MENKES INTERNATIONAL:

Making Menkes disease history

2022 Annual Report

Menkes International Association
2022 Annual Report

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Menkes International Association - Executive Summary

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Menkes International Association - Executive Summary

Dear Friends and Partners of Menkes International Association,

2022 was a breakthrough year for Menkes International Association (MIa) and our mission to make Menkes disease history.

Menkes disease is a rare genetic disease. Children born with Menkes and their families continue to face acute lack of information, limited medical support and treatment options, and few connections to other families facing similar challenges.

MIa was created by the family and supporters of Marco, a young boy from Malaga, Spain who was born in 2020 and diagnosed with Menkes immediately after birth. Marco is our son. Over the time, MIa enlarged to associate other Menkes families, as well as researchers, medical doctors, pharmacists and pharmacologists, lawyers, policy-advisers, chemists etc. MIa was founded as a charity on 7th November 2020 and got registered in the national Spanish registry of associations on 16 March 2021 with number 4599. It is working to provide children born with Menkes and their families with information and acess access to life-saving expertimental therapies. It also aims to unite international scientific researchers, medical teams and pharmceutical partners to develop new forms of medical support and hope for children with Menkes.

In 2022, MIa established the first and only global Menkes Patient Registry, supported patients with access to Menkes treatments, including copper histidinate and experimental treatment with elesclomol-copper, joined the EURORDIS European rare disease alliance, presented the results of research by our team at the International Copper Meeting, and hosted our first charity fundraiser in Malaga.

As the mother of a son with Menkes, every day is a race to ensure that our son Marco, and all children with Menkes, have access to cutting-edge science, treatment and support. Parents of other children with Menkes have given us incredible support – coming out of the shadows, sharing their stories and giving us hope. Every day, MIa connects with an amazing network of scientific researchers and medical teams who are exploring new directions towards making Menkes history.

I can't be grateful enough to the international scientific team, gathering the best world experts on Menkes, who have voluntarily given their time to pilot and supervise Marco's treatment. They meet – virtually – every week and constitute what has been called the Copper(less) Committee. Their dedication and professional excellence have been – and continue to be - key to Marco's success against the disease.

We hope you enjoy our first annual report, and invite you to support the work of Menkes International.

AURORA MATEOS

EXECUTIVE SECRETARY

02

Menkes Patient Registry

Menkes Patient Registry

[January 2022 - to date]

Children with Menkes disease and their families experience loneliness and fear as they face a painful lack of connection to other children living with Menkes. This makes it difficult for families to support each other, get referrals to the few medical teams in the world with expertise in caring for children with Menkes, and struggle to enroll their children in potentially life-saving clinical research.

In 2022, MIa established the first and only global Menkes Patient Registry. Through this free, online resource, the Menkes Patient Registry provides families of children with Menkes with voluntary, confidential access to the few medical and scientific research teams working on Menkes research at accredited research institutions. Through this registry, MIa also invites accredited researchers worldwide to link up with other researchers and patients, and contribute to growing efforts to develop more effective treatments and a cure:

Leonardo Cervera, MIa board member, developed the MIa data protection policy, ensuring that MIa's Patient Registry conforms to the laws and policies of Spain and the European Union.

As it is a rare disease, it is exceeding difficult to identify and connect with children with Menkes who could participate in scientific research and potential clinical trials. MIa encourages families of children with Menkes, particularly those living in Europe, to contact us and consider enrolling their child in the Menkes Patient Registry on a voluntary basis. MIa can give families of children with Menkes much needed information, links to accredited scientific and medical experts, and the voluntary option of enrolling their child in current or future potential clinical research and clinical trials.

