an international meeting.

Below is a list of Pompe programmes we are currently aware of; visit https://clinicaltrials.gov/ for further details of clinical studies currently underway.

Next Generation Enzyme Replacement Therapies

Amicus Therapeutics

Amicus has completed their clinical trials for their second generation ERT in the Late-onset Pompe population and are beginning to seek approvals in countries around the world. As of November 2023, they have received approval for Pombiliti + Opfolda in the European Union, the United Kingdom and the United States of America. They continue to work with other regulators and reimbursing authorities to provide commercial access

In addition, Amicus currently has 2 Phase III clinical trials recruiting Pompe children from the age of 0 to 17. One studies infantile onset children (IOPD) and the other late-onset children (LOPD). For more information, please visit www.clinicaltrials.gov/

Eleva Biologics (previously known as Greenovation)

Eleva is developing a moss-produced recombinant GAA; Repleva GAA/RPV-002 (glyco-improved Pompe-ERT) which still appears to be in the pre-clinical stage of development. They claim that their approach shows superior uptake into muscular cells, thanks to the inherent glycan pattern of moss.

JCR Pharmaceuticals

According to JCR Pharmaceuticals website, as of November 2023, they are still in Pre-Clinical Development of an ERT that has the potential to cross the blood-brain barrier.

M6P Therapeutics

M6P Therapeutics is working on a next generation ERT that is "naturally produced with the highest levels of M6P as compared to other rhGAA ERTs." As of November 2022, their program is in Pre-Clinical Development. They anticipate applying for Investigational New Drug status (IND) in the second quarter of 2024. The company has not issued any press releases since February 2023.

Pharming Group NV

Unfortunately, Pharming has announced that it is stopping its Pompe program.

Sanofi-Genzyme

The next generation ERT, Nexviazyme, was approved and commercially available in the US for late-onset Pompe in 2021. The European Union and the United Kingdom have now both given their approval for the same treatment, which is known there as Nexviadyme outside the US. However, work continues with reimbursers around the world to make this treatment commercially available.

In addition, Sanofi has a clinical trial for infants under 6 months, which is due to complete in April 2025. In addition, Sanofi has initiated a trial in China to evaluate efficacy and safety in Chinese Patients With Late Onset Pompe Disease with Alglucosidase Alfa Treatment (APOLLO-LOPD).

Substrate Reduction Therapies

Substrate reduction therapies (SRTs) seek to affect the disease process by reducing the accumulation of glycogen in the muscles of Pompe patients by reducing the amount of glucose that is turned into glycogen. Below we have listed the two companies who are currently working on Substrate Reduction Therapies for Pompe.

ARO Biotherapeutics

Aro Biotherapeutics is a biotechnology company pioneering the development of tissue-targeted genetic medicines with a platform based on a proprietary protein technology called Centyrins.

On October 25, 2023, Aro announced the enrolment of the first subject in its Phase 1 trial of ABX1100. The trial, which was initiated in Canada, will commence with a placebo-controlled, double-blinded, single ascending dose portion in normal, healthy volunteers. The study is designed to assess safety, tolerability, pharmacokinetics along with various pharmacodynamic biomarkers that will be evaluated to demonstrate target engagement.

Maze Therapeutics

Maze Therapeutics is developing MZE001, an investigational oral glycogen synthase (GYS1) inhibitor that aims to address Pompe disease by limiting disease-causing glycogen build-up. GYS1 is an enzyme responsible for glycogen production in human muscle cells, but not in human liver cells.

Maze completed a Phase 1 study in healthy individuals and announced positive results in February 2023.

In May 2023, Maze Therapeutics announced that it had entered into an exclusive worldwide license agreement with Sanofi for MZE001. Under the agreement, Maze will receive a $150 million payment consisting of both upfront cash and future equity investment for the rights to further develop and commercialize MZE001, as well as an exclusive license to related GYS1-targeting back-up programs and intellectual property. Maze will be eligible to receive up to an additional approximately $600 million in potential development, regulatory and sales milestones, as well as meaningful royalties on sales if MZE001 is successfully commercialized. We are hoping to hear news of the start of a Phase 2 trial in Pompe patients soon.

