ANNUAL REPORT

2022

esperare foundation

The EspeRare Foundation's mission is to develop therapeutic solutions and address severe unmet medical needs in rare diseases. As a not-for-profit biotech, we achieve this through a collaborative and patient-centered approach that uncovers the potential of existing technologies and healthcare products. With the ultimate aim of giving underserved patients universal access to these new medicines.

Leaving no one behind

At EspeRare we are committed with our hearts and collective expertise to transform the lives of children battling life-threatening rare diseases.

Every minute, a child is born with a rare disease that has no cure and ONE out of FOUR of these children will not live to celebrate their 5th birthday. Approved treatments exist for only 5% of these conditions and where they exist, they are generally not well adapted for use in children and access can be challenging.

This is why, the EspeRare Foundation focuses on bringing to life and accelerating the development of innovative and accessible treatments to children affected by these underserved diseases. We put the patients and their families at the center of everything we do. The patient community guides how we tackle diseases, informing our approach: from therapeutic product selection to supporting clinical testing and helping develop new strategies for therapeutic distribution.

EspeRare

For further information on EspeRare, please visit www.esperare.org

> “Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world” -
>
> **Louis Pasteur**

Word of the Executive Committee

A decade ago, as co-founders, we embarked on a journey to establish EspeRare as an innovative, inclusive, and efficient force in the development of therapies for rare diseases. We were driven by the belief that everyone deserves access to life-changing medical treatments, and we sought to transform the landscape of rare disease research. Today, we celebrate together our many accomplishments and reaffirm our commitment to this mission.

Our daring strategy, built on three pillars – challenging and rethinking traditional drug development pathways, leveraging philanthropic and public capital, and reinvesting profits in new developments through our not-for-profit model – has produced tangible results. Our accomplishments are a testament to the strength and resilience of the rare disease ecosystem, which thrives on the collective efforts of clinicians, patient associations, pharmaceutical partners, and the unwavering support of public and private donors.

The pioneering work we carry out has brought us closer to addressing the high unmet medical needs of the often-overlooked individuals, particularly children affected by orphan diseases. A prime example is our ER-004 treatment for X-linked hypohidrotic ectodermal dysplasia (XLHED), which has reached clinical proof of concept and regulatory endorsement and is now advancing through a commercial partnership and clinical study (page 14). Together with Pierre Fabre, EspeRare aims for ER-004 to become the first approved and effective treatment for XLHED patients globally.

In 2022, we made further strides in addressing medical needs of patients with Congenital Heart Defects. To protect the innovative concept of NeoCare, its design that matches premature neonate’s anatomy and indications, we filed a patent application in June 2022 (page 24). The promising research program for Duchenne Muscular Dystrophy entered the next phase of clinical development (page 21). Our Rimeporide project has shown positive results in models of Pulmonary Arterial Hypertension and Coronavirus infections leading to patent filings (page 22).

EspeRare remains agile, bold and fosters a collaborative environment to catalyze innovation for the global orphan disease population, illuminating the path towards a brighter future.

As we continue to grow as a not-for-profit biotech, our focus is on advancing prenatal therapeutic development, as with ER-004, which has the potential to transform the lives of children born with irreversible pathology. This approach offers numerous benefits, including improved treatment effectiveness, enhanced quality of life, and cost savings for patients, families, and the healthcare system (page 25).

Our vision exceeds boundaries as we drive established rare disease paradigm into uncharted territories. Guided by a venture philanthropic model that embraces shared scientific knowledge and accessibility for all, we want to unlock and accelerate prenatal healthcare in an ethical and responsible way.

We extend our deepest gratitude to the Board, our dedicated team, volunteers, advisors, consultants, donors, and funders for their immense support and faith in our mission. We believe that together with our strong allies, we can achieve more than we can imagine and continue to illuminate the path towards a healthier, more inclusive future.

With sincere thanks, optimism and anticipation for the future,

Béatrice Greco

Founder and Board Member

Caroline Kant

Founder and Executive Director

Florence Porte-Thomé

Founder and R&D Director

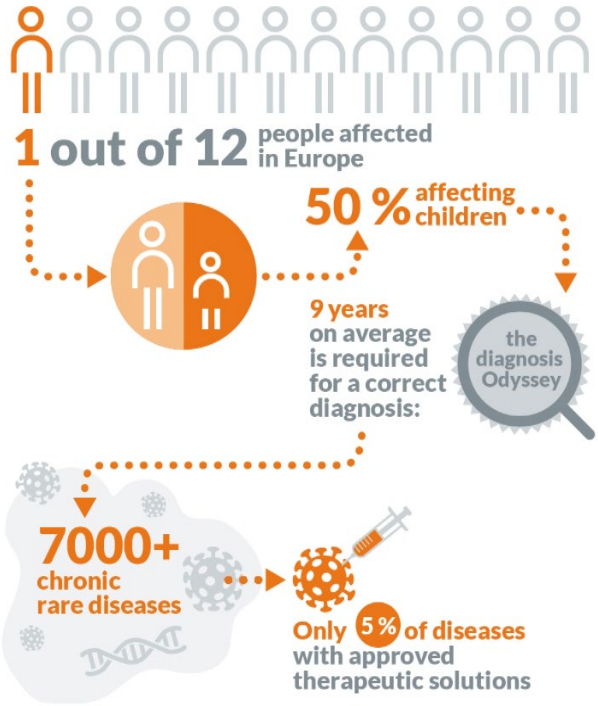
Why do only 5 % of rare diseases have approved treatments ?

Addressing rare diseases

RARE DISEASES: A MAJOR GAP IN THE MEDICAL LANDSCAPE, PARTICULARLY FOR CHILDREN

In Europe, up to 30 million are impacted by a rare disease. It is considered a rare disease when it affects less than **1 person in 2,000.** In the United States, a disease or disorder is defined as rare when it affects less than 200,000 people*. Rare diseases are **chronic, progressive, degenerative, and often life-threatening.** Due to their low prevalence and high complexity, their management requires special combined efforts.

* Source: Orphanet and the US Orphan Drug Act



DRUG DEVELOPMENT: A LONG, COMPLEX AND COSTLY PROCESS

Developing new treatments is expensive, lengthy and requires tight coordination between a large spectrum of research and development (R&D) activities and expertise. Recent reports estimated an average expenditure of at least 1 billion dollars and a time frame of 10 to 15 years to bring a drug to the market.

INSUFFICIENT EFFORTS IN DRUG DEVELOPMENT FOR RARE DISEASES

Despite significant progress made in scientific research and technologies, **drug development efforts remain insufficient to address medical needs in rare diseases.** Therapeutic development suffers from the heterogeneity and complexity of these diseases, the limited number of patients, the fragmentation of medical expertise and the lack of pathophysiological understanding.

New hope for children with life-threatening rare diseases

ESPERARE DISEASE FOCUS

EspeRare is driven by the urge to improve the lives and healthy development of children suffering with rare genetic diseases.
Leveraging a strong disease community and a ripe "drug development infrastructure" (e.g., scientific knowledge, patient registries, diagnostic tests, etc.), EspeRare focuses on novel approaches to therapeutic development and on activities with the most significant impact for rare disease patients.

> "As a not-for-profit organization, our priorities are not determined by the size of the market. They are solely defined by high unmet medical needs and great science. Above all, we strive to apply our patient-centric model and pharma know-how to advance and accelerate new treatments for underserved patients" –
>
> **Caroline Kant**
> Founder and Executive Director

ESPERARE RESCUES AND REPOSITIONS DRUGS TO ACCELERATE THE DEVELOPMENT OF ACCESSIBLE TREATMENTS FOR RARE DISEASES

EspeRare focuses on bringing to life discontinued treatments and developing them into safe and life changing therapies. The drugs selected by EspeRare are at various stages of development and have been discontinued because of several reasons that may include changes in therapeutic focus, lack of efficacy in the original indication or unwillingness to invest the necessary funds to pursue their development.

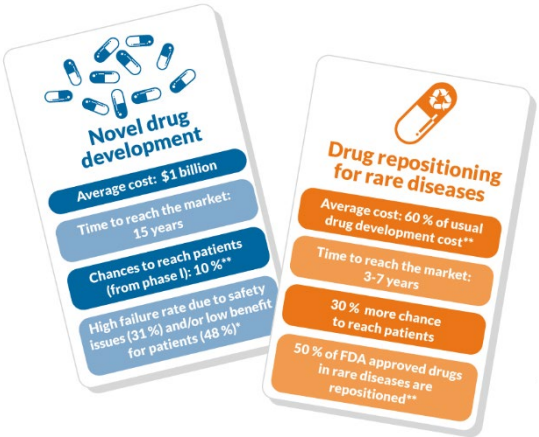
The Foundation's goal is to develop treatment opportunities that remain economically attractive for commercial partners as well as beneficial and accessible for patients and the healthcare system at large.

The inherent incentives to drug repositioning:

- Existing drugs are already known to exert a biological response in humans and this response may become beneficial for other health conditions.
- Many steps in the drug development process such as drug activity and good safety profile in humans have already been demonstrated during the initial development of the drug.

Rationale for repositioning drugs:

- Faster, de-risked and cost contained approach,
- Less costly and more accessible treatments,
- Accelerated development of new therapies for rare disease patients.



** Ref: M. Hay et al., Nature Biotechnology 32, 40–51 (2014)*
*** Ref: Anne Pariser, Director at CDER*

EspeRare's patient-centered approach

PATIENTS ARE AT THE CORE OF CURRENT PROGRESS IN RARE DISEASES

EspeRare is uniquely positioned to work hand-in-hand with patient associations at each step of the development process. Notably, because of the foundation's not-for-profit model and strategic partnership with Genetic Alliance, a network of more than 1,200 disease advocacy organizations.

Patients are at the core of healthcare progress in rare diseases: individuals affected by rare diseases, their families, communities and advocacy organizations have increasingly been recognized as critical partners in their process.

A COLLABORATIVE AND ACCELERATED APPROACH

EspeRare combines pharmaceutical know- how and a mix of philanthropic and public investments to uncover and accelerate the development of treatments that have been discontinued. The Foundation focuses on reviving treatments, with its well-characterized modes of action and well-established safety profiles in non-clinical and clinical studies. More specifically, EspeRare concentrates on driving preclinical and clinical development activities that are required to demonstrate the therapeutic benefits of the therapies under investigation.

EspeRare works hand-in-hand with patients' community at every step of the therapeutic development. Every effort is made to put the **patients' interests first, ensuring the patients' safety, maximizing patients' medical benefits, patients' access to treatment and enhanced care.**

For each of its drug development program EspeRare develops Product Development Partnerships with the patients' community, medical experts and commercial partners that :

- mobilize research and clinical experts and biomedical centers of excellence to conduct pre-clinical and clinical development activities;
- integrate "patient voice" through working collaboratively with patient advocacy groups;
- ethically engage industry partners to manage transition into late clinical development and commercialization;
- interact directly with regulatory agencies and health authorities to best pave the way to drug/therapy approval and patient access to treatment.

For each programme, we strive to establish trusted collaborations with patient organizations, to drive patient-centered drug development.

EMPOWERED PATIENT ADVOCACY IN RARE DISEASES

Particularly in rare conditions, patient advocacy contributions are key at each stage of drug development:

Given the scarcity and fragmentation of medical expertise, patients are highly knowledgeable and have a strong influence on drug development. They collect and share the natural history data, provide feedback on characterization of the disease and unmet medical needs.

Through their support, research efforts, fundraising and advocacy activities, they actively develop expert networks, manage disease related knowledge, engage in and support biomedical research. They also support the market launch of new treatments and equitable access to healthcare.

PATIENT ADVISORY COUNCIL (PAC)

For each of our programmes, we strive to put in place a Patient Advisory Council (PAC)

The PAC serves as a patient advisory board to EspeRare team members, senior management, and partners. Within the PAC's shared governance, patients' representatives take an active part in the development of a drug or treatment. The framework enables patient representatives to:

- ✓ Share views with the patient community concerning the therapeutic programme;
- ✓ Receive regular programme updates and information to foster patients' and families' access to key programme insights;
- ✓ Provide input into development activities to co-development partners;
- ✓ Make recommendations to help plan, implement and refine efforts towards meaningful patient involvement.

A SNAPSHOT OF OUR STRONG AND ENGAGED NETWORK OF PARTNERS TO ADVANCE TREATMENTS FOR ORPHAN DISEASES

Pharma and Biotech Partners

Pierre Fabre Médicament
Boehringer Ingelheim
National Institutes of Health
edimer — Bringing Hope to XLHED
MERCK
MMV — Medicines for Malaria Venture

Biomedical and R&D Partners

IQVIA
Universitätsklinikum Erlangen
Necker — Enfants Malades
Precision for medicine
HUG — Hôpitaux Universitaires Genève
Université de Genève
CHUV
Unil — UNIL | Université de Lausanne
HEIG-VD
GIG Cymru NHS Wales
Washington University in St. Louis
Institut de Myologie
Great Ormond Street Hospital Charity
Centre Léon Bérard

Patient Organisations

Genetic Alliance
EURORDIS — Rare Diseases Europe
EDIN — Ectodermal Dysplasias International Network
nfed — National Foundation for Ectodermal Dysplasias
ed
aade — Asociación de Afectados por Displasia Ectodérmica
eds — ectodermal dysplasia society
Associazione Nazionale Displasia Ectodermica
IRDiRC — International Rare Diseases Research Consortium
AFMTÉLÉTHON — Cure through innovation
Duchenne Parent Project
Duchenne UK
Action Duchenne

Funders and Sponsors

Loterie Romande
Fondation Prim'Enfance — ...invest in infancy
ALPS Safety
McKinsey&Company
ALPS Automation
26D Creative
Same but Different
Ashoka
Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra
Swiss Confederation
Innosuisse – Swiss Innovation Agency
Connect in Pharma
the ella fund
WATCHESTV — Viva Watchmaking