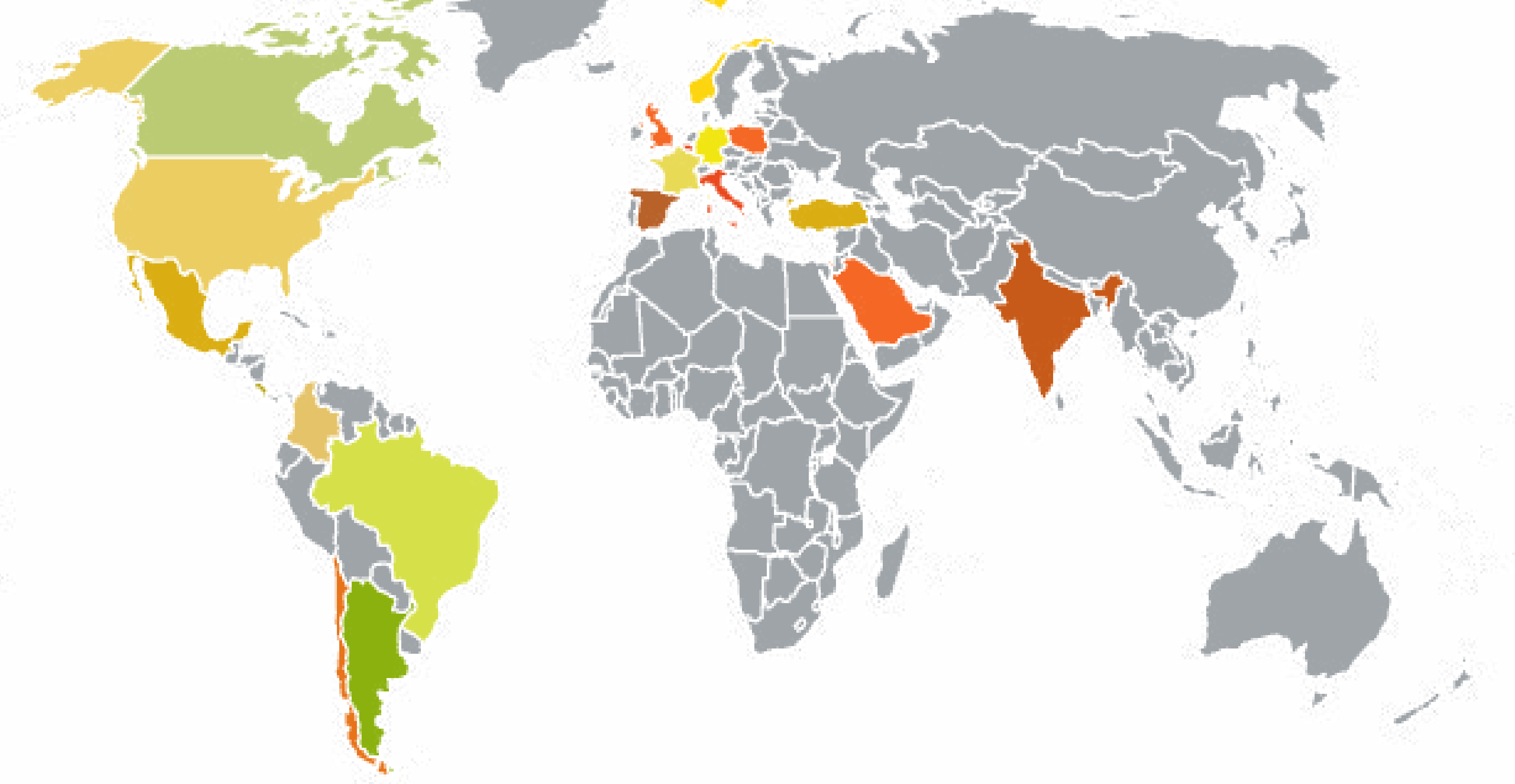
Since the launch of the Menkes Patient Registry, **over 97 children** have enrolled from **20 countries**, including from:

SPAIN - 12
ARGENTINA - 15
BRAZIL - 26

COLOMBIA - 7
MEXICO - 5
USA - 7

FRANCE - 4
INDIA - 3
ITALY - 4
UK - 4

BELGIUM - 1
CANADA - 1
CHILE - 1
COSTA RICA - 1
GERMANY - 1
ISRAEL - 1
NORWAY - 1
POLAND - 1
SAUDI ARABIA - 1
TURKEY - 1



The Menkes Patient Registry is now the world's only database of patients with Menkes, linking together a large and growing number of children with Menkes disease.