Cell and Gene Therapies (Regenerative medicine)

Regenerative medicine across rare disease has continued to gain interest. Below we have listed a number of different approaches that may each provide a solution for Pompe.

Amicus Therapeutics.

Amicus's 2023 Financial Guidance in April 2023 stated five areas in which it intends to focus. One of those was to advance next-generation programs for Fabry GTx and Pompe GTx, which are gene therapy programmes. However, there is no other information available as of November 2023.

Astellas Gene Therapies

Astellas Gene Therapies continues with its phase I/II clinical trial for LOPD adults, FORTIS. Their Gene Therapy, AT845, utilizes a muscle-directed approach with an AAV8 capsid serotype that is being investigated to determine whether it can deliver a functional GAA gene to express GAA directly in tissues affected by the disease, including skeletal and cardiac muscle. The trial aims to recruit 12 patients at three locations (California, Utah, and Newcastle UK). The Primary completion date of this trial is May 31, 2025.

A peripheral sensory polyneuropathy event was reported in one trial participant in the trial, which led to an FDA clinical hold in June 2022. The FDA lifted this clinical hold in January 2023.

AVROBIO

In July 2023 AvroBio took the strategic decision to halt all programmes and to conduct "a comprehensive exploration of strategic alternatives focused on maximizing shareholder value".

This is disappointing to the Pompe community because AVR-RD-03, the Lentiviral gene therapy platform used by AvroBio had the potential to cross the blood-brain barrier, which may be helpful to those IOPD children suffering white matter abnormalities

Bayer/AskBio

AskBio, a Bayer company, is currently enrolling adults (18+) with Late-Onset Pompe Disease (LOPD) into a phase I/II clinical trial to assess their gene therapy ACT-101.

ACT-101 is infused intravenously and designed to deliver a functioning copy of the GAA gene to the liver. The goal is to restore GAA production to a level sufficient to no longer require ERT.

Only one study centre is currently active in this trial, Duke University, NC, which has enrolled 7 patients.

CODEXIS/Takeda

In July 2023, Codexis announced the discontinuation of investment in Biotherapeutics, which included their Pompe programme.

Takeda had licensed the Pompe program from Codexis, and earlie5r this year they discontinued their work in Gene Therapy - which impacted Pompe. Takeda is still assessing what they plan to do with that program.

Erasmus MC – Pim Pijnappel, Associate Professor Molecular Stem Cell Biology

Research continues at the Erasmus MC to study several regenerative therapies for Pompe, including stem cell regenerative therapies and RNA Oligonucleotides, as well as lentiviral gene therapy. There was a webinar with Dr. Pijnappel held by the AMDA on October 10, 2023. A recording of that webinar is available on the AMDA website at: https://amda-pompe.org/teleconferences/

GeneCradle Therapeutics

GeneCradle is working on an AAV-mediated gene therapy for Infantile-Onset Pompe. According to ClinicalTrials.gov, there is trial based out of China that is currently recruiting. It will include 6 patients with IOPD who are younger than 6 months of age. This study was first posted on October 5, 2022, and we are still waiting for more information to be released.

LogicBio Therapeutics/CANbridge Care

CANbridge holds an exclusive global license from LogicBio Therapeutics, Inc ("LogicBio") to develop, manufacture and commercialize gene therapy candidates for the treatment of Fabry and Pompe diseases, based on LogicBio's AAV sL65 technology. The company are at very early stage of development in their Pompe programme, as they continue to make progress on their Fabry disease candidate.

Regeneron

According to the June 2022, Annual Shareholder Meeting Report, Regeneron has a Pre-Ind research program for Pompe in their pipline that is exploring CRISPR/Cas9 + AAV Transgene Insertion. This Program is in a very early stage, so we will continue to keep an eye on it as the program develops further.