Thank You

Our alternative and sustainable business model

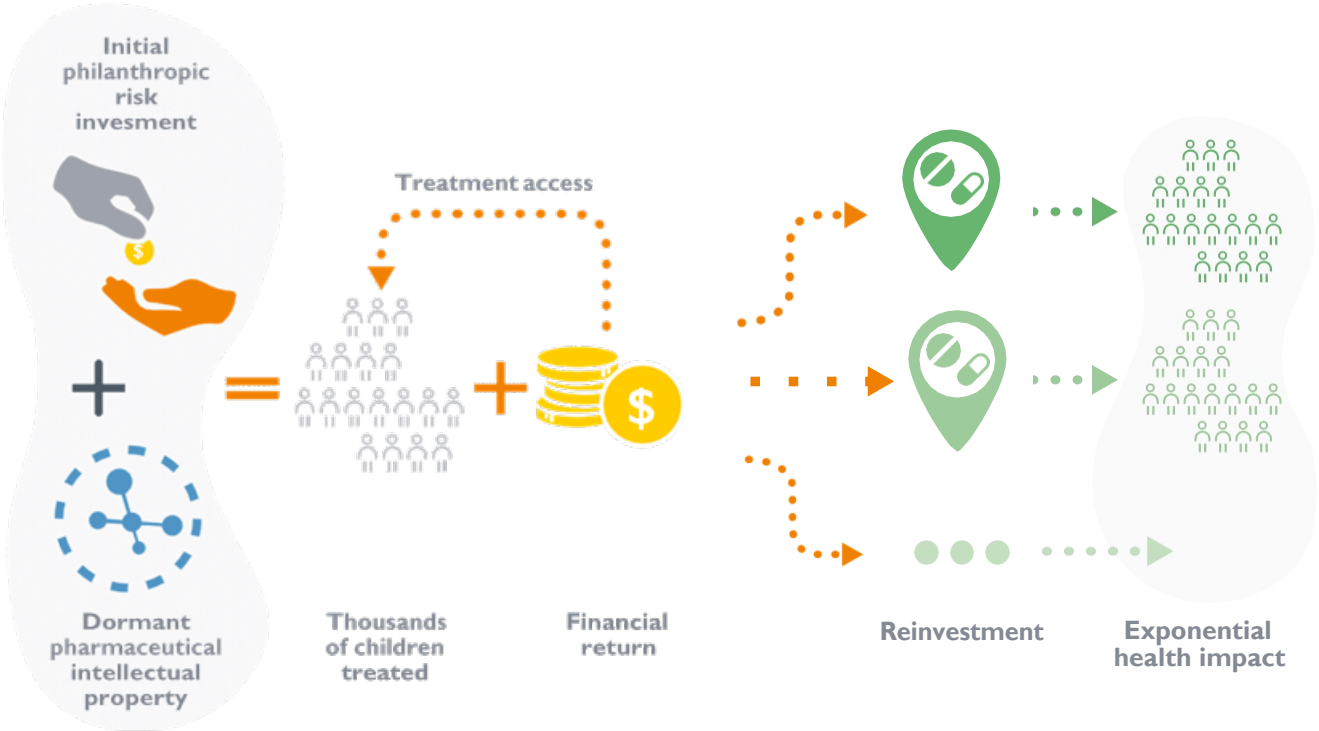
IMPACT OF ESPERARE'S NOT-FOR-PROFIT BUSINESS MODEL

OUR VENTURE PHILANTHROPY MODEL MULTIPLIES THE IMPACT OF PHILANTHROPIC INVESTMENTS AND PHARMACEUTICAL KNOW-HOW TO ADDRESS THE UNMET NEEDS OF MILLIONS OF CHILDREN WITH RARE DISEASES AND THEIR FAMILIES

EspeRare combines pharmaceutical know-how and philanthropic investments to revive existing yet discontinued drugs to treat children with rare diseases, who are otherwise underserved due to the lack of current therapeutic options, and drug development efforts.

As an organization of public interest, EspeRare is committed to using its funding resources in a socially responsible and not-for-profit manner. **It reinvests all of its profits to further achieve its mission** of developing treatments for underserved rare disease patients, improving their quality of life and driving access to medicine it develops.

All financial returns that EspeRare generate are being used to strengthen EspeRare's organization and its portfolio of therapeutic programs and collaborative partnerships. These financial returns are enabling EspeRare to establish itself as a major drug development player within the paediatric rare disease space and confirm the viability of its novel not-for-profit model and its ability to accelerate accessible treatments for these vulnerable patients.



Innovative approach to advance treatments and care for patients

ESPERARE'S DIGITAL PLATFORM FOR THE IDENTIFICATION AND DEVELOPMENT OF TREATMENTS IN RARE DISEASES

BIOMEDICAL INFORMATICS ENGINE

Our "*in silico*" approach enables to discover novel therapeutic opportunities for existing drugs. EspeRare is currently developing a **collaborative digital platform** to systematize discovery and support the efficient development. It is constituted of different layers of:

Discontinued treatments database: compiling data on 2'000 existing drugs with the potential to be "redeveloped" in rare diseases. This database aggregates and structures data about these drugs such as their initial disease(s) of development, their safety and toxicity profile and their biological mechanism of action. A collaboration with the National Institute of Health (US) has enabled to have access to data on all drugs developed worldwide.

Rare disease analytics system: integrating biomedical data on the molecular pathophysiology of targeted rare diseases. The information is extracted from scientific literature and specialized databases. This understanding of the biological cascades involved in these diseases is validated and enhanced by integrating data and insights from EspeRare network of biomedical experts.

Patients' Vault: the platform integrates patients' insights. By working hand-in-hand with the patients' community, the identification of new therapeutic approaches and their development are powered by a patient-centered approach.

In support of:

LOTERIE ROMANDE

Genetic Alliance

NATIONAL INSTITUTES OF HEALTH

We are currently seeking like-minded partners and funders to further develop this platform.

Our portfolio of treatments

Since its establishment in 2013, EspeRare continuously gives a chance to dormant therapeutic opportunities to reach its major goal: the discovery and development of new medicines for the treatment of rare diseases. Thanks to public and philanthropic funding, and collaboration within rare disease ecosystem, the Foundation advances a diverse portfolio of therapeutic programmes.

The pioneering protein replacement therapy, **ER-004** is on its way to become the first effective prenatal treatment for XLHED patients. The EDELIFE clinical trial is up and running in all 6 planned countries (p. 14).

Rimeporide, a drug exhibiting a therapeutic potential in children affected by Duchenne, undergoes discussions of the phase II/III study to pave the way for a therapy that specifically targets DMD boys who lost ambulation (p. 21). In addition to DMD, Rimeporide has shown its potential in other disease indications (p. 22).

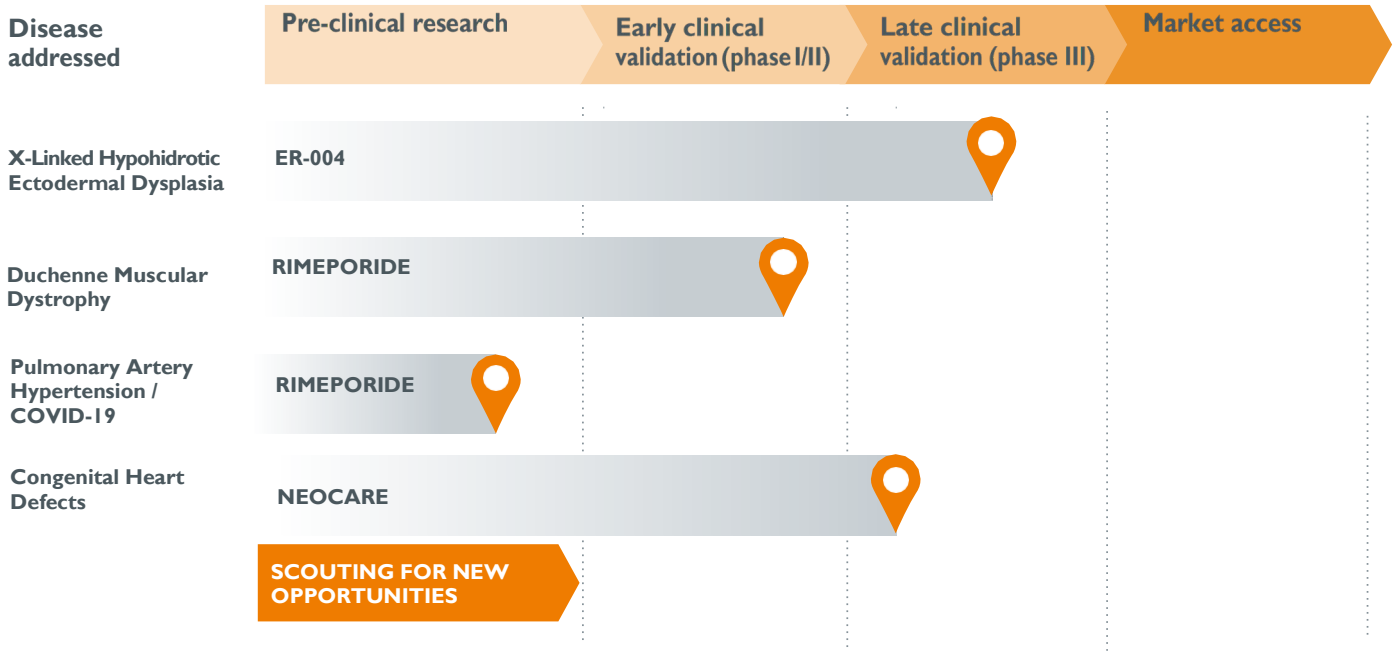
Following the successful completion of the prototype phase, EspeRare filed a patent application in June 2022 to protect the innovative concept and indications of **NeoCare** before entering the last phase (industrialization) of its development (p. 24).

Capitalizing on the unprecedented development pathway of ER-004, EspeRare is invested in exploring novel therapeutic interventions in the field of **prenatal medicine** to correct genetic defects before birth (p. 25).

EspeRare is diversifying its partners and developing its portfolio in rare diseases by:

- working with pharmaceutical companies, patient organizations and academic partners to evaluate opportunities that fit EspeRare's development model and address high unmet medical needs;
- developing its Platform, a bio-medical informatics engine that systematically identifies and evaluates drug rescue and repositioning opportunities.

A PROGRAMME PORTFOLIO UNDER DEVELOPMENT WITH MULTIPLE PARTNERS



X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED)

A LIFE-THREATENING DISEASE WITH A WIDE RANGE OF DEBILITATING SYMPTOMS THAT PERSIST THROUGHOUT LIFE

XLHED is a rare genetic disorder caused by a defect in the EDA gene inherited on the X-chromosome. Individuals with XLHED lack a functional EDA-A1 (EDA protein, essential to the normal development of a dermal layer during fetal development).

Consequently, the development of ectodermal structures such as skin, teeth, glands and hair are impaired. As boys have one single copy of this gene on their X-chromosome, they usually display the full spectrum of the syndrome as opposed to girls that are in general less affected.

XLHED is a life-threatening disease, particularly in the first years of life when infants are at risk of sudden death due to hyperthermia and/or pneumonia. Disease morbidity, including psychosocial challenges, often persist into adulthood.

XLHED represents also an important medical and healthcare burden. Recurrent infections, hyperthermic episodes and other health issues cause frequent hospitalizations, especially in the first part of childhood. It is estimated that, in the United States, direct hospital costs amount to over $ 50'000 in the first 3 years of life alone and dental costs amounting to up to $150'000 throughout a patient's lifespan can be expected. Consequences of brain damage, treatments related to hair, dentition issues as well as psychosocial challenges require important and costly medical care throughout the life of patients affected by XLHED.

The incidence of XLHED is estimated to be ~4/100,000 male births.

ER-004 PROGRAMME IN X-LINKED HYPOHIDROTIC ECTODERMAL DYSPLASIA

The development of ER-004 (previously named EDI200) was stopped by Edimer Pharmaceuticals, due to treatment's lack of efficacy when treating newborns with XLHED.

EspeRare has revived ER-004 using a novel intra-amniotic administration route. It has also entered into a partnership with Pierre Fabre and launched a clinical study with the aim of bringing this protein replacement therapy to the market.

BACKGROUND

2017

Edimer Pharmaceuticals closed its operations because of the lack of positive results when administered

ER-004 to neonates. Then EspeRare was approached by Edimer Pharmaceuticals to revive ER-004's clinical development of this programme in XLHED, then stalled.

EspeRare establishes a collaboration with Prof. Holm Schneider, the German paediatrician who worked closely with Edimer on the development of this therapy and pioneered the first intra-amniotic administrations of ER-004 to 3 unborn XLHED foetuses.

The development of ER-004 in XLHED using an intra-amniotic administration approach before birth was accepted in the European Medicines Agency's PRIority Medicines scheme. The "PRIME scheme" aims at accelerating the development of therapies for unmet needs. Furthermore, ER-004 also benefits from Orphan Drug Designation in the EU and the US and Fast Track Designation by the FDA in the US.

2018

EspeRare through a Protocol Assistance meeting seeks advice from the EMA to present all data collected and to understand whether this pioneering intra-amniotic administration route can be developed. The EMA has agreed with EspeRare's proposal that prenatal treatment of XLHED through intra-amniotic drug administration is the way forward to develop ER-004 into a treatment for XLHED.

2019

A similar meeting was conducted with the FDA, who are also supportive of ER-004 as a prenatal treatment for XLHED. This gives EspeRare the green light to actively start seeking a co-development partner and finalize a robust clinical development plan.

2020

EspeRare and the Pierre Fabre Group signed a co-development agreement to jointly develop ER-004 towards commercialization as a prenatal treatment for XLHED. As partners, they sign up and commit to an Ethical Charter that governs their relationship and places the XLHED patient community at the heart of the development. Together, EspeRare and Pierre Fabre are setting up a clinical trial that aims at bringing ER-004 to the market in the EU and the US.

Pierre Fabre

2021

EspeRare and the Pierre Fabre Group successfully launched the EDELIFE pivotal clinical trial to probe the safety and efficacy of ER-004 as a prenatal treatment for XLHED, with a first center open for enrolment in Erlangen, Germany, in November 2021.

In parallel to the clinical activities conducted to confirm the safety and efficacy of the ER-004 treatment, research activities are conducted in collaboration with Dr. Pascal Schneider at the University of Lausanne to address main gaps in the basic understanding of the ER-004 therapeutic approach. EspeRare and the laboratory of Dr. Schneider have been awarded an Innosuisse grant for this research from the Swiss Confederation in June 2021.

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Innosuisse – Swiss Innovation Agency

2022

In 2022, pivotal trial investigator sites opened in the rest of the world (France, Italy, Spain, the UK, and the USA) and the first patients were treated. The edelifeclinicaltrial.com website was launched, serving as a source of information on study description, design, eligibility criteria, and contact details of investigators and patient representatives. With the EDELIFE trial up and running, EspeRare's focus turned to overcoming the main challenges, namely boosting recruitment and completing all development activities in time to take ER-004 to market, with a submission of the registration dossier anticipated for 2025.