Currently, the management and maintenance of the Menkes Patient Registry is performed by one volunteer, part-time during weekends). We will endeavor to raise funds to finance staff to develop and manage this important resource.

Links:
https://menkesinternational.com/menkes-patient-registry/

Funds raised:	None
Funds spent:	None

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03

Marco´s experimental treatment for Menkes

Marco´s experimental treatment for Menkes

[January 2021 - to date]

Marco, a Spanish child diagnosed with Menkes, started to receive elesclomol-copper in January 2021 – the first patient with Menkes disease ever to receive this experimental medicine. The decision to start this treatment was made by Marco’s medical team ‘in extremis’, in response to the deterioration of Marco’s pulmonary fibrosis.

Marco’s family had decided to establish MIa on 7th November 2021 to give more attention to Marco’s condition and provide information and hope to other families with children born with Menkes. Marco’s parents, Aurora Mateos and Andrey Galaev, are members of the MIa board.

At the beginning of his treatment, Marco´s parents had to travel with him weekly to the San Joan de Deu Children’s Hospital in Barcelona to let Marco’s medical team administer the elesclomol-copper treatment and monitor his progress. Since September 2022, Marco and his family have only visited the Barcelona clinic every three months for an overall check-up.

Following the start of his treatment with elesclomol-copper, the improvement in Marco´s health and development has been spectacular. Marco’s progress should give hope for other children with Menkes and their families. MIa hopes that the treatment with elesclomol-copper may change the natural history and prospects for Menkes disease.

Links to Media coverage of Marco:

- Marco, la esperanza de niños con Menkes (rtve.es)
- Un tratamiento experimental para Marco, el niño malagueño afectado por el síndrome de Menkes (canalsur.es)
- La evolución de Marco abre el camino a otros niños con la enfermedad de Menkes (EFE)
- La proeza de Marco, el niño sin cobre | Diario SurMarco, el niño con la enfermedad de Menkes que sobrevive gracias a un tratamiento pionero en España (ABC)
- The fight for Marco, the boy with no copper (Sur in English)
- El pequeño Marco consigue caminar gracias a un tratamiento pionero en España (Antena 3)
- Enfermedad rara de Menkes: Marco, el único niño del mundo con una terapia excepcional (EFE)
- La mejoría de Marco abre la puerta a otros niños con la enfermedad de Menkes (elDiario.es)

Funds raised *[for Marco´s treatment, including travel]*:	€100,000 (source)
Funds spent:	€38,934, including: €11,816.61 (travel), €1,118 (Bayley-III test), €25,000 (contract for clinical researcher)

04

Copper-histidinate project (Cu-His)

04

Copper-histidinate project (Cu-His)

[January 2022 - to date]

The only treatment currently available for Menkes disease is based on daily injections of copper-histidinate, which improve clinical outcomes and prevent death if initiated shortly after birth. Copper-histidinate is an experimental copper replacement given through sub-cutaneous injections, which has been administered to children with Menkes since 1976, thanks to the pioneering research of Dr. Bibudhendra (Amu) Sarkar, at The Hospital for Sick Children in Toronto, Canada. Copper-histidinate has changed the condition of several patients with Menkes disease, giving them a better quality of life.

Copper-histidinate is currently not manufactured by any pharmaceutical company, although Cyprium Therapeutics has obtained “orphan drug status” for it in the USA and Europe, which will give them a monopoly for its manufacture and distribution, once approved by drug regulatory agencies. For the moment, the drug is not available in pharmacies or hospitals. It has to be prepared as a magistral formula by a qualified pharmacist for each single patient, according to a prescription and following strict technical standards.

Dr Amu Sarkar is member of MIa’s Copper(less) Committee, providing his voluntary expert advice and sharing the formula for copper-histidinate. While copper-histidinate is not a cure for Menkes, it has been reported to improve moods, seizures and neurological pain in children with Menkes, even those who did not start treatment within 10 days of birth, which is the ideal scenario.