Sarepta Therapeutics/Lacerta Therapeutics

Sarepta has an agreement with Lacerta Therapeutics to develop AAV-9 gene therapy for Pompe disease. As of November 2022, this approach remains in the Research Phase of Development.

Spark Therapeutics

Spark Therapeutics is developing SPK-3006, an investigational gene therapy for treatment of Pompe disease.

Spark have put their phase I/II clinical trial, RESOLUTE, on voluntary hold until a manufacturing move is complete. They plan to reopen the trial in the first half of 2024 when active recruitment and enrolment will continue of 30 participants across their 29 study locations in the US(10), Canada(3), UK(3), Netherlands, Germany, Italy(5), France(5), and Denmark.

The Pompe program is in a state of evolution but continues to have the company's commitment. They have moved manufacturing to be fully in-house ahead of the Gene Therapy Innovation Center, which will be completed in 3-3½ years.

Campaigns

Dose Flexibility

The IPA board continues to have concerns over the inflexibility of ERT dosing for Pompe Disease. This extends beyond the current commercially-available treatment to future treatment options as well. Several treating physicians are interested in exploring higher doses but cannot because of the prohibitive cost of additional drug. The IPA continues to raise this topic with clinicians and drug companies to explore ways forward. A major hurdle currently is the interaction between country labels for approved treatment and reimbursing authorities' ability to pay. Especially in light of the economic situation around the world, we anticipate that in the coming years it will be even more difficult to get treatments approved and reimbursed, let alone at higher doses. However, just because it is a difficult journey we face, the IPA is committed to advocating for patients around the world when it comes to equal access to optimal dosing.

Treatment Transition and Expectation Guidelines

One common question that Patient Organizations get from new patients is: "How will I respond to treatment?" Unfortunately, there is not a clear answer to this question. Patient response to treatment varies from patient to patient. In some cases, the degree of progression at time of treatment onset will affect response. In other cases, a high-sustained immune response will reduce efficacy. And in others, it is not clear why some patients respond better than others.

The only thing that *is* clear after over twenty years of experience with ERT is that patients WILL respond differently, and it is important for patients to have realistic treatment expectations. This is especially true now that there are more treatment options available to patients. Now, the questions are becoming: What criteria should patients use (in consultation with their physicians) to determine whether they should try a new treatment option? What should my expectations be if I switch treatments? How do I know if the new treatment I am trying is better for me?

These are important questions, and ones that the IPA Board is committed to helping to answer. It was our intention to focus on this topic in 2023, however work on an International Registry for Pompe became the first priority. That will be discussed below. We still believe this is a vital topic to be addressed for our community so it is our hope to focus on this project in 2024 with leading experts in the Medical Community to develop Treatment Transition and Expectation Guidelines for our Community. We believe this is a vital topic, and one that deserves our full commitment.

IPA-Erasmus COVID-19 Survey

The IPA would like to thank everyone who participated in the COVID-19 one-time Survey, as part of the overall IPA/Erasmus Survey. The purpose of this survey was to look at both the effects of the pandemic on the life-style of Pompe patients, as well as the effects of infections with COVID-19 on Pompe patients. We believed that it was critical to gather this data so that we could properly and timely document these effects. The results of this one-time Survey were recently published in the Journal of Neurology.[1] Thanks to the support and participation of all of our Members and the Pompe Community as a whole, the article reports on 342 respondents from 25 countries around the world. The results highlight the significant impact that the pandemic had on our community for both physical and mental health. We would encourage everyone to take a moment to read the article. Thank you to Dr. Maudy Theunissen and the rest of the team at Erasmus University for working with the IPA to conduct this research. And a very special thank you again to all who participated.

IPA-Erasmus Survey

The IPA/Erasmus Survey (the "Pompe Survey") was first started in 2002. It is a collaboration between the International Pompe Association (IPA) and Erasmus MC.

The goal at the time it was started was to better understand, from the patient perspective, the disease burden that patients with Pompe face. The timing of the initiation of the Survey was very intentional. There was an understanding at the time that it was imperative to begin collecting this information so that we would have a patient-owned, patient-reported questionnaire and data to capture the natural history of the disease in the early days, and then to capture how that may change over time with treatment.

Today, the large number of potential future therapies makes it even more imperative that we remain strong in our commitment to the Survey, and to expanding it as appropriate. This is because each new drug that is approved will likely come with a commitment to track its clinical outcomes and patient-reported outcomes. That could mean a separate registry for each drug unless an independent registry can be developed to hold all the data. This would, necessarily, result in patient data being spread throughout multiple registries depending on which treatment they are on at the time, and whether they choose (upon discussion with their treating physician) to switch between therapies.

Without an effort like the Erasmus Pompe Survey in existence, it will be impossible to truly track, on a global level, how patients are doing throughout their disease and treatment experience. To that end, the IPA Board has been working very closely with Erasmus MC to update and streamline the existing Pompe Survey. We are happy to announce that in 2023 current patients enrolled in the Survey were able to complete the updated survey. In addition, to further the reach of the survey, we have worked with Erasmus to have it translated into additional languages. Once all translations are completed, the Survey will be available in the following languages: English, Dutch, Spanish, German, French, and Italian. We anticipate being able to begin enrolling new patients soon.

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[1] Theunissen, M.T.M., van den Elsen, R.M., House, T.L. *et al.* The impact of COVID-19 infection, the pandemic and its associated control measures on patients with Pompe disease. *J Neurol* (2023). https://doi.org/10.1007/s00415-023-11999-2

Finally, the IPA Board continues to advocate for new modules that would allow for patients to track their own results. These meetings will continue in 2024.

For more information on the IPA/Erasmus Pompe Survey, please visit the updated webpage on the Erasmus University Website: https://www.erasmusmc.nl/en/research/project/ipa-erasmus-mc-pompe-survey.

This website also includes a partial list of publications that have come from the data so our Members and the Patient Community as a whole can see how their contribution has led to important understanding of Pompe disease.

Independent Global Pompe Patient Registry

As of November 2023, there are multiple silos of Pompe patient data around the world. These include: the Sanofi Patient Registry, the IPA/Erasmus Survey Data (Patient Reported Outcomes), national data pools (ie Australia, France, Netherlands, etc), and data collected at all of the expert centers around the world.

While there is, and always has been, good collaboration amongst the expert centers, with Amicus's treatment now approved, and others on the horizon, it is very likely that within the next year there will be at least one more Patient Registry required for post-marketing approval, and the potential for many others in the next 5-10 years. It is a Regulatory requirement in many cases that as a post-marketing commitment Industry must collect specific data for a period of time.

While data collection is imperative, it is just as important to be able to aggregate information across data silos to be able to best understand trends, and best disease management practices. This is especially vital now that patients are fortunate to have treatment options.

As a community, it is in our best interest to start collecting data in a uniform manner to allow patient data to be compared across data sets. This will allow our community to be able to collect enough data from around the world and across the disease spectrum to better understand how treatment options, disease management approaches, and combinations of therapy affect different subsets of patients across the Pompe spectrum.

Therefore, the IPA has been working with a group of expert Pompe clinicians around the world to collaborate on developing an Independent, Global Pompe Patient Registry. In addition to regular meetings with the expert clinicians, the IPA Board has been collaborating with and learning from other key parties in the rare disease registry space. These include RareX and the International Niemann-Pick Disease Registry.

In addition, from May to June 2023 the IPA conducted a survey of the Pompe Community to understand the desires of the community when it comes to patient data and registries. This survey was sent out to the community and made available in: English, Dutch, French, Portuguese, Italian, German and Chinese. The results from this survey can be found on the IPA website. While it is clear that more education about the existing Registries is needed, it was equally clear that there is a strong commitment in our community to participating in an Independent Global Pompe Patient Registry that collects clinical data.

We look forward to continuing this important work in 2024 and providing updates as we progress on this Project.

Website Re-Design

Based on feedback from the community, the IPA completed a redesign of its website this year. We've made it easier to find historical information; stories and videos are available from our community; and, the updated Pompe Connections, a patient-focussed resource, are available and currently being updated into many languages. Please let us know if there are any other features that you'd find useful for us to include. Also, please be patient as we continue to update the pages in the coming months.

Communications

Maryze Schoneveld van der Linde prepares the IPA newsletters and also acts as a point of contact for international inquiries. Maryze is a valuable source of information to people who don't have support from patient organizations in their countries.

All relevant news and announcements (e. g. International Pompe Day, Conferences, Industry updates, etc) are published on the IPA's website www.worldpompe.org. Suggestions for articles are welcome and will be published if they are relevant to the global Pompe community (not of national relevance only). Please send your contribution to the Webmaster:

info@worldpompe.org.

On Facebook, there are two IPA pages:

IPA: www.facebook.com/International-Pompe-Association-IPA-119237914814204/) and **International Pompe Day**: www.facebook.com/InternationalPompeDay

For IPA Members only, a confidential (closed and publicly not visible) Facebook group is used for communication between the member organisations (https://www.facebook.com/groups/850602065054870/). If you want to join as a representative of your national patient organisation please contact the IPA Board at info@worldpompe.org.

Newsletters and updates are sent out on an as-needed basis. Suggestions for new topics to be covered are always welcome.

Pompe Connections

Throughout 2022-23, the Board focused extensively on updating all of the existing Pompe Connections, and Pompe Connections Treatment Edition Brochures. Ultimately, the Pompe Connections (English version) brochures were updated to remove redundant links, product names and manufacturers names. Some revision of wording was undertaken to reflect multiple ERT types and multiple manufacturers. In addition, a number of Treatment Edition brochures were removed, as they could not be updated to fit the new requirements or in the case that the information contained in the brochure is available from other sites or is updated regularly.

We are currently working with a translation company to get the revised Pompe Connections translated into multiple languages. We hope to have those up on the website soon. We believe that this is a good resource for patients at all stages of their Pompe journey, and would encourage our members to share them with patients in their communities.

In addition, we would also like to ask our members, and the broader Pompe Community of patients, family members, and the medical community, to contact us at info@worldpompe.org if there are additional topics that you would like to see covered. In addition, please contact us if you would be willing to help with translations of current and future Brochures.

Meetings

In 2023 we saw the beginning of more in-person meetings, in addition to hybrid meetings that were in-person and virtual. Below please find short summaries of some of the Conferences that took place during 2023 that were attended by IPA Board members.

WORLD Symposium 2023

Several Board Members (and members of the Pompe Community) attended the WORLD Symposium in February 2023. Attendance was a combination of virtually (following the conference) and in person. The WORLD symposium is an annual conference which brings together clinicians, scientists, industry and patients from all over the world to learn and share knowledge on all Lysosomal Diseases (LDs). Many presentations and posters highlight the current level of research activity for Pompe disease. We look forward to attending again next year.

Sanofi Rare Disease Registries Patient Council

The IPA Board has had a consistent presence on the Patient Council. The purpose of the Council is to provide the Patient Community's perspective on Sanofi's Pompe Registry.

IPA AGM 2023

The IPA's Annual General Meeting in 2023 will take place virtually on November 25, 2023.

Looking ahead

For 2024, the IPA welcomes ideas from the Pompe community for projects to raise global awareness, improve our support and engagement with national groups, and develop our relationships with the growing number of research and industry networks. We are a very close community and there is little doubt that Together we are Strong!

Thank you,

IPA Board
November 2023