2023 and beyond

In 2023, with all clinical sites open, we are looking to recruit as many patients as possible into the EDELIFE study, and many strategies will be put into place for doing so. A Natural history study will be launched, to enrich the existing body of data and ensure a fully comparable dataset for the clinical study results. In parallel, completing all development activities in time for Marketing authorization will be challenging and will require iterative engagement and discussions with the Regulatory Authorities, starting with an initial focus in 2023 on the FDA.

> "I sincerely wish that efforts of all partners involved in the development of a treatment for XLHED will be rewarded when ER-004 can be made available to XLHED families as the first successful treatment to prevent or reduce symptoms of the disease" -
>
> **Pascal Schneider**
> PhD-PD, UNIL

ER-004 - A "SINGLE COURSE" THERAPY TO INDUCE NORMAL ECTODERMAL DEVELOPMENT IN BABY BOYS WITH XLHED

ER-004 – AN INNOVATIVE PROTEIN REPLACEMENT THERAPY (PRT)

Ectodysplasin-A1 (EDA1) is an essential protein for the normal development of ectodermal structures in the foetus and is missing in patients with XLHED. Without this protein, XLHED-affected boys have many serious and life-long health challenges, with the inability to sweat being the biggest of these challenges, potentially threatening the lives of small children.

ER-004 is a novel in-utero therapy to replace EDA1. ER-004 is a man-made synthetic form of the EDA1 protein that is administered by intra-amniotic injections during the late stage of foetal development. The protein is given through the mother's abdomen into the amniotic sac where it is swallowed by the baby.

During the clinical trial, the efficacy of the treatment will be measured after birth by assessing, as the main outcome, the restoration of the ability to sweat. This assessment is achieved by probing the development of sweat glands, which are visible as pores on the skin surface using a high-resolution imaging device called a VivaScope®.

This equipment is key to the success of the conduct of the clinical trial and EspeRare will face the last steppingstone of securing funding in 2022 for the purchase of three of these VivaScopes®, to equip clinical investigational sites.

ER-004 has already demonstrated a significant improvement in the normal development of key ectodermal structures such as glands, teeth and hair. Six patients treated with ER-004 before birth by Prof Holm Schneider at the University Hospital Erlangen in Germany were born with normalized sweat gland function and the initial results obtained in the first three patients were published in New England Journal of Medicine*.

This breakthrough in medicine opens the door to a brighter future for couples who are carriers of the XLHED gene variant, as is the case of Laura and Milo Reiser, an American couple from Oregon.

* Schneider H, et al. Prenatal Correction of X-Linked Hypohidrotic Ectodermal Dysplasia. N Engl J Med. 2018 Apr 26;378(17):1604-1610

Laura grew up watching her father suffer from overheating and she did not want to provide such a future for her children. For years she put off starting a family and stayed tuned to the American patient association, the **National Foundation For Ectodermal Dysplasias** (**NFED**), in the hope of advancements in medical research. The NFED's mission is to empower and connect people affected by ectodermal dysplasias through education, support and research. The NFED is also a place where individuals and families can learn about clinical trials, get tips and advice as part of this large community.

Medical research progress in XLHED and support from the NFED patient association turned out to be the trigger for Laura and Milo to start a family.

THE REISER FAMILY PATIENT STORY – *HOW ER-004 CHANGED MY SON'S LIFE*

After having their first baby girl, Evie, who was unaffected by XLHED, the couple decided to have another child. The genetic test done at 8 weeks in the pregnancy confirmed they were expecting a boy. When the Reisers reached out to Prof. Holm Schneider, they received the news that their unborn baby boy was affected by XLHED. The couple was ready to face the difficulties this medical condition meant for their son, until Prof Schneider asked if they were willing to consider treating their son with an experimental medicine named ER-004, to which Laura answered:

> "I was like 'yes, I've been wanting to be part of this for 15 years!' We knew that it would work and that it would change his life. Otherwise, we would not have done it".

Despite the pandemic and a storm of mixed emotions from happiness to fear, Laura was determined to fly across the Atlantic Ocean to Germany so that their unborn son could receive the ER-004 treatment during the last couple of weeks of his fetal development. Her motivation grew the moment she was put in contact with Emily, another mother whose son Finley had been treated pre-birth by Prof Schneider a few months earlier and who had been born healthy.

"I don't think I would've committed to doing it if I didn't have the opportunity to talk with Emily beforehand. She was able to answer so many questions".

Laura received three injections of ER-004 during her stay in Germany, along with other usual tests such as blood drawings, ultrasounds and COVID tests. She felt really welcomed and supported by the whole team of Prof Schneider.

She tested positive for COVID on the day she welcomed her son Bennett:

"Bennett was so cute and so very tiny. He didn't have any effects from COVID and tested negative for it."

***I knew that it would work. I had no doubt, because I knew Emily's son, Finley, and the other twin boys who were treated could sweat. Also, I had built a really good relationship with Dr. Schneider, and I totally trusted what he was doing".* – Laura reported.**

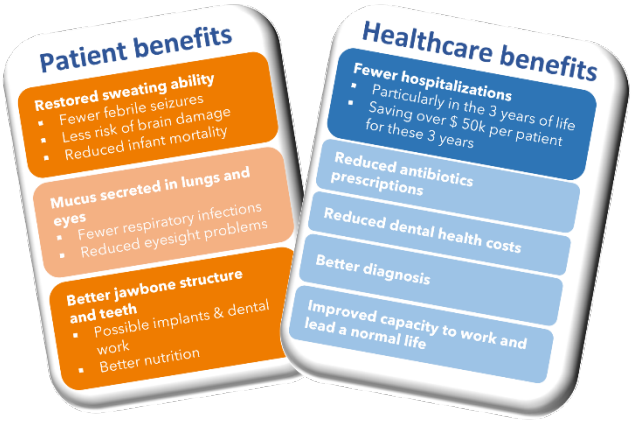
Moreover, so far, Bennett has not had any respiratory problems, shows an increased number of meibomian glands in his eyes and has tooth buds. All are encouraging signs that the treatment has not only restored Bennett's ability to sweat but might also have improved the functionality of other ectodermal structures that are affected in XLHED patients.

Laura, who went through this journey with Prof. Holm Schneider, has expressed her willingness to help other pregnant women who are considering taking part in the trial and support them in building a new future for their children, saying that the ability to sweat and regulate body temperature is the most wonderful gift we can offer to those children.

> "Bennett's the sixth baby in the world, I believe, to have something like this done, not just for ectodermal dysplasia, but any sort of prenatal therapy. It's just amazing. It's going to take enough people willing to do it, to get to where it is available for other purposes as well. So, to me to be the sixth is pretty incredible. I hope he understands one day what it took" -
>
> **Laura Reiser**
> Bennett's mother

To the delight of the Reiser family, it did not take long to confirm that Bennett could sweat:

"At two months, we went on a little trip, and we slept on one of those egg crate mattresses. Bennett was sleeping next to me and he was drenched in sweat. So we knew that he could sweat from that moment.

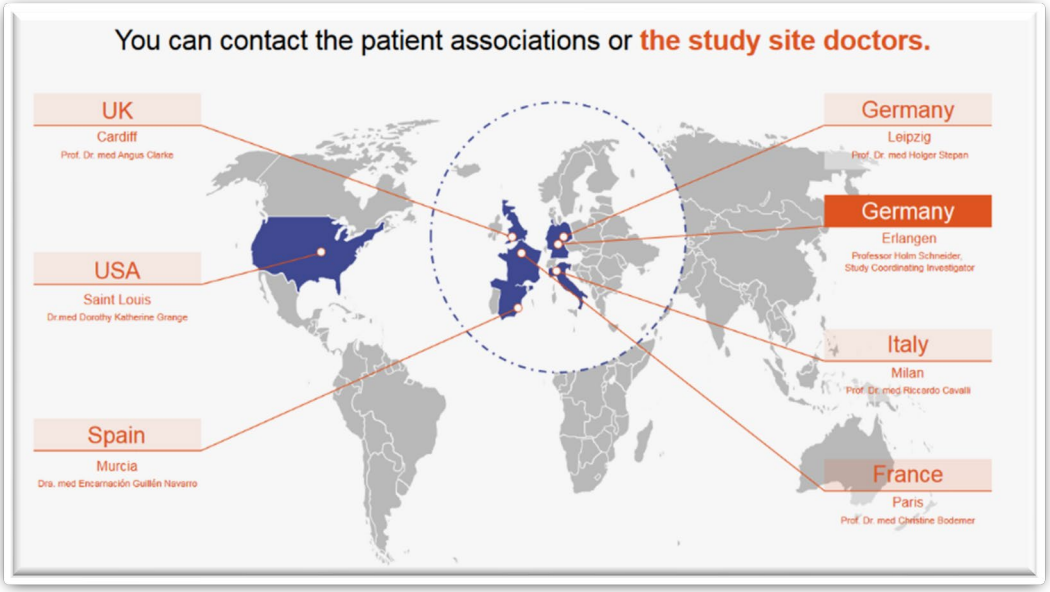


nfed
Supporting you. Supporting each other.
NATIONAL FOUNDATION FOR ECTODERMAL DYSPLASIAS

> *"Thank you to the NFED for everything that you're doing. It is super helpful to have everything and to have been able to track it all of these years. I would not be in this seat right now had it not been for all the countless hours. I can't even imagine everything that has gone into the research to get to this point. Thank you for everything. Bennett is the most amazing, amazing little guy ever!"* - Laura Reiser.

At EspeRare we are very grateful to the NFED for sharing this inspiring story on its blog. Together with other Ectodermal Dysplasia patient groups, the NFED has been at the forefront of advancing research and healthcare for individuals affected with XLHED, for the best part of three decades.

THE EDELIFE CLINICAL STUDY FOR XLHED IS NOW RECRUITING PREGNANT WOMEN !

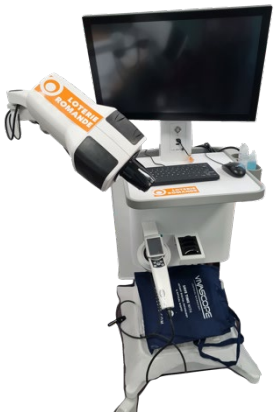


EDELIFE is a pivotal clinical study for the prenatal treatment of XLHED-affected boys. It has been set up to offer to all interested XLHED-affected families that meet certain criteria, the treatment Laura and a handful of other families benefited from. Indeed, these fetuses were treated by Prof Schneider under a "named patient use" scheme, and not within a clinical study yet.

The first investigational site opened for recruitment in Germany in November 2021, followed by the sites in France, Italy, Spain, the UK, and finally the US in August 2022 to offer to as many eligible patients as possible, the chance to participate in the clinical study.
In 2022, the first fetal patients were recruited in the EDELIFE clinical study and received three injections of the ER-004 treatment as planned. This experimental treatment (not approved for commercial use yet) is administered through the mother's abdomen into the amniotic fluid surrounding the baby. The pivotal study aims to treat approximately 15 to 20 unborn baby boys across 8 investigational centers in Europe and the US to assess the safety and efficacy of the ER-004.

The efficacy will be measured after birth by assessing the restoration of the sweating function. Studying the development of sweat glands, which are visible as pores on the skin surface is achieved by using high-resolution imaging devices, the VivaScopes®.

Thanks to the generous support of the Swiss Lottery (Loterie Romande), EspeRare was able to fully equip the clinical sites with these devices, specific to dermatological diagnosis and essential to the successful conduct and approval of the EDELIFE clinical study.



LOTERIE ROMANDE

Interested participants are encouraged to get in touch with the Investigators or their ED Patient Associations, even if they do not live in the countries where the study is conducted, as travelling from abroad to the investigational site is allowed and expenses are covered by the study.

Based upon EspeRare's patient-centered approach, a dedicated web site for interested families has been launched (www.edelifeclinicaltrial.com) providing more information on the trial in 6 languages, including who can take part in the study, what taking part in the study will involve and who to get in touch with for further information.
Additional details are also available on www.clinicaltrials.gov.
Study NCT04980638

edelife

An open-label phase 2 trial to investigate efficacy and safety of intra-amniotic administrations of ER004 in male subjects with X-linked hypohidrotic ectodermal dysplasia (XLHED)

espeRare

Pierre Fabre

OUR COMMITMENTS, PRINCIPLES AND VALUES

COMMITMENTS TO THE

XLHED PATIENT COMMUNITY

EspeRare regards the continuing engagement of the patient community as critical for the success of the programme. With its unique patient-centered approach, we fully engage the patient community at each step of the drug development process.

JOINT PRINCIPLES AND VALUES

These principles and values guide all interactions with any other stakeholders involved in the programme. Every effort is made to extend their largest application possible.

PATIENTS FIRST, including:

- Patient safety (comes first);
- Maximization of patient medical benefits and patient access to treatment;
- Ensure patient engagement and continued information sharing with the patient community.

TRANSPARENCY about roles, responsibilities, constraints, potential conflicts of interest as well as the outcomes of the ER-004 programme.

RESPECT, including:

- Fairness in all situations;
- Consultation and accessibility;
- Ability to hear and take into account diverging views;
- Equal partnership, co-learning with mutual added-values.

INTEGRITY of behaviors, processes, use of funds, as well as being driven by moral soundness and account-ability.

EspeRare has convened a **Patient Advisory Council** (PAC), composed of patient groups representatives, whose mission is to serve as the primary interface between the XLHED patient community and the Foundation to streamline information-sharing and collect insights from the patient community for the development of ER-004. Within the framework of joint principles and values, PAC promotes patient-centeredness in the conduct of activities at different stages of the therapy development process.

Since the early development of ER-004, the patient groups representatives played invaluable role in providing the disease expertise, identifying unmet needs, participating in the discussions with authorities, and facilitating the design and recruitment process of the EDELIFE clinical study.

Clinical study design:

- Synopsis review
- Protocol feasibility
- Site selection feedback
- Glossary review for the clinical study documents

Clinical study recruitment:

- Review of study guide
- Review of study leaflet to advertise research
- Leverage on their communication channels to help recruiting families
- Advocate for EDELIFE clinical study at family conferences

Duchenne Muscular Dystrophy (DMD)

ABOUT DUCHENNE MUSCULAR DYSTROPHY (DMD)

Duchenne Muscular Dystrophy (DMD) is a severe genetic paediatric disease that **affects 1 in 3,500 boys worldwide.**

Patients affected by DMD have **progressive weakness and loss of muscle function in their early childhood.** The degeneration of muscle cells is accompanied by an immune reaction (inflammation) and scarring of the muscle (fibrosis). This progressive muscle wasting typically leads to loss of ambulation (ability to walk) around 10 years of age. It eventually spreads to the arms, neck and other areas of the body.

Later in the twenties, increasing difficulty in breathing requires using a ventilator at night, while cardiac muscle dysfunction progressively leads to heart failure.

Cardiac dysfunction is present in most DMD patients and is the primary cause of premature death. While there has been recent progress in the management of these patients, heart failure is becoming the primary cause of premature death.

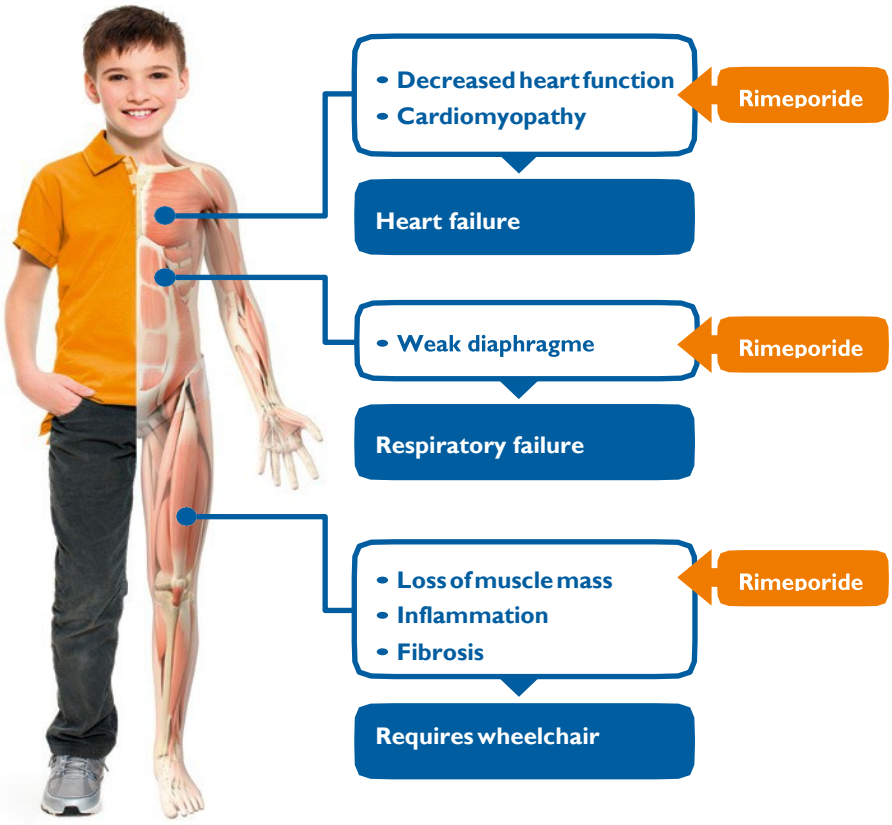
The use of corticosteroid is the main pharmacological intervention, but it has limited efficacy and induces severe side effects upon chronic use.

While additional therapies and treatments exist to alleviate symptoms associated with skeletal muscle pathology, they do not alter the ultimate outcome of the disease.

There is therefore an urgent need for new therapies to halt the progression of the disease and in particular treatments that help preserve heart and respiratory functions for all Duchenne boys, e.g., regardless of their mutation.

> “Treatment for Duchenne is currently largely limited to glucocorticoids that have been shown to prolong ambulation and also help to prevent scoliosis. More satisfactory treatments are urgently needed. Efforts are focused on identifying drugs or biological agents that have the potential to maintain long term muscle function alongside an acceptable side effects profile” -
>
> **Duchenne UK**
> DMD Patient Association

> “Duchenne is a heartbreaking disease. Children like Laurent, my cousin, affected with this disease are bright and engaged but as they grow up, they inexorably get weaker and experience the loss of the few abilities they had acquired. I have in my genes the eagerness to find treatments for this disease and I am committed to giving them the strength to fight their disease” -
>
> **Florence Porte-Thomé**
> Founder and R&D Director



300 000 boys affected worldwide

Affects the longest gene in the body: the dystrophin gene

Symptoms appear between the ages of 2 and 5 years

Described by Dr. Duchenne in 1861

A SOLID NETWORK OF PATIENT GROUPS AND DISEASE EXPERTS TO ADVISE AND STRENGTHEN RIMEPORIDE DEVELOPMENT STRATEGY

R&D funding and collaboration with patient groups: French Telethon (AFM) & Swiss Technology & Innovation (CTI) supported research in non-clinical studies; AltroDomani Onlus, Duchenne Parent Project Onlus (PPMD) and Merck Serono support the clinical development.

Strategic partnership with clinical centers of Excellence: Great Ormond Street Hospital (London, UK), Armand Trousseau Hospital (Paris, France), Santa Creu i Sant Pau Hospital (Barcelona, Spain) and San Raffaele Hospital (Milan, Italy).

RIMEPORIDE PROGRAMME IN DUCHENNE MUSCULAR DYSTROPHY (DMD)

BACKGROUND

2013

EspeRare obtained the rights to Rimeporide from Merck KGaA.

2014 to 2018

Repositioning of Rimeporide for Duchenne Muscular Dystrophy (DMD)

Repositioning program launched to confirm the scientific hypothesis and the therapeutic benefit of using Rimeporide to prevent skeletal and respiratory damage related to the loss of dystrophin in DMD. Short- and long-term studies confirmed that chronic oral administration of Rimeporide is anti-inflammatory, anti-fibrotic, and provides a clinically relevant effect to protect the skeletal muscles, the respiratory muscle (diaphragm), and is cardioprotective.

Orphan Drug Designation granted by the European Medicines Agency (EMA) for Rimeporide in DMD in 2015.

Phase Ib clinical trial treating 20 young patients with DMD has been completed. The study, coordinated by Prof. F. Muntoni was conducted in leading neuromuscular centers: the Great Ormond Street Hospital (London, UK), the Armand Trousseau Hospital/ I-motion (Paris, France), the San Raffaele Hospital (Milan, Italy) and the Santa Creu i Sant Pau Hospital (Barcelona, Spain). It showed that the administration of Rimeporide to young DMD boys (aged from 6 to 11 years old) was well tolerated. That was a significant achievement opening the way for Rimeporide to be used as a treatment to prevent muscles wasting due to the lack of dystrophin.

Orphan Drug Designation for Rimeporide in DMD granted by the US FDA in 2017.

2019 to 2022

Designing of the next phase of clinical development for Rimeporide in DMD

EspeRare has launched a large biomarker study in order to identify noninvasive biomarkers to be measured in clinical phase.

An International Scientific Advisory Board with Pr C. Spurney, Pr J. Soslow, Pr F. Muntoni, Pr P. Spitali was set up to support the designing of the clinical plan for Rimeporide as the first treatment to specifically address the life-threatening cardiomyopathy in DMD boys.

Biomarkers study results were presented at the World Muscle Society meeting in Copenhagen, DK and at the Congress of Myology in Bordeaux, FR.

In May 2020, Rimeporide programme received advice from the Duchenne Community Advisory Board (CAB), organized by the Duchenne Data Foundation (DDF). This meeting helped to integrate the patients' voice in the clinical plan.

In September 2020, Rimeporide was granted **Rare Paediatric Disease Designation** (RPDD) for cardiomyopathy in children with DMD by the FDA in the United States. Rimeporide is the first drug to receive a RPDD for **DMD related cardiomyopathy**. Rimeporide will be eligible to receive a **Priority Review Voucher** at the time of marketing approval.

A sound clinical plan has been developed with the Scientific Advisory Board and expert statisticians at Precision for Medicine, an organization with significant experience in rare disease clinical design, including DMD studies. A phase II efficacy study of Rimeporide in DMD boys was designed using recent natural history data (to understand the progression of the disease and the variability among patients) from DMD boys generated by key stakeholders from the community. With this new strategy, the clinical development path is de-risked and timelines to reach the market are optimized. Potential conditional approval could be achieved within 3 years of starting the phase II trial.

Late 2021 and early 2022, a new Rimeporide Business Development campaign was kicked off, aimed at finding a commercial partner to take over the next phase of development.

2023 and beyond

Finding the partner for the pivotal development

EspeRare is seeking a partner to further develop Rimeporide as a major life-changing treatment for DMD boys.

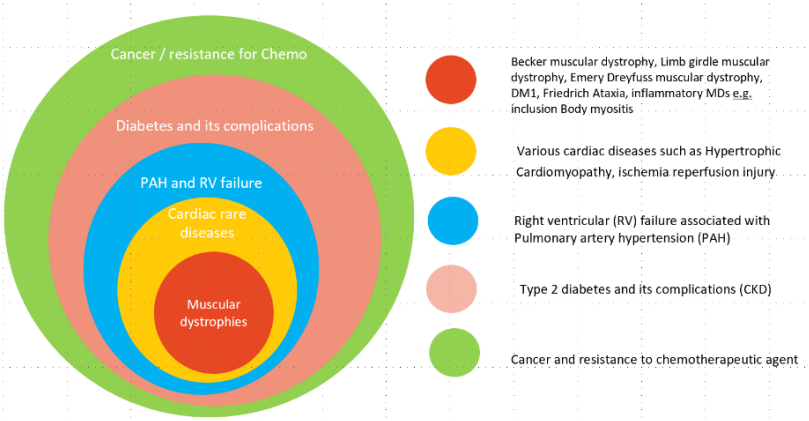
Continued discussions of the phase II/III study design will occur with the International Scientific Advisory Board, Patients Groups and Health Authorities in order to pave the way for a therapy that specifically targets DMD boys who have lost ambulation.

EspeRare is committed to discuss with Health Authorities the pivotal study in order to obtain endorsement on the design for the next phase of clinical development.

Rimeporide is intended to be administered as an oral daily, and chronic treatment in combination with dystrophin replacement therapies and other approved treatments, in all patients with DMD, regardless of their mutation, and as soon as early signs of myocardial fibrosis are detected.

RIMEPORIDE POTENTIAL IN OTHER DISEASES

A pipeline in a product



Rimeporide is an NHE-1 inhibitor. NHE-1 is a Na/H exchanger that participates in the maintenance of the pH balance inside and outside the cell and the prevention of intracellular acidification. It is moreover involved in several other critical cell processes such as cell migration, proliferation control, adhesion, and apoptosis, as well as expression and function changes (that influence inflammation) and that are closely associated with a number of diseases (including cardiovascular disease and diabetes). The inhibition of NHE-1 by Rimeporide is therefore expected to bring benefit in multiple indications.

From 2020 onwards, Rimeporide has been tested in other disease indications, in addition to Duchenne Muscular Dystrophy:

Rimeporide for Pulmonary Arterial Hypertension

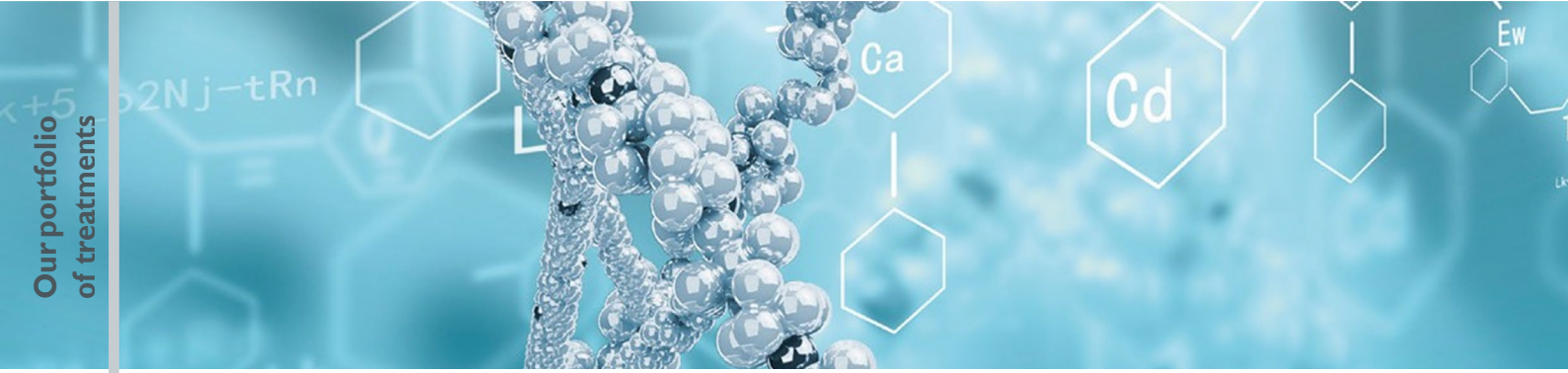
Pulmonary Arterial Hypertension (PAH) is one form of a broader condition known as pulmonary hypertension, which relates to high blood pressure in the blood vessels of the lungs.

PAH is a rare, progressive disorder characterized by high blood pressure (hypertension) in the arteries of the lungs (pulmonary artery) leading to right ventricular failure and premature death. Symptoms of PAH include shortness of breath (dyspnea) especially during exercise, chest pain, and fainting episodes. Although treatable, there is no known cure for the disease. It is important to treat PAH because without treatment, high blood pressure in the lungs causes the right heart to work much harder, and over time, this heart muscle may fail.

- EspeRare has collaborated with the Lausanne University Hospital (CHUV) to confirm the utility of Rimeporide for patients suffering from pulmonary hypertension, addressing both the pulmonary vascular resistance and the maladaptive right ventricular failure.
- During that collaboration, the efficacy of Rimeporide in PAH models was confirmed. Chronic curative treatment with Rimeporide was shown to partially reverse PAH, **with results not seen with available PAH drugs. Rimeporide elicited a decrease in right ventricle fibrosis and pulmonary vascular fibrosis.**

Rimeporide Patent filing for coronavirus infections

While knowledge around the COVID-19 multifaceted illness has progressed, EspeRare has been looking into the potential of Rimeporide to address the cardiovascular life-threatening complications occurring after virus infection, with potential for application in the setting of long-term COVID-19 cardiovascular complication prevention and treatment. In August 2020, EspeRare co-filed with Merck KGaA a priority patient application. Data on the potential benefit of Rimeporide were generated and confirmed the utility of adding Rimeporide to the arsenal of multiple drugs that work in different ways to prevent life threatening complications related to Coronavirus infections. These data were added to the patent and a European PCT was filed in 2021, and subsequently published in March 2022 (International Publication Number WO 2022/043343 AI).



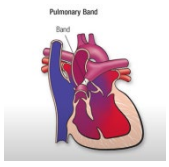
Congenital Heart Defects (CHD)

SEVERE CONGENITAL HEART DEFECTS IN NEWBORNS AND PULMONARY ARTERY BANDING (PAB)

Congenital heart defect (CHD) affects 1 in 100 newborns each year. In 5% of cases the severity of CHD is life-threatening and is responsible for the largest proportion of mortality caused by birth defects. Severe cases are treated by cardiac surgery at birth; when this is not possible, because the health status of the neonates, in particular premature neonates, does not allow open heart surgery at birth, pulmonary artery banding (PAB) is used as a palliative technique to control blood flow in the pulmonary artery (PA) and avoid subsequent development of life-threatening issues known as a pulmonary vascular resistance. With standard PAB, additional surgeries are often required to adjust the PAB and the blood flow in the pulmonary artery. This impacts survival, complications, and the quality of life of newborns and their families and implies prolonged hospital stays.

A REMOTELY ADJUSTABLE DEVICE DESIGNED TO OVERCOME CHALLENGES OF CONVENTIONAL PAB

Conventional Pulmonary Artery Banding (PAB) which consists of a simple GORE-TEX band is far from being optimal for newborns and infants with severe congenital heart defects. The band is placed under general anesthesia and artificial respiration which makes the adjustment of the device very difficult. Long stays in intensive care and further operations to readjust the band tightness are sometimes required. Moreover, GORE-TEX band often leads to scarring and fibrosis of the Pulmonary Artery (PA) vascular walls and requires PA's reconstruction at the time of PAB removal. This situation is traumatic to newborn and their parents, and results in increased mortality and morbidity.



This problem is even more acute in developing countries where surgery and post-operative care are often basic at best.

To address this high unmet medical need, EspeRare has initiated the development of **NeoCare: a new generation of remotely adjustable medical device** that can regulate the blood flow to overcome challenges of a conventional PAB.

NeoCare is an innovative and a life-changing device addressing the healthcare needs of patients with severe Congenital Heart Defects (CHDs). The technology which applies a Swiss watch-making precision allows to perform non-invasive adjustments of the Pulmonary Artery flow and pressure in patients with CHD.

In addition, the innovative adjustment capabilities of NeoCare allow surgeons and cardiologists to develop new treatment possibilities tailored to the needs of their patients.

NEOCARE

NeoCare is aiming to become the first life-saving device addressing key limitations of traditional Pulmonary Artery Banding (PAB) applicable to a broad population of patients suffering from Congenital Heart Defects.

PAB is a palliative approach to open heart cardiac repair used in patients with CHDs to prevent irreversible damage to the lungs and the heart due to over circulation.

The NeoCare device will be indicated for newborns, infants, and children up to adults born with life threatening Congenital Heart Defects. This device was designed to reach a broad number of patients, in particular premature neonates who cannot tolerate an open-heart surgery at birth.

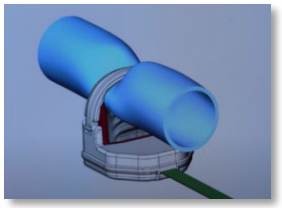
THE DEVICE

NeoCare has been developed by leveraging on public and philanthropic funding. It is designed as a miniature, implantable and battery-free device suited for banding arteries.

The technology that applies a Swiss watch-making precision, allows to perform non-invasive adjustments of Pulmonary Artery flow, especially in premature newborns.

NeoCare is composed of an implant that is placed around the pulmonary artery and controls the flow with an external control unit. Once implanted, the banding of the pulmonary artery can be adjusted remotely through the chest avoiding repeated surgeries to adapt its tightness.

NeoCare flattens the PA which regulates the blood flow whilst preserving the circumference and anatomic properties of the PA and even allows for growth. As a result, no reduction in elasticity of the PA tissue occurs and crucially, fibrosis is avoided.



At the time of cardiac repair, the device is simply removed, and the PA spontaneously expands back to its original anatomy.

A WORLDWIDE CONSORTIUM TO SET THE GOLD STANDARD FOR SAFE AND EFFICIENT PAB DEVICE WITH ACADEMIC ENGINEERING PARTNERS:

The first challenge for the NeoCare system was to miniature the banding device to make it match to the neonatal anatomy. The second challenge was to accurately, safely and efficiently regulate blood flow and pressure in the pulmonary artery of various diameters in order to prevent irreversible damage of overflow to the lungs.

At end of 2-year collaboration with the School of Engineering and Management (HEIG-VD) funded by the Innosuisse Confederation first NeoCare prototypes were successfully produced.

Thanks to its unique geometry, design and precision the device is fully applicable to a broad population of patients suffering from multiple Congenital Heart Defects, including premature or small babies of less than 1kg, as confirmed by the Advisory Board.

PATENT FILING

Following the successful completion of the prototype phase, in June 2022, the EspeRare Foundation filed a patent application to protect the innovative concept and indications of NeoCare. Relying on a new collaboration with HEIG-VD engineers and Swiss clinicians, EspeRare envisions to develop new functionalities such as wireless transmission of energy and information to the device and the production of devices of various sizes.

HEIG VD

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Innosuisse – Swiss Innovation Agency

COMMUNITY IMPACT

NeoCare as an innovative and life-saving device presents many therapeutic benefits for CHD community members and the healthcare actors. It avoids re-operations, reduces hospitalization stays in the intensive care unit and releases some of the financial burden on the healthcare system at large. Ultimately it gives hope to a broad range of CHD patients, including premature babies and their families for safer and quicker management of heart conditions with higher survival chances in severe cases.

LONG-TERM VISION

The strengthening of the technology and intellectual property is an essential step in adding value to NeoCare device and identifying a MedTech partner to finalize the development, production and commercialization of these devices, which have the potential to save the lives of infants with severe heart defects. This new technology, with its unique design and flexibility of precise adjustment across the chest, paves the way for a platform of banding vessels in other therapeutic indications. Indeed, once the device is launched for cardiac indications, EspeRare envisions to develop the technology for other equally important applications; for example: to prevent complications in partial liver transplants, or to prevent complications in arteriovenous fistula dialysis observed for example in dialysis patients.

Fulfilling EspeRare's humanitarian commitments, part of the NeoCare financial return will be used to enhance diagnostics of CHDs, improve care in neonates born with CHDs in order to avoid irreversible injury caused by pulmonary overflow in these children.

Prenatal Medicine

ESPERARE IS UNIQUELY POSITIONED IN THE SPACE OF ADVANCING PRENATAL THERAPEUTIC DEVELOPMENT

Since its creation 10 years ago, EspeRare is driven by the urge to improve lives and the healthy development of children suffering with rare genetic diseases. Starting in 2018, with its ER-004 programme (see page 14), it has expanded its reach into the space of prenatal medicine and is accelerating the development of an unprecedented prenatal therapy.

ER-004 programme is currently undergoing the last step of clinical development and is aiming at correcting symptoms of X-linked ectodermal dysplasia, a life-threatening disease causing the inability to sweat, among other symptoms. To seek this corrective effect, a protein replacement therapy known as ER-004 is injected in the amniotic fluid surrounding foetuses, during pregnancy.

If the EDELIFE clinical study proves to be successful, ER-004 will become the first therapy to treat a genetic disease prior to birth.

Indeed, to date no prenatal therapies have yet been approved by regulators and are accessible to patients. With its ER-004 programme, EspeRare and its partner Pierre Fabre are striving to bring the first treatment that corrects a genetic disease before birth on the market in Europe and the United States by 2026. Thus, setting a precedent for other prenatal treatments to gain regulatory approval in the future.

> “It is an exciting time for the Hypohidrotic Ectodermal Dysplasia community and for prenatal medical research. For the first time, we can hope to correct major symptoms of XLHED for those who are diagnosed before birth” –
>
> **Caroline Kant**
> Founder and Executive Director

Pierre Fabre

ESPERARE PRENATAL PERIOD – A WINDOW OF OPPORTUNITY TO ENHANCE THERAPEUTIC EFFECTS

The prenatal period (i.e., period before the baby is born) provides a compelling therapeutic window to address genetic diseases before birth. The potential of this therapeutic period is due to several factors related to the unique properties of the fetus (unborn baby) and the maternal environment inside the womb within which the baby develops.

The rationale for treating certain genetic diseases before birth is to target diseases at their earliest manifestation, which is the in-utero stage, i.e., while the unborn baby is still in the womb. Thus, enabling the potential to prevent the onset of irreversible pathology in newborn babies. Treating during this particular prenatal stage can also enhance treatment outcome of fetal-specific conditions such as infectious diseases and certain embryonic and fetal developmental diseases that can only be treated during fetal development.

Moreover, addressing therapeutic needs before birth has the potential to boost postnatal treatment effectiveness, and enhance health benefits. This could result in long-term improvements in quality of life and cost savings for affected patients, their families and healthcare systems.

PRENATAL THERAPY ACCELERATOR

EspeRare shares the vision that the multidisciplinary exchange of bio-medical research data and knowledge is essential to advance diagnosis and therapeutic development, and ultimately prenatal healthcare. As such, in the emerging space of prenatal therapeutic development, EspeRare has identified the need for creating an integrated and precompetitive knowledge platform that can foster collaborations and exchange of information. Creating a Biobank and a Knowledge Hub entail sharing expertise and knowledge of all actors in the prenatal medical space: patient organizations, researchers, biotech companies, healthcare providers, regulators, and many more, within a unified hub where the information and data can be accessible to all relevant stakeholders and can support collaboration and advancements in this emerging field of therapeutic development.

Synergies created between various experts in the prenatal space will accelerate research and increase the chance of success of bringing life-changing prenatal therapies to families affected by genetic diseases. Academia brings their expertise and dise3ase understanding regarding genetic conditions that may benefit from prenatal treatment. Biotech and pharmaceutical companies have the chance of better understanding opportunities and challenges related to prenatal Research & Development and provide regulatory and commercialization insights. Patient organizations play a major role as their view is essential to understand the unmet medical needs of individuals affected by these diseases, and opportunities and risks associated with addressing genetic diseases before birth.

The learnings and knowledge registered as well as accessibility of biological samples in one place will facilitate prenatal diagnosis and conducting research and development efforts. In addition, this platform will enable the collection and sharing of regulatory intelligence in the prenatal space further opening the new regulatory path for innovative prenatal therapies. A common ethical framework will also be developed to address the ethical and legal implications unique to this new frontier in medicine and provide the appropriate boundaries to prenatal therapies.

Developed and hosted by EspeRare, this Prenatal Collaborative Hub will be powered by a multidiscipline network of key experts in the prenatal space and supported by a digital backbone that is designed to facilitating digital collaboration of the user.

Organization

The Board and the management team constitute EspeRare's statutory structure.

The Board is the supreme body that ratifies all decisions. In line with EspeRare's not-for-profit status, Board members act on a voluntary basis. They are key opinion leaders in the healthcare and rare disease space. The President is Sharon Terry, a pioneer of patient empowerment and citizen health, and the CEO of Genetic Alliance, Washington DC, USA.

The strategic and day-to-day activities are managed by the management team, appointed by the Board. Ad-hoc committees such as the Scientific Advisory Committee and the Business Advisory Committee have also been constituted to support the development of the Foundation.

The Management Team drives a number of employees, part-time consultants and volunteers to deliver on EspeRare's objectives.

EspeRare has significantly scaled up its workforce to support its growing portfolio of therapeutic programmes.

> "Fostering access to health for patients that are the most in need is what this Foundation is about, and is what I am about" –
>
> **Béatrice Greco**
> Founder and Board Member

THE FOUNDATION BOARD

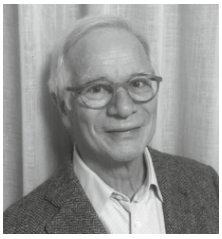
SHARON F. TERRY

Sharon Terry is President of EspeRare and CEO of Genetic Alliance, a network of more than 10,000 organisations, including 1,200 disease advocacy organisations. Genetic Alliance enables individuals, families and communities to become full participants in the medical research process. She is the founding CEO of PXE International, a research advocacy organization for the rare genetic condition pseudoxanthoma elasticum. She is, among others, a member of the Executive Committee of the International Rare Disease Research Consortium and the US personalised medicine initiative, a member of the Board of Telethon-Italy and an Ashoka Fellow. Sharon links EspeRare with patient organisations and orphan disease advocacy.

BÉATRICE GRECO

Béatrice Greco is a co-founder of EspeRare. She is a Board member and plays an active role in the Executive Committee. Béatrice has a strong background in neurosciences. In the Serono pharmacology department, she led a number of drug discovery projects while heading the translational testing of investigational drugs. Since 2009, within the Platform of Global Health she has led novel and integrated translational research programs in neglected diseases. Béatrice's passion for innovation and her particular interest in applying science to address vulnerable patients naturally drove her to co-develop this Foundation.

DENIS MORTIER



Denis Mortier is chairing EspeRare's Business Advisory Committee. During his extensive carrier he served, among others, as a Partner of Coller Capital Ltd., on the Executive Committees of Credit National, as an Executive Officer in The World Bank Group and as the Chairman of the European and the French venture capital and private equity associations, as well as a Vice Chairman of NASDAQ Europe. He also took part in Advisory Boards and Investment Committees for multiple Venture Capital funds. Denis provides excellent counsel and guidance to support the growth of EspeRare's activities and business model. He is also a Treasurer of the Foundation.

PETER POTTER-LESAGE

Peter Potter-Lesage, the current CFO of the International Electrotechnical Commission, served as a member of the Board of Trustees of the Malaria Consortium (UK) and Senior Advisor for fundraising, donor relations and strategy at Medicines for Malaria Venture (MMV) in Geneva, where he previously held the position of founding Chief Financial Officer for 12 years. Peter provides to EspeRare his expertise in financial representation and strategic business planning, in financial and fundraising analysis, and in support, risk identification and management.

EWEN SEDMAN

Ewen Sedman was appointed a SVP Strategy and Business Operations at Merck Healthcare until the end of 2021. He has led key projects and functions from early discovery research to late-stage clinical development in a variety of different therapeutic areas. Previously he was responsible for the successful build-up of the Neurodegenerative Disease Research unit at Merck Serono. Ewen brings to EspeRare a wide range leadership expertise across the whole pharmaceutical R&D value chain.

ERIN GAINER

Erin Gainer is a Board member of EspeRare. She has a pharmaceutical industry and not-for-profit experience spanning from drug development , chief executive, board member, and philanthropist roles. In 2017, Erin created the Ella fund, a venture philanthropy fund devoted to backing social entrepreneurs working to empower women worldwide through education, health and entrepreneurship. Erin provides her expertise in R&D, fundraising and business development to support the growth of EspeRare's therapeutic pipeline, patient engagement, and innovative health management approaches.

BERTRAND KIEFER

Bertrand Kiefer is a distinguished member of the Geneva and Swiss scientific community and a newly appointed Board member of EspeRare. He served for 12 years as a member of the Swiss National Commission for Ethics in the Human Domain. After receiving his medical degree in infectious diseases from the University of Geneva, Dr. Kiefer studied theology and philosophy of science at the University of Fribourg and then in Rome, before engaging in bioethics research. Bertrand is the editor-in-chief of the Swiss Medical Journal and the author of over 600 articles, columns, and editorials. He brings to EspeRare a wealth experience in medicine and ethics to help guide the Foundation through next stages of its development.

MANAGEMENT TEAM

CAROLINE KANT

Founder & Executive Director

After supporting the build-up of an IT start-up in Silicon Valley and a successful career in the pharmaceutical industry, Caroline Kant co-founded and is leading EspeRare since 2013. By driving forwards EspeRare, Caroline is realizing her dream of dedicating herself to address rare diseases in honour of her daughter, and for all children suffering with orphan diseases. She is also advising leading NGOs to find new ways of applying venture philanthropy and social entrepreneurship to other pressing health challenges. Caroline was educated in Switzerland and the United States and holds degrees in neurobiology and product development. She is an ASHOKA fellow and was appointed "Swiss woman entrepreneur" of the year in 2015.

FLORENCE PORTE-THOMÉ

Founder and R&D Director

Florence Porte is in charge of leading and developing EspeRare's R&D portfolio and platform, selecting new programmes and driving them until proof of concept in patients. After a successful carrier of 20 years of experience in pharmaceutical R&D, in particular leading translational research and managing clinical studies within the pharmaceutical industry, Florence co-founded EspeRare. Growing up with a cousin affected with Duchenne Muscular Dystrophy and seeing him gradually decline, Florence has an unconditional motivation to drive this EspeRare forward.

MONIQUE A. CAILLAT

General Counsel

Monique A. Caillat is an Attorney at Law based in Geneva, Switzerland, specialized in the healthcare sector. During over 20 years, she has represented the private sector's interests in its relations with the authorities, international organizations, academia and NGO's. While specialized in the counsel to pharmaceutical companies, start-ups and not-for-profit organisations in the healthcare sector, Monique is also engaged in supporting interactions between patients and healthcare professionals, through medical mediation and through her membership on the Geneva Health Ethics Committee. Monique is the General Counsel of the Foundation.

JULIAN GRAY

Chief Medical Officer

Julian Gray supports EspeRare in all medical aspects related to programmes of EspeRare's portfolio. In addition, he advises on clinical development strategies and assists in the interactions with regulatory agencies. As a medical expert in Central Nervous System (CNS) and clinical research for the pharmaceutical industry, he led clinical studies on Parkinson's and Alzheimer's diseases. He has a strong track record in designing clinical and regulatory strategies for orphan drug and obtaining subsequent approval in Europe and USA. Among others, he worked as medical advisor to Santhera Pharmaceuticals on the development of idebenone in Duchenne Muscular Dystrophy.

URSULA VOGEL

Chief Business Officer

Ursula works with EspeRare in an advisory capacity for various development projects. She has over 25 years of global Biopharma industry experience, having started her career at Merck Sharp & Dohme and Sanofi, followed by a pivotal leadership role at pioneering US biotech Genetics Institute where she set up and managed the European affiliate until its acquisition by Wyeth (now Pfizer). She has been a major contributor to the success of 2 marketed products (*Infuse®/InductOs, BeneFIX®*). Since 2000 she has worked as an independent consultant helping conclude a multitude of licensing transactions and bring biopharmas to successful exits. Her main focus areas are Business & Corporate Development, and C-level or Board level representation. She holds a PhD from Cambridge University, and an MBA from INSEAD.

TEAM

RESEARCH AND DEVELOPMENT

SAMEERA ALLIE
Medical Director
Sameera is a physician-scientist with experience in academic and clinical drug development research, health systems strengthening and global health. Her area of expertise spans infectious disease (HIV and TB), with more recently, experience in translational rare disease drug development. At EspeRare, Sameera provides medical, scientific and strategic leadership, and support in rare disease drug development (translational and clinical development).

AGNÈS JAULENT
Project Leader & Alliance Manager
Agnès studied for her PhD in chemistry at Imperial College London. She is an expert in all fields pertaining to peptide chemistry and brings academic and industrial experience in developing New Biologics Entities to EspeRare as a clinical programme leader for ER-004, for the CMC and Business Development. Agnès is also responsible for developing patient-centered approach and implementing patient engagement strategy.

CAROLINE DURAND-AVALLONE
Project Leader
Caroline was previously in charge of Pharmaceutical Affairs for a French biotech company. She has experience in the field of development and biomanufacturing and has held various positions in R&D, industrialization, and analytical development at Sanofi Pasteur (Lyon, France). She has also led and coordinated several pre-clinical and clinical studies. At EspeRare Caroline is leading the clinical aspect of the ER-004 programme.

CENDRINE GRANGEON
Clinical Development and Quality Manager
Cendrine received her Masters degree in immunology and signalization at Paul Sabatier University, Toulouse, France. Over her carrier, she built a successful background as a biology team leader and project leader in drug development. At EspeRare, Cendrine is managing clinical programme activities for the ER-004 project.

RONAN GODOY
Archivist
Ronan is a qualified archivist, who has worked on several projects, spanning historical, scientific and administrative archiving. At EspeRare, he is in charge of inventorying and sorting historical documents resulting from a full asset transfer after an acquisition. Ronan holds a BSc in Information Science from the Haute Ecole de Gestion (HEG, Geneva, CH).

ANNA CHIARA NASCIMBENI
Discovery and Biomarker Expert
Anna Chiara holds a PhD in Neurosciences and a postgraduate specialization in Medical Genetics. She was previously involved in research and diagnosis on rare neuromuscular diseases and cell biology research, mainly on autophagy. At EspeRare, she is responsible for new therapeutic discovery in drug repositioning.

CHRISTOPHE BARCELLA
Quality Management Advice
Christophe is President of Montrium GXP Consulting and auditor. He brings EspeRare over 27 years of international experience in GxP regulatory compliance as per ICH, EMA, FDA regulations & directives, and in quality management.

OLIVIER FAVRE-BULLE
Chemistry, Manufacturing & Control
Olivier has over 25 years in the pharmaceutical industry, helping companies and clients in their pharmaceutical development for their biologicals. Olivier is advising EspeRare on the manufacturing and commercialization strategy for the ER-004.

CAROLE PUGH
Regulatory Affairs
Carole is Managing Director at EUDRAC Limited, a regulatory consultancy company (UK). She has worked with small start-up, mediumand large global companies during her time at EUDRAC, and performed due diligence activities, undertaken agency scientific advice procedures and presented on current regulatory intelligence topics. She is EspeRare's regulatory affairs consultant.

ERIC TEILLAUD
Chemistry, Manufacturing & Control
Eric has over 30 years of experience in pharmaceutical R&D and quality. Now he runs his own consultancy firm that offers services in drug development strategies and pharmaceutical quality management. He brings to EspeRare his experience in Quality and Chemistry, Manufacturing and Control.

ALEXIS COLETTE
Chemistry, Manufacturing & Control
Alexis is a senior CMC consultant with 15+ years of international experience at the cornerstone of science, regulatory and business aspects. Alexis is providing support to EspeRare on the manufacturing and commercialization strategy for ER-004.

FINANCE AND ADMINISTRATION

SARAH DELACOSTE
Accounting & Human Resources
Sarah is an accounting and controlling specialist. In addition, she combines Human Resources and IT expertise. She is active in not-for-profit organizations for various humanitarian causes engaged in creating a better world. At EspeRare, Sarah links ledger accounting to reporting and auditing activities, as well as support Human Resources Management.

ANNA HEITZMANN
Communication & Fundraising Manager and Quality Archivist
Anna has more than 10-year experience in managing relations within the private and public sector, in various countries and cultures. Throughout her volunteer work and professional engagement, Anna has continuously committed herself to managing children's wellbeing and education. She brings to the Foundation an excellent track record in managing communication and fundraising activities. She also oversees quality assurance archiving activities.

IT & BIOINFORMATICS

CÉDRIC MERLOT
BioInformatics & IT Consultant
Cédric is the CEO of Drugdesigntech which he founded in 2007. He has vast experience in Management and Bioinformatics and Data Management. He applies his expertise to support the development of the foundation's data Platform and provides IT support.

GENIX SECURITY GROUP
Cyber Security Support
The Swiss company specializes in the installation and maintenance of corporate surveillance and security systems. As a trusted partner, Genix ensures EspeRare`s digital security and applies innovative technologies which increase security. Thus, providing the Foundation with data safety and integrity and its employees with data protection.

SCIENTIFIC ADVISORS

PROF. MAURICE BEGHETTI

Prof. Beghetti is the medical chair of the Paediatric Cardiology and Orphan Diseases Units for the Western Swiss Hospitals. He is a European Medicines Agency expert advisor for paediatric pulmonary hypertension and congenital heart defects and has taken part in multiple paediatric drug development efforts as a medical strategic advisor for key pharmaceutical companies in the orphan space.

PROF. STÉPHANE BLOT

Prof. Blot is heading the neurobiology laboratory of the Veterinary School of Alfort (ENVA), France. He participates among others to the instruction of students preparing the myopathology diploma of the French Institute of Myology. He provides EspeRare with his expertise in conducting animal models of Duchenne Muscular Dystrophy.

PROF. ANNA DAVID

Prof. David is a consultant in Obstetrics and Maternal / Fetal Medicine at UCLH. Her team is developing new treatments for fetal growth restriction using maternal gene therapy and is pioneering the first clinical trial of in utero stem cell transplantation for brittle bone disease. She supports the development of the ER-004 antenatal treatment in XLHED.

PROF. PEDRO DEL NIDO

Prof. Del Nido is a thoracic surgeon in Boston, Massachusetts and is affiliated with Boston Children's Hospital. He has been in practice for more than 20 years. As one of the world's leading paediatric cardiac surgeons, he is the Chief of Cardiac Surgery at Boston Children's Hospital. Prof. Del Nido is particularly renowned for performing cardiac chirurgical procedures in the womb.

PROF. JOEL DUDLEY

Prof. Dudley was the Director of Genomic Sciences and Biomedical Informatics at Icahn School of Medicine at Mount Sinai, New York. Prof. Dudley is a world leader in computational drug repositioning and molecular profiling. In 2014, he was named one of the 100 Most Creative People in Business by Fast Company magazine.

DR. NEIL KIRBY

Neil is a seasoned biotech veteran and ex-CEO of Edimer Pharmaceuticals, the company from which EspeRare acquired the rights of ER-004. Neil is still involved in the ER-004 programme, providing EspeRare with strategic advice.

DR. ETHAN KUNG

Dr. Kung is an assistant Professor at the University of Clemson (USA). Dr. Kung's research integrates experimental, computational, and clinical aspects of cardiovascular biomechanics. Dr. Kung obtained his PhD in Bioengineering from Stanford University and in Electrical Engineering from Queen's University. He is contributing to the development of NeoCare.

DR. CHRISTIAN LAVEILLE

Dr. Laveille is Director of Cavalgone and has more than 25 years of drug development experience within the pharmaceutical industry and has also contributed to several registrations for new drug applications. He is EspeRare's advisor in pharmacology and toxicology.

ELIZABETH LUNDINGTON

Elizabeth holds a PhD in Biostatistics from the University of Iowa and a MA in Mathematics/ Statistics from Boston University. Elizabeth Lundington has approximately 20 years of experience in providing statistical, technical, and strategic expertise for pre-clinical studies, INDs, Phase 1-Phase 4 clinical studies, eCTDs, and post-marketing requirements.

PROF. FRANCESCO MUNTONI

Prof. Muntoni is a Paediatric Neurologist at University College London. He is one of the world's leading clinical experts of the pathological and molecular aspects of neuromuscular disorders. Prof. Muntoni is key in driving Duchenne Muscular Dystrophy medical research and drug development globally. He is the principal investigator of EspeRare's Rimeporide project in that indication.

VANN PARKER

Vann Parker, PhD, is a highly experienced biopharmaceutical developer with over 25 years of experience in the industry. He specializes in providing strategic advice for clinical development of drugs, preparing IND, NDA and BLA documentation and facilitates interactions with the FDA. In addition to pre-IND activities, Vann is well-versed in the application process, including Orphan Drug Designation, Fast Track, Breakthrough and Paediatric Plans.

PROF. RENÉ PRÊTRE

Prof. Prêtre is the Head of the Paediatric Cardio- Vascular surgery unit at Lausanne University. He is recognized as one of the world's leading paediatric surgeons, an international leader in congenital heart defects repair. He was elected "Swiss of the year" in 2009. He advices EspeRare for the NeoCare programme.

PROF. HOLM SCHNEIDER

Prof. Schneider is a professor of Paediatrics at the University Hospital in Erlangen (Germany) and has been focusing for many years on treating children with genetic diseases. He has worked closely on the development of ER-004 for Edimer and pioneered the first intra-amniotic administrations of ER-004 to 3 unborn XLHED children. Prof. Schneider is the Principal Investigator for the upcoming clinical intra-amniotic study of ER-004 in XLHED.

DR. PASCAL SCHNEIDER

Dr. Pascal Schneider is a tenured senior lecturer and researcher at the University of Lausanne. He is a biochemist with long-standing experience and interest in the TNF family ligands, including EDA. ER-004 was originally developed in his laboratory and Pascal still lends EspeRare his expertise for this programme.

DR. TONY SCIALLI

Dr. Scialli is a specialist in reproductive and developmental toxicology and in obstetrics and gynecology. In addition to his consulting services, he is Clinical Professor of Obstetrics and Gynecology at George Washington University School of Medicine and Adjunct Professor of Obstetrics and Gynecology and of Pharmacology and Physiology at Georgetown University Medical Center.

PROF. UMBERTO SIMEONI

Prof. Simeoni is Professor of Paediatrics at the Faculty of Biology and of Medicine at University of Lausanne and Director of the Division of Paediatrics and of the Developmental Origins of Health and Disease (DOHaD) Research Unit at CHUV University Hospital in Lausanne, Switzerland. His research is oriented towards the Developmental Origins of Health and Disease. He is also highly interested in perinatal bioethics. For EspeRare he advices the development of ER-004 antenatal treatment in XLHED.

DR. ELIA STUPKA

Dr. Stupka is a bioinformatics leading expert who started his genomics career in the Human Genome Project. He also led the development of the first Translational Genomics and Bioinformatics Center in Italy at San Raffaele Hospital in Milan. He is currently a strategic Advisor for many ventures in the bioinformatics space. He provides his computational biomedical expertise to develop EspeRare's proprietary data analysis platform.

BUSINESS AND STRATEGIC ADVISORS

DR. DIEGO BRAGUGLIA

Dr. Braguglia is General Partner at VI Partners AG focusing on life-science and biotech investments. He held various managerial positions in the pharmaceuticals and medical devices sectors as well as in biotech start-ups in Europe and United States. He also serves or has served on the Board of various biotech and MedTech companies and as Director of Swiss Private Equity & Corporate Finance Association. He brings Business Development advice to EspeRare.

DR. ALEXANDRA RICHARDSON

Dr. Richardson heads marketing and business development for Clayton Biotechnologies, Inc. She has over 15 years of experience in licensing and managing intellectual property portfolios. She has assisted in the creation of several biotech start-up companies. Alexandra advices EspeRare in Intellectual Propriety and Business Development topics.

REGI AALSTAD

Mrs. Aalstad is an experienced board member, Private Equity adviser and a former General Manager in Fast Moving Consumer Goods in Asia, Europe and Middle East & Africa. She has served women and children globally for over 25 years with innovation and health education in Feminine and Baby Care at Procter & Gamble. Regi is committed to voluntary humanitarian board and adviser work to continue to improve people's lives.

NB : For ease of reading, all the amounts are rounded

Financial view

EspeRare receives funding from project partners, patient associations, private foundations and donors as well as international, governmental and public bodies. These funds are used to finance EspeRare's diverse activities geared towards accelerating the cost-effective development of unexplored therapeutic opportunities for rare neuromuscular, cardiovascular, and dermatological diseases. In partnership with patient organizations, EspeRare addresses the drug development gaps and clinical development challenges, acting as trusted partner for pharmaceutical companies, academic centers and regulatory agencies to drive effective development and foster affordable access to new treatments for rare disease patients. Established as a not-for-profit Swiss foundation under statutes dated 28 March 2013, EspeRare is managed by a Foundation Board, two senior managers, with 6 employees, and 25 contractors. EspeRare as an organization is exempt from cantonal and federal taxes and is the equivalent of an exempt organization within the meaning of Section 501(c)(3) of the United States Internal Revenue Code.

Accounting is outsourced to a local accounting firm, D-Fox Sàrl while KPMG Switzerland acts as external auditor.

A global banking relationship was created with a major Swiss bank for current accounts and cash-management facilities in multiple currencies.

THE FINANCIAL YEAR TO 31 DECEMBER 2022

The year was characterized by a number of factors. During the year 2022 the Foundation focused on developing its current R&D portfolio, in particular the ER-004 program (page 14) and in developing new therapeutic projects as well as its repositioning platform. The overall staff was maintained, and contractors were recruited to address the needs of the Foundation and its programs. At the end of the year the portfolio was composed of 5 ongoing programs. 2022 R&D expenditures amounted to CHF 1'490'788 with a 15% decrease in expenses as compared to 2021. Income from R&D activities amounted to CHF 811'328 while income from Donations amounted to CHF 959'236 (note 7a). Overall, this year, the Foundation generated a profit (more income than expenses) of CHF 809.

Founding Capital

The Capital Fund of CHF 50,000 contributed by the three founders, was already fully subscribed on 31 December 2013.

Donations

Donations recognized in 2022 amounted to CHF 959'236 and consisted of CHF 937'931 received from Espoir XLHED Sàrl for R&D program activities, CHF 6'455 donation from Connect in Pharma for the NeoCare program. In addition, two CHF 150'000 grants were received in 2022 from the Loterie Romande (GE and VD). Both grants were used to buy two medical devices needed for the EDELIFE clinical study (page 17) and have been accounted as fixed assets.

In 2022, from these Loterie Romande grants CHF 12'484 and CHF 2'385 were respectively recognized, and the remaining portions of these grants were distributed as short-term and long-term differed income (note 2d). Donations received to cover future activities are deferred to the balance sheet for a total amount of CHF 1'613'887. From this amount CHF 1'024'929 is allocated to short-term activities and CHF 588'958 to long-term activities (note 7).

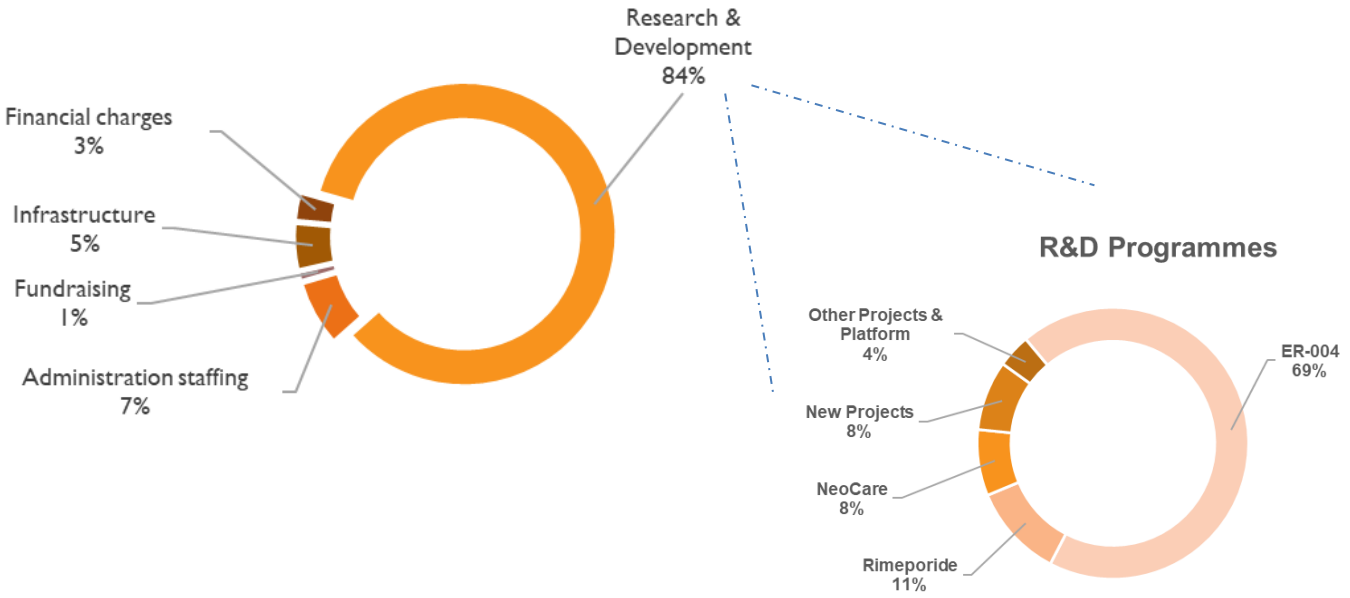
Staff

At end-year the senior management team consisted of an Executive Director and a R&D Director. The administrative, fundraising and program management activities were run by 6 employees, a Chief Medical Officer, 25 contractors and with the support of many other people including Board Members, Senior Scientific Advisors and Volunteers.

General Administration

The total 2022 general and administration expenses amounted to CHF 233'623. Expenses here reflect the Foundation's general expenses in overall support of R&D activities (note 8f).

SNAPSHOT OF ESPERARE EXPENDITURE 2022



THE FINANCIAL YEAR AHEAD TO DECEMBER 2023

EspeRare operates in a complex multi-currency environment in Geneva, Switzerland. The bulk of donations are currently received in CHF, although other currencies such as EUR and USD are also involved. Outflows for projects are mainly in CHF and EUR as per the agreements signed between Pierre Fabre Médicament and Espoir XLHED Sàrl. Clinical activities expenses for ER-004 started to decrease in 2022 as the project entered a steady development phase. The expenses continue to be cross-charged to Espoir XLHED Sàrl in EUR. The resulting exposure of exchange risk is evaluated at the beginning of each calendar year, to provide a realistic fixed EUR/CHF budget rate for the year. The accounts are kept in CHF.

A well-developed treasury management and accounting approach, matching inflows to outflows by currency and taking timely multi-currency investment and foreign exchange decisions is now in place.

The philosophy underlining EspeRare's financial management is that of prudent, conservative control, including appropriate return on interim treasury investments, coupled with the use of the latest IT solutions for bank information, transfers and accounting requirements. As the EspeRare portfolio of therapeutic programmes is maturing and moving into these later stages of development, the foundation's need for financial support is increasing.

The post COVID-19, inflation and geopolitical instability linked to the ongoing war in Ukraine negatively impacted EspeRare's fundraising efforts. However, in alignment with its fundraising strategy and the maturing of the organization, EspeRare will enhance funding efforts to enable EspeRare increase R&D activities and its impact, thus diminishing the burden on the patients suffering from rare diseases.

Conclusion

The detailed financial tables that follow – Balance Sheet and Statement of Income & Expenditure – represent EspeRare in its tenth year of operation where all the various basic financial components of the organization have been established step by step to create a prudent, transparent financial management framework. The scale-up of EspeRare activities has been dampened by inflation, economic and geopolitical situation linked to the ongoing global instability. Despite these external challenges, the ER-004 partnership with Pierre Fabre shall secure organizational continuity for the upcoming years. Moreover, the Foundation is striving in the most efficient way to reach its major goal: the discovery and development of new therapeutic interventions for the treatment of rare diseases and advancing the space of prenatal medicine.

ESPERARE BALANCE SHEET

ASSETS		NOTES	2022 CHF	2021 CHF
Current Assets				
	Cash & Cash Equivalents		2 490 489	3 218 572
Prepaid & Receivables				
	Trade Accounts Receivable	11	131 775	85 019
	Other Current Receivables		0	6 800
	Withholding Tax		-	-
	Prepaid Expenses and Accrued Income		41 015	68 136
TOTAL CURRENT ASSETS			**2 663 279**	**3 378 527**
Non-Current Assets				
	Financial Assets		13 639	13 639
	Investments	4	20 000	20 000
	Tangible Fixed Assets (Equipment)	2d	358 639	64 715
	(less depreciation)		(75 819)	(55 312)
TOTAL NON-CURRENT ASSETS			**316 460**	**43 042**
TOTAL ASSETS			**2 979 739**	**3 421 569**

LIABILITIES		NOTES	2022 CHF	2021 CHF
Short Term Liabilities				
	Trade Accounts Payable		296 228	87 902
	Employee Accounts		-	-
	Other Short Term Liabilities		32 125	17 234
	VAT Payable		-	-
	Short Term Provisions	2f	-	-
	Accrued Expenses	2g	163 278	142 937
	Deferred Income ST	7a	1 024 929	1 000 000
			1 516 560	1 248 073
Long Term Liabilities				
	Covid Loan	15	158 712	192 128
	Long Term Deferred Income		588 958	1 266 667
TOTAL LIABILITIES			**2 264 229**	**2 706 869**
Capital & Reserves				
	Foundation Capital	10	50 000	50 000
	Operations Reserve	3	664 700	864 484
	Net Excess of (Expenditures)/Income		809	(199 784)
TOTAL CAPITAL AND RESERVES			**715 509**	**714 700**
TOTAL LIABILITIES AND CAPITAL			**2 979 739**	**3 421 569**

ESPERARE STATEMENT OF PROFIT AND LOSS

		NOTES	2022 CHF	2021 CHF
TOTAL INCOME		7	**1 783 695**	**1 713 536**
Research & Development Expenses		8		
	Espoir004 Project	8a	(1 024 802)	(1 384 828)
	Rimeporide Project	8b	(165 829)	(149 907)
	NeoCare Project	8c	(117 253)	(123 586)
	New Projects	8d	(123 990)	(71 463)
	Other Projects	8e	-	-
	Repositioning Platform	8f	(58 914)	(32 723)
TOTAL RESEARCH & DEVELOPMENT EXPENSES			**(1 490 788)**	**(1 762 507)**
General Foundation Administration		8g	(233 623)	(141 389)
Operating Result (Expenditure)/Income			**59 284**	**(190 360)**
	Financial Income & Expenses	9	(58 475)	(9 424)
Non-operating & Extraordinary Income & Expenses		12	-	-
NET EXCESS OF (EXPENDITURE) / INCOME			**809**	**(199 784)**

NOTES TO FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2022

1. ORGANISATION

The EspeRare Foundation ("EspeRare") is a Swiss Foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated 27th March 2013 and in accordance with article 80 and those that follow of the Swiss Civil Code. It is managed by a foundation board, an executive director, R&D director and 2 senior managers.

With its head office in Geneva, the aim of EspeRare is to bring public and private sector partners together to both fund and provide managerial and logistical support to drive the identification and development of treatments for rare diseases. The Foundation focuses on selecting deprioritized therapies and technologies assets with high therapeutic potential in rare diseases and accelerating their cost-effective therapeutic development. In partnership with patient organizations, EspeRare addresses the key translational gaps and clinical development challenges, acting as a trusted partner for pharmaceutical companies, academic centers and regulatory agencies to drive effective development and foster accessible access to new treatments for rare disease patients.

As with all Swiss foundations recognized for international public good, EspeRare is oversighted by the Swiss Federal Supervisory Board for Foundations.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

The significant accounting policies adopted by EspeRare in the preparation of the financial statements are set out below.

a) Accounting principles

The accounting principles followed are those of the Swiss Code of Obligations.

b) Recognition of donations

Contributions from donors (both public, private and philanthropic sources) are recognised in the financial statements when they have been received or confirmed in writing by pledges. Contributions which are subject to donor-imposed stipulations for a specific purpose or use in future years may be deferred or attributed to a restricted reserve according to the particular nature of the specified conditions.

c) Foreign Currency Transactions

Transactions in foreign currencies are translated at the foreign exchange rate ruling at the date of the transaction.

Monetary assets and liabilities denominated in foreign currencies at the balance sheet date are translated to CHF at the foreign exchange rate ruling at that date. Foreign exchange differences arising on translation are recognised in the profit and loss statement. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate at the date of the transaction.

The following exchange rates were used at year-end:
1 EUR = CHF 0.987450
1 USD = CHF 0.925228
1 GBP = CHF 1.112933

d) Fixed assets

Fixed assets are stated at cost less accumulated depreciation. Depreciation is charged to the statement of income and expenditure on a straight line basis over the estimated useful lives of the assets. The estimated useful lives of assets are as follows:

- office furniture (second hand and low cost) 3 years
- office furniture (new) 5 years
- special imaging equipment 5 years
- fixtures and installations 3 years
- computer and equipment 3 years

Assets	2021	Acquisitions	Disposals	2022
IT Equipment	32'611	1'234	-	33'845
Furniture	32'104	-	-	32'104
Special equipment	-	292'690	-	292'690
Total	**64'715**	**293'924**	**-**	**358'639**

Depreciation	2021	Depreciation	Disposals	2022
IT Equipment	24'871	4'245		29'116
Furniture	30'441	1'412		31'853
Special equipment	-	14'850		14'850
Total	**55'312**	**20'506**	**-**	**75'819**

Total net value	**9'403**			**282'821**

e) Research and Development

Expenditure and grants are allocated for research activities with the prospect of gaining new scientific or technical knowledge and understanding in order to progress the development of therapeutic assets in rare diseases. They are recorded on a contract or letter of understanding basis, the expense being accounted by EspeRare at the moment of allocation and initial payment. In the case of any portion remaining unpaid at the year-end, it is included under current provisions and accruals.
Regulatory and other uncertainties inherent in the development of new products in this sector preclude EspeRare from capitalising development costs.

f) Provisions

A provision is recognised in the balance sheet when EspeRare has a present legal or constructive obligation as a result of a past event, and in

EspeRare's opinion it is probable that an outflow of economic benefits will be required to settle the obligation.

g) **Accruals**
An accrual is recognised in the balance sheet when EspeRare has a fair certitude of the outflow of economic benefits that will be required to settle the expense.

h) **Employee Benefits - Pension Plan**
EspeRare's pension plan is classified as a defined contribution plan. Contributions to the defined contribution pension plan are recognised as an expense in the statement of income and expenditure as incurred.

i) **Cash and Cash Equivalents**
Cash and cash equivalents comprise cash balances of current accounts and are valued at nominal value.

j) **Impairment**
The carrying amounts of the EspeRare's assets are reviewed at each balance sheet date to determine whether there is an indication of impairment. If any such indication exists, the asset's recoverable amount is estimated. An impairment loss is recognised whenever the carrying amount of an asset exceeds its recoverable amount.

k) **Financial Income**
Interest income is recognized in the income statement as earned.

l) **Income Tax**
EspeRare has received exoneration from income tax from the Geneva cantonal and Swiss federal authorities from the year 2013 for 10 years.

3. RESERVES

a) **Operations Reserve**
The Operations Reserve represents excess of donations over expenditure for the period and is freely available to be utilised for future operation and project funding costs as the evolving research and development project pipeline dictates.

4. INVESTMENTS

The EspeRare Foundation owned 100% of the capital of EspoirXLHED Sàrl. EspoirXLHED is a limited liability company incorporated on March 28, 2018 and based at avenue Sécheron 15, 1202 Geneva, Switzerland. The purpose of the company is the Research and Development of treatments modulating to the Ectodysplasin Pathway.

5. COMMITMENTS

As at 31 December 2022, there were no significant capital expenditure commitments.

6. SUBSEQUENT EVENTS

No events occurred subsequent to 31st December 2022 and prior to the approval of the financial statements that would require modification of or disclosure in the financial statements.

7. INCOME

The income is split as follow

Income	2022	2021	
Income from Donations	959 236	661 286	(a)
Direct Income from R&D Activities	811 328	1 039 854	(b)
Other Operating Income	13 131	12 396	(c)
Total	**1 783 695**	**1 713 536**	

a) Income from R&D Donations and differed income

During 2022 the following donations were granted:

Donors	Notes	Currency	Total Grant	Deferred from 2021 CHF	Received during 2022 CHF	Recognised during 2022 CHF	Deferred to 2023 CHF	Deferred short term (2024) CHF	Deferred long term CHF	Notes
EspoirXLHED Sàrl	3a	CHF	2 400 000	2 266 667	0	937 931	1 328 736	1 000 000	328 736	Grant – R&D program & foundation
Connect in Pharma (Easyfairs UK)	3a	CHF	6 455	0	6 455	6 455	0	0	0	Grant – R&D program & foundation
Loterie Romande Genève	3a i)	CHF	150 000	0	150 000	12 464	137 536	12 464	125 071	Grant – EspoiR004 (Vivascope #1)
Loterie Romande Vaud	3a i)	CHF	150 000	0	150 000	2 385	147 615	12 464	135 150	Grant – EspoiR004 (Vivascope #2)
TOTAL			**2 706 455**	**2 266 667**	**306 455**	**959 236**	**1 613 886**	**1 024 929**	**588 958**	

As a comparison during 2021 the following donations were granted:

Donors	Notes	Currency	Exch. rate	Total Grant	Deferred from 2020 CHF	Recognised during 2021 CHF	Deferred to 2022 CHF	Notes
EspoirXLHED Sàrl		CHF		2 400 000		133 333	2 266 667	Grant – R&D program & foundation
Tell et un Tel		CHF		10 000		10 000	0	NeoCare
Private Geneva Foundation		CHF		500 000		500 000	0	Grant – deficit coverage 2020
Ashoka Covid-19 grant		EUR	1,091	21 500	17 953	17 953	0	Grant – New Prospect/Rim in COVID
TOTAL					**17 953**	**661 286**	**2 266 667**	

b) Direct Income from R&D activities consisted of CRO services to Espoir XLHED Sàrl for the development of EspoirR-004 in X-linked Ectodermal Dysplasia for an amount of CHF 873'800.
c) Other Operating Income consists of the subletting of part of EspeRare offices to a partner.

8. EXPENSES

The R&D expenses are allocated by project as follow:

R&D Expenditures	2022	2021	
Espoir 004 Direct Costs	264'710	447'681	
Espoir 004 Support Costs	760'092	937'147	
Total Espoir 004	**1'024'802**	**1'384'828**	(a)
Rimeporide Direct Costs	18'619	71'526	
Rimeporide Support Costs	147'210	78'381	
Total Rimeporide	**165'829**	**149'907**	(b)
NeoCare (Flowatch) Direct Costs	12'848	84'651	
NeoCare (FloWatch) Support Costs	104'405	38'935	
Total NeoCare (FloWatch)	**117'253**	**123'586**	(c)
New projects prospect Direct Costs	14'194	2'731	
New projects prospect Support Costs	109'796	68'732	
Total New Prospects	**123'990**	**71'463**	(d)
JNK Direct Costs	-	-	
JNK Support Costs	-	-	
Total Other Projects	**-**	**-**	(e)
Repositioning Platform Direct Costs	12'258	8'053	
Repositioning Platform Support Costs	46'656	24'670	
Total Repositioning Platform	**58'914**	**32'723**	(f)
Total	**1'490'788**	**1'762'507**	

a) Development of EspoiR-04 in X-linked Ectodermal Dysplasia.
b) Development of Rimeporide in Duchenne muscular dystrophy.
c) Development of the NeoCare technology for infants with Cardiac defects.
d) Prospection & generation of new drug development projects for rare diseases, including Rimeporide for COVID-19 and another therapeutic asset initially developed by a pharmaceutical partner that EspeRare is looking to reposition in a rare genetic indication.
e) Repositioning platform development to support the systemic discovery and evaluation of new projects and prenatal therapeutic development.

The support costs are allocated to each project based on the following rules:

- Salaries and social charges are allocated according to the percentage of the time spent by employees on each project
- Rental charges are allocated according to the percentage of surface used by the Administration and used by the R&D organization, then according to the percentage of the time spent by employees on each project for the R&D part of the rental charges
- Accounting expenses, office supplies, telephone and IT expenses are allocated according to a percentage of the direct activities by project including the Foundation.

f) General Foundation expenses in overall support of R&D activities are split as follow:

General Foundation	2022	2021
Administration staffing	130'196	75'690
Office Rental	5'654	5'685
Audit Expenses and accounting	17'300	12'740
General Insurance	19'581	12'314
IT Expenses	-	361
Communications	-	-
General Legal Fees	21'112	8'613
Fundraising direct costs	13'028	1'823
Advertising Costs	1'909	8'722
Board meeting	4'338	4'463
Depreciation	20'506	10'978
Total	**233'623**	**141'389**

9. FINANCIAL INCOME AND EXPENSES

The financial income and expenses are split as follow:

Financial Income and Expenses	2022	2021
Financial Income	-	3
Financial Charges	(2'708)	(1'467)
Exchange Differences (loss) gain	(55'767)	(7'960)
Total	**(58'475)**	**(9'424)**

10. FOUNDATION CAPITAL

The Capital Fund is fully subscribed at CHF 50'000.- as stipulated under the original legal statutes of EspeRare dated 27 March 2013.
This founding capital was donated by the three initial individual founders.

11. TRADE ACCOUNTS RECEIVABLES

There is a receivable amount of CHF 130'843.35 from Espoir XLHED Sàrl.

12. PERSONNEL EXPENSES

Total staff benefits for 2022 amount to CHF 1'194'849.59 in comparison of a total of CHF 1'102'644 for 2021.

13. GOVERNANCE

The Foundation Board is the Foundation's supreme body. It takes all decisions necessary or effective for the achievement of the Foundation's aims. It has general responsibility for the affairs of the Foundation and supervises all activities carried out under its authority by the Foundation's other bodies to which power and authority have been delegated.
Members of the Board act on a voluntary basis and may not claim any financial compensation other than expenses incurred such as travel and accommodation. For activities over and above the normal requirements of the position, each Member may receive appropriate reimbursement and compensation. Payment of any such reimbursement or compensation is only permissible where it corresponds to a service carried out for the benefit of the Foundation.
Employees paid by the Foundation such as the Executive Director and the R&D Director serve on the Board only in an advisory capacity and have no voting rights.

14. RISKS AND UNCERTAINTIES

EspeRare encounters certain risks and uncertainties in conducting its affairs. These risks and uncertainties have financial statement implications. In all instances, these have been considered in the financial statements, despite the fact that the outcomes of these uncertainties cannot be predicted with absolute certainty. Management has concluded that provisions for these risks are appropriate, and any adverse resolution of these uncertainties will not have a material impact on the financial position or results of the Foundation.

15. LONG TERM LIABILITIES

Corresponds to a bridging loan granted in the context of the COVID-2019 crisis amounting to CHF 192'128. This loan is contracted on honour and assorted by special conditions of the Swiss Federal Government, EspeRare is compliant with these conditions. This loan is guaranteed by the Swiss Federal Council and is without interest and to be repaid on free terms, however at the latest within a period to be determined by the Swiss Federal Council and is without interest and to be repaid on free terms, determined by the Swiss Federal Parliament. Starting January 1st 2022 the loan is being repaid with quarterly instalments of CHF 8'354.

16. CONTINGENT LIABILITIES

EspeRare has potential liability that may occur, depending on the outcome of an uncertain future event. The contingent liability relates to work performed by a consultant who agreed to be paid only if an out-licensing deal for Rimeporide is achieved. As of December 31st 2022, a total of 687 hours were incurred, representing a total of CHF 206'100 amount that stayed unchanged since 2019. EspeRare has not accrued nor provisioned these costs (off balance sheet).

17. FULL-TIME EQUIVALENTS

The annual average number of full-time equivalents for the reporting year, as well as the previous year, is less than 10.

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Report of the Statutory Auditor on the Limited Statutory Examination to the Board of Trustees of Fondation EspeRare, Geneva

As statutory auditor, we have examined the financial statements (pages 35 to 39) of Fondation EspeRare for the year ended 31 December 2022.

These financial statements are the responsibility of the Board of Trustees. Our responsibility is to perform a limited statutory examination on these financial statements. We confirm that we meet the licensing and independence requirements as stipulated by Swiss law.

We conducted our examination in accordance with the Swiss Standard on the Limited Statutory Examination. This standard requires that we plan and perform a limited statutory examination to identify material misstatements in the financial statements. A limited statutory examination consists primarily of inquiries of personnel and analytical procedures as well as detailed tests of documents of the unit as considered necessary in the circumstances. However, the testing of operational processes and the internal control system, as well as inquiries and further testing procedures to detect fraud or other legal violations, are not within the scope of this examination.

Based on our limited statutory examination, nothing has come to our attention that causes us to believe that the financial statements do not comply with Swiss law and the Foundation's charter and regulations.

KPMG SA

Cédric Rigoli
Licensed Audit Expert
Auditor in Charge

Pierre-Henri Pingeon
Licensed Audit Expert

Geneva, 28 March 2023

How can I support EspeRare?

EspeRare is a Foundation recognized by the Swiss authorities to be operating for the international public benefit. As such, it is fully tax exempt and eligible for **Swiss and international subventions** as well as non-financial support.

The Foundation is also a member of the **Transnational Giving Europe (TGE) network**, and has created the **American Friends of EspeRare fund, hosted by the King Baudouin Foundation** which allows **European and USA citizens** to make cross-border donations while still benefiting from the tax advantages of their country of residence.

AS AN INDIVIDUAL OR AS A CORPORATE ORGANISATION, THERE ARE MANY WAYS TO SUPPORT ESPERARE

I WANT TO SUPPORT THE FOUNDATION FINANCIALLY

Supporting us financially, you will help us to further secure theimpact of EspeRare and the identification of new treatments for children with rare diseases.

I WANT TO DONATE TO A SPECIFIC R&D PROGRAMME

Our financial structure is composed of several sub-funds, each of them dedicated to a specific R&D programme. Your donation will support and accelerate the development of a new treatment for the disease of your choice.

I WANT TO ESTABLISH A CORPORATE PARTNERSHIP

If you would like to engage in fund-raising activities or in a corporate donation to EspeRare, we would be happy to discuss the modalities that best fit your aims.

WE ARE HAPPY TO GIVE YOU FURTHER INFORMATION AND ANSWER YOUR QUESTIONS :

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