Menkes families continue to face challenges regarding access to copper-histidinate, particularly in low-income countries. MIa provides contacts and referrals for families requesting help by linking them to pediatricians and national laboratories which can manufacture magistral formulas. Once a suitable laboratory is selected, MIa shares the steps for formulation of copper-histidinate that are used in Spain.

MIa unites medical and pharmaceutical experts to address issues regarding manufacturing of copper-histidinate. MIa works with Miquel Villaronga (at Hospital Sant Joan de Deu in Barcelona) and Conicet, the Argentinian national laboratory (located at the National University of Cordoba) to facilitate access and local magistral production of copper-histidinate. In addition to Spain, MIa has also been working with Menkes families and medical teams in Mexico and Costa Rica with successful results.

The MIa website now features a section that lists laboratories which are able to manufacture copper-histidinate. This list will be maintained and expanded.

During the recent Mia charity event (see page 12), Dr Yusuf Hamied, a businessman and philanthropist, generously offered to ensure that copper-histidinate and elesclomol-copper will be available for free, so that it can be formulated and administered to children with Menkes anywhere. With the support of Mr Yusuf Hamied, MIa plans to support the production and distribution of these life-saving drugs for the treatment of Menkes. MIa does not have its own laboratory and manufacturing capacity, but we plan to develop a legal policy and voluntary network to support this essential task.

Amount fundraised for this activity:	Non-specified MIa funds
Amount spent:	None

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05

MIa - EURORDIS membership

MIa - EURORDIS membership

[September 2022 - to date]

EURORDIS - Rare Diseases Europe is a non-profit alliance of over 1000 organizations of patients with rare diseases that work together to improve the lives of over 300 million people living with a rare disease globally.

In September 2022, Leonardo Cervera, MIa board member, connected MIa with EURORDIS, which promotes research on rare diseases and the development of orphan drugs. Founded in 1997, Eurordis is supported by its members as well as the French Muscular Dystrophy Association (AFM), the European Commission, corporate foundations, and the health industry.

MIa submitted its application to join EURORDIS in July 2022. At the meeting of its Board of Directors, EURORDIS extended an associate membership to Menkes International. Only full members can vote at the EURORDIS General Assembly and be elected. Currently, MIa cannot claim full EURORDIS membership, as its sources of funding are too concentrated. We will apply for full membership once MIa sources of funding have been diversified[1].

Links:
https://www.eurordis.org

Funds raised:	N/A
Funds spent:	€200 /per year for Eurordis membership (if MIa raises between €100,000-€249,000 per year)

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[1] MIa applied for full membeship in February 2023.

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06

12th International Copper Meeting

12th International Copper Meeting

[September 2022]

Members of the Copper(less) Committee participated in the 12th International Copper Meeting in Sorrento (Naples), Italy from 18-22 September 2022. The conference included investigators from the chemical, biological, and medical fields, spanning different facets of copper biology. At the opening of the conference, the 1st Menkes International-William de Rycke-Corthier Award was announced by MIa to reward important contributions to research in the Menkes field.

This was the first time that MIa publicly presented the results of the experimental treatment with elesclomol-copper at an international scientific conference. The main presentation was made by Natalia Serrano (Sant Joan de Déu Children's Hospital), followed by Vishal Gohil (Texas A&M University) and Mick Petris (University of Missouri), who received the David Danks Award.

Marco and his family also attended the conference, which had a positive impact on the scientific community. Scientists could observe Marco´s motor skills and neurological development at the conference. The conference enabled MIa to enlarge its scientific network and feature Marco´s case as a highlight of the conference. The MIa team also held meetings to explore future cooperation with Engrail pharmaceutics, which intends to bring elesclomol-copper to the status of a registered medicine in the USA.

Links:
https://sites.northwestern.edu/copper/

Amount raised for this activity:	€6685
Amount spent:	€7549

07

1st Menkes International-
William de Rycke-Corthier Award

1st Menkes International-William de Rycke-Corthier Award

[September 2022 - June 2023]

At the opening of the 12th International Copper Meeting in Sorrento (Naples), Italy, 18 September, 2022, MIa announced the launch of the 1st Menkes International-William de Rycke-Corthier Award for €10,000.

William de Rycke-Corthier was a one-year-old Belgian boy with Menkes Disease who recently passed away while waiting for a therapeutic option. In his honor, his family through Voor William (Menkes association Belgium) and Menkes International Association (MIA) launched this award to be given to a researcher for an important contribution in the Menkes field.

Candidates for this award are physicians, scientists and/or investigators who are making important contributions in the research field of Menkes disease related to early diagnosis, clinical aspects and therapeutic options.

This award will recognize the efforts of scientific and medical professionals who are committed towards breakthroughs against this rare disease, and support enthusiastic professionals to enable future progress in the field.

The funds for this award were raised by Menkes Belgium, together with MIa.

This year, the deadline for applications is 2 September 2023 (the anniversary date of baby William´s death). Information about the award is available on the MIa website. The selection of the award winner will be done by the Copper(less) Committee, and will be announced in September 2023.

Links:
1st Menkes International- William de Rycke-Corthier Award (2022) – MIA

Amount raised for 1st Menkes International-William de Rycke-Corthier Award:	€10,000 (funds yet to be transferred to MIa)
Amount spent:	None to date

08

Metallothioneins (MTs) project

Metallothioneins (MTs) project

[December 2022 - to date]

Metallothioneins (MTs) are a class of metal binding proteins present in all the branches of the tree of life. Given the lack of biomarkers for Menkes disease, several experts of the MIa's Copper(less) Committee have recommended a research project to explore the possibilities to apply MTs for the diagnosis and monitoring of Menkes disease.

The MTs project is led by Professor Mercé Capdevila (University Autonoma of Barcelona) in conjunction with a group of experts, including Gabriel Meloni (University of Texas at Dallas).

While the MTs project has been announced, suitable candidates have yet to apply. MIa has transferred €20,000 to the Universidad Autonoma of Barcelona, and subsequent payments will be made only if the appropriate candidate is identified to lead the project. MIa will also discuss with the Universidad Autonoma of Barcelona to decide if support should be used for a PhD research position for three years instead of one.

Links:
https://scholarshipdb.net/jobs-in-Spain/2022-Dileua123-Postdoc-Researcher-Universitat-Aut-noma-De-Barcelona=vWh_P4hn7RGUYQAlkGUTnw.html

https://www.alphagalileo.org/en-gb/Item-Display/ItemId/228046?returnurl=https://www.alphagalileo.org/en-gb/Item-Display/ItemId/228046

Amount fundraised:	€40,000
Amount spent:	€20,000

09

Mla website

MIa website

[October 2021 - to date]

The MIa website was created in 2021 and it is updated on a regular basis.

The design and regular updates of content were provided by the team at Texas A&M University (an in-kind donation by Jim Sacchettini, Head of the Laboratory). Sid Rath and Saswati Panda at Texas A&M University manage the design and content. Aurora Mateos, member of the MIa board, writes the content updates.

The most recent updates to the website include:

- Pharmacy (how to find local access to copperhistidinate)
- 1st Menkes International-William de Rycke-Corthier Award

Links:
https://menkesinternational.com

Amount paid:	€311 (Bluehost.com for webhosting)

10

Financial accountability

Financial accountability

The finances of MIa are managed in a transparent manner. With the support and oversight the MIa Board Members, the day-to-day management of the MIa finances and bank account are managed by a part-time accountant, provided as a voluntary contribution from the firm Autocares Mateos.

The finances of MIa are managed under the direction of Aurora Mateos, MIa executive secretary. The Secretary and Treasurer, as well as the part-time accountant have regular access to the bank account.

The MIa finances are audited by the auditing firm Medina y Rubio asesoría in Malaga, Spain, at a discounted rate.

MIa is up-to-date with taxes following its transparency policy. MIa has submitted the “impuesto de sociedades 2021” modelo 200, and in February 2022 submitted “modelo 347” for MIa providers whose amount is bigger than 3,000 euros.

MIa’s bank account is at Caixabank in Malaga, Spain. Currently, MIa is concerned about the levels of commission and fees paid to Caixabank, and will endeavor to find more economical options.

Links:
https://menkesinternational.com/fundraising/

Cost of accountant: 181,50 euros

Income in 2022:

+40,000 euros (Mia-VoorWillian fundraised money for MTs project)
+50,000 euros (donated by Engrail)
+6685 (donated by Engrail therapeutics)
+300 individual donations
+20,000 (donation from VoorWilliam, member of MIa)

TOTAL: +119,685 euros
Engrail donations: 47,3%

Expenditure in 2022:

-38,934 € (Marco´s treatment: travel, complementary tests and clinical researcher)
-200 € (Eurordis)
-7549 € (Copper meeting)
-40,000 € (MT project)
-311 € (website)

ANNEX I

BRIEFING ON ONGOING ACTIVITIES 2023

January 2023: Experimental treatment with elesclomol-copper for a Second child with Menkes Disease (MD)

In November 2022, twins were born in León (Spain) both of them with Menkes Disease. Early diagnosis was possible because an elder brother had died of Menkes disease several months earlier.

MIa has been working intensely to make possible the administration of the experimental treatment for these children. The treatment was started in January 2023 once the requirements of the Spanish Medicament Agency were met. Unfortunately, one of the twins died at one month of age and MIa speeded up the procedure to start the treatment for the second one.

Many activities were conducted:

- MIa has been lobbying the Spanish Medicament Agency to obtain a Second authorization for the Leon twins.

- MIa has sent two professionals (Natalia Serrano, MIa researcher for the new treatment and Rosa Marques, Marco´s physiotherapist) to train the León medical team in charge of the treatment.

- MIa´s Copper(less) Committee has developed the dosing plan for the experimental treatment.

- MIa has donated the drug for the treatment.

At the time of releasing this report, the baby is now receiving elesclomol-copper and doing well.

Amount spent up to date:	€1200

MIa Charity Fundraiser at the Russian Museum in Malaga

[February 2023]

On 11th February, 2023 MIa worked in partnership with the Friends of the Russian Museum of Malaga Foundation to organize MIa's first charity fundraiser and lunch event at the Russian Museum in Malaga.

Due to limited space, only 100 people were able to attend, each buying a charity ticket for €100. Additional donations to MIa were announced during the event.

MIa engaged a range of public figures to advocate for MIa and the importance of Menkes at the event. Businessman and philanthropist, Dr Yusuf Hamied, explained the role of copper and described Menkes disease; Aurora Mateos and Denis Broun spoke on behalf of MIa governing body; Dr Francesc Palau spoke on behalf of Marco´s medical team, and Vikram Sudarsan spoke on behalf of Engrail, the pharmaceutical company planning a clinical trial to study a new drug for the treatment of Menkes.

The event was supported by renowned local chefs, Diego Gallegos, Juan Morcillo and Antonio Calderón, together with Pablo Molina, from the Sollo, Yamur and Matiz restaurants. Excellent local companies also contributed to the success of the event, such as Calma Eladio Frutas y Verduras, Picking Málaga, Pastelería Ramos, Bodega La Melonera, Bodega Doña Felisa, Antigua Casa Guardia, Juanito Baker, Cerveza Victoria, CapriSur, Dehesa de los Monteros, and Quesos Santa Maria del Cerro and Quesos Argudo.

The public interest and media coverage was positive. Several leading media outlets profiled the work of MIa. Marco´s photo and MIa's work on Menkes was featured on the front page of Diario Sur, Malaga's main newspaper.

Links:
El Museo Ruso acoge un almuerzo benéfico para apoyar la investigación de la enfermedad de Menkes | Diario Sur

CELEBRAMOS UN ALMUERZO BENÉFICO EN APOYO A LA LUCHA CONTRA LA ENFERMEDAD DE MENKES - Colección del Museo Ruso / