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Annual Report 2021

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 better understand Pompe. As you read the 2021 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 2021-2022 (and beyond), will fill you with the same hope for the future that we have.

Chairman's statement 2021

While the COVID pandemic continued to have unanticipated consequences for the world, after a brief disruption, clinical developments of several next generation therapies for Pompe continued in 2021. We now have one next generation Enzyme Replacement Therapy (ERT) that is commercially available in the United States, and on the verge of approval in other regions. In addition, other ERTs have anticipated regulatory decision dates for next year. There are also multiple gene therapies under clinical development, with trials already underway.

In addition to the clinical developments in our field, we have also seen increased interest in incorporating patient perspectives. This has been seen in an increased activity of the IPA's Community Advisory Board (CAB), as well as increased interest in Patient Reported Outcomes (like the IPA/Erasmus Patient Survey).

While the pandemic dramatically disrupted in-person patient meetings and scientific conferences, it also jump-started the amount of interaction via virtual methods. This was true for many international meetings (i.e., WORLD), and also for the IPA's CAB program and meetings of our national members. This increased reliance on virtual meetings has had the added benefit of allowing patient representatives for whom travel is more difficult to attend more meetings with ease. It is our hope that going forward, now that virtual meetings have become more regular, that future meetings will involve a hybrid model to continue to allow for more participation.

Throughout the year, however, the IPA Board has remained committed to our mission statement: Campaign for early diagnosis and effective, affordable and safe therapies. Strive to provide information and support to all patients, their families and others with interests in Pompe disease.

In the rest of this report, you will read about the activities that have occurred over the last year, and how we have sought to stay true to our mission. Together We Are Strong!

2021 International Pompe Day

April 15, 2021 was our 8th Annual International Pompe Day. Despite the challenges we have faced, it is an exciting time for the Pompe Community worldwide with new studies and treatments on the horizon, and Hope is what drives the patient community, and what inspires the medical/scientific community, and industry to keep working.

The IPA believes that raising awareness about Pompe Disease is key, and the theme selected for 2021 was **Pompe Around The World**. The intent was to show what it is like to live with Pompe, how we cope, or how we are connected through Pompe all over the world. In effect, no matter where we live, we are all connected as a united international community. We encouraged our members and the global Pompe Community to submit posts to our blog by taking a picture that represents where they live and share a short statement about their life. The blog features 31 wonderful contributions from: Italy, Greece, USA, UK, Portugal, France, Switzerland, the Netherlands, Japan, and Canada. The stories have been, and will continue to be, shared at: https://ipompeday.blogspot.com/2021/

The IPA Board expresses its gratitude to the international Pompe community that contributed by submitting their personal stories and encourages everyone to read and share them in order to inspire others.

Patient Affiliates

We currently have 61 contacts with patient organisations and individuals, representing almost 54 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 22 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 22 members with new additions to the board from the US, the Netherlands, Hong Kong and Japan.

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 pandemic made that impossible. Instead, the IPA gave the opportunity to host online CAB meetings, and has already facilitated 4 virtual one-on-one CAB meetings with several different industry partners throughout 2020 and 2021: AskBio (July 2020), Sanofi Genzyme (September 2020. June 2021, expected December 2021), Avrobio (2 CAB meetings in September 2021). We are constantly working with all parties to continue this valuable program, and an increasing number of industry partners have expressed their appreciation and interest in the IPA CAB. Further CAB meetings are expected in the months to come with Genzyme, Amicus Therapeutics, and Spark Therapeutics.

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 www.clinicaltrials.gov for further details of clinical studies currently underway.

Next Generation Enzyme Replacement Therapies

There are currently two next-generation ERTs in clinical studies, and two more are being proposed using lower cost platforms.

Amicus Therapeutics

In February 2021, Amicus announced the initial results from its Phase 3 PROPEL Pivotal Trial for AT-GAA (cipaglucosidase alfa and miglustat) for Pompe—its investigational two-component therapy for the treatment of

late-onset Pompe disease (LOPD) that has previously received Breakthrough Therapy Designation from the U.S. FDA and the Promising Innovative Medicine designation from the MHRA in the United Kingdom.
As of October 2021, the Marketing Authorization Application for AT-GAA is expected to be submitted in the EU in the fourth quarter of 2021. In June 2021, the U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) granted AT-GAA a positive scientific opinion through the Early Access to Medicines Scheme (EAMS). Further, the US Food and Drug Administration (FDA) had set a date of May 29. 2022 to make a determination on the New Drug Application (NDA) for AT-GAA, and July 29, 2022 for the Biologics License Application (BLA) for AT-GAA.

Eleva Biologics

Eleva continues to work on it's moss-produced recombinant GAA. According to their website, they are still in the Pre-Clinical phase. In addition, they claim that their approach shows superior uptake into muscular cells, thanks to the inherent glycan pattern of moss.

JCR Pharmaceuticals

As of May 2021, JCR Pharmaceuticals has stated that they are in Pre-Clinical Development of an ERT that has the potential to cross the blood-brain barrier.

Maze Therapeutics

Maze Therapeutics is working on a substrate reduction therapy that has potential therapeutic benefits for Pompe. As of October 2021, their program is in Pre-Clinical Development.

Pharming Group NV

Pharming continues to develop a transgenic ERT for Pompe. According to their website as of November 2021, they are currently studying their alpha-glucosidase therapy in IND-enabling studies.

Sanofi-Genzyme

In July 2021, The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for avalglucosidase alfa, a long-term enzyme replacement therapy for the treatment of people with Pompe disease. The positive opinion is based on data from the Phase 3 COMET study, which found that avalglucosidase alfa showed clinically meaningful improvements in respiratory function and movement endurance measures in people with late-onset Pompe disease. However, The CHMP did not grant New Active Substance Designation (NAS), and as of October 2021 Sanofi had requested re-examination on this conclusion.

Following this, in August 2021, the U.S. Food and Drug Administration (FDA) approved Nexviazyme® (avalglucosidase alfa-ngpt) for the treatment of patients one year of age and older with late-onset Pompe disease. Nexviazyme is an enzyme replacement therapy (ERT) designed to specifically target the mannose-6-phosphate (M6P) receptor, the key pathway for cellular uptake of enzyme replacement therapy in Pompe disease. Nexviazyme has been shown in clinical trials to provide patients with improvements in respiratory function and walking distance. This is the first new treatment for Pompe to be approved since 2006.

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.

Bayer/AskBio

In October 2020, Bayer acquired AskBio, and its gene therapy platform. The intent is to help to bring their therapies to commercial market. In regards to Pompe disease, AskBio continues to enrol patients with Late-Onset Pompe Disease (LOPD) to assess multiple doses of its gene therapy ACT-101 (also known as ACTUS-101). The first patient was dosed in January 2019, and trial is on-going.

Amicus Therapeutics.

Amicus is working with the Gene Therapy Program in the Perelman School of Medicine at the University of Pennsylvania (Penn) to pursue research and development of novel gene therapies for Pompe disease. This program remains at the Pre-clinical development stage as of October 2021.

Astellas Gene Therapies/Audentes Therapeutics
As of April 1, 2021, Audentes Therapeutics is now known as Astellas Gene Therapies. Despite the name change, their work in Pompe continues uninterrupted. According to their website, Astellas Gene Therapies is developing AT845, a novel gene replacement investigational therapy to address the recognized limitations of ERT by targeting the muscle tissues, the primary tissue affected in Pompe disease. 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 that is efficiently transduced to express GAA directly in tissues affected by the disease, including skeletal and cardiac muscle.

AvroBio
AVR-RD-03, the Lentiviral gene therapy platform used by AvroBio modifies the patient's own stem cells taken from the bone marrow. As of October 2021 this program is still in pre-clinical research.

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.

LogicBio Therapeutics
LogicBio's GeneRide technology is a program to watch as a second-generation gene therapy. They claim that their technology will be suitable for infants and will not require re-dosing. They are looking across the range of LSDs and GSDs, but say that applying their technology to Pompe disease is more challenging. As of October 2021, this program remains in the Research Phase of development.

Sarepta Therapeutics (formerly Lacerta Therapeutics)
Sarepta has an agreement with Lacerta Therapeutics to develop AAV-9 gene therapy for Pompe disease. As of October 2021, 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, and has begun recruiting Late-onset Pompe patient (after an initial pause due to the Covid-19 pandemic) for their RESOLUTE clinical trial. The purpose of the RESOLUTE clinical trial is to study the effects of gene therapy SPK-3006 (investigational study drug). Spark announced in February 2021 that the first patient had been dosed in the Phase 1/2 trial.

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.

IPA-Erasmus Survey
The large number of potential future therapies raises additional concerns because each new drug that is approved will likely come with a commitment to track its clinical 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.

The IPA is in discussion about the potential to develop a patient-owned registry of medical data, potentially to be connected with the IPA/Erasmus patient-reported questionnaire. This will continue to be an on-going exploration over the next year.

The IPA/Erasmus MC Pompe Survey ('the Pompe Survey') collects information on the effects of Pompe disease on patients' lives of patients, and how these may change with treatment. Patients themselves provide this information through an annual questionnaire. Launched in 2002, the Pompe Survey is a collaboration of the International Pompe Association (IPA) and Erasmus MC.

In addition, throughout 2021 the IPA Board met multiple times with the team from Erasmus regarding our desire to see more information made available to patients regarding the importance of the Survey, our desire for new modules of the survey that would allow for patients to track their own results, and also the desire to have the Survey updated and translated into more languages. These meetings will continue in 2022. However, one result of these meetings can be seen in the updated website on the survey, which provides information on the importance of the Survey. It also contains a partial list of publications that have come from the data: https://www.erasmusmc.nl/en/research/project/ipa-erasmus-mc-pompe-survey

Communication Initiative

The IPA Board has hired a communication firm, ZUID, to assist us in better evaluating and meeting the needs of our Members. Prior to selecting ZUID, the IPA Board met with several different firms to find one that had the best fit for our needs. ZUID was ultimately selected because of their individualized approach and focus, and ability to understand the needs of a rare disease community.

The first step of this Communication Initiative will include a combination of written surveys and phone calls with some of our members to gather feedback on how the IPA can better serve our Members. We truly hope that you all participate and provide feedback when you receive the survey.

Following the first step of surveys and phone calls, it is the Board's intent to take the information gathered and to proceed with new initiatives next year. This will likely also include an overhaul of the website, and our communication strategies to our members. We look forward to working with all of you on this in 2022, and welcome any thoughts you may have.

Communications

Maryze Schoneveld van der Linde prepares the IPA newsletters and also acts as a point of contact for international inquiries. Maryze is a great source of comfort to people who don't have the support they need in their own countries. I In the past year she has helped Pompe families in 8 countries to get access to treatment: Kenya, Tunisia, Morocco, Egypt, India, Ukraine, United Arab Emirates and Pakistan.

All relevant news and announcements (e. g. International Pompe Day talent contest) are published on 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: webmaster@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.

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

Pompe Connections

The IPA, with the help of its Board and Advisors, has been working on developing a Pompe Connections devoted to Gene Therapy. This Brochure is now available on the IPA website. We intend to begin the translation process in 2022.

We would 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

Due to the ongoing COVID-19 pandemic, many Conferences were moved to a virtual setting in 2021. Below please find short summaries of some of the Conferences that took place during 2021 that were attended by IPA Board members.

WORLD Symposium

Allan Muir attended the virtual WORLD Symposium in February 2021. 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. Following the Symposium, Allan and fellow IPA Board member, Raymond Saich (Australian Pompe Association) hosted a webcast to discuss what was learned.

This webcast can be viewed at: https://worldpompe.org/news/647-world-symposium-2021-webcast. You can activate the auto-translate feature to have subtitles in your own language. This feature is only available on personal computer browser.

IPA AGM 2021

The IPA's Annual General Meeting in 2021 will take place virtually in early December 2021.

Looking ahead

For 2021 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
October 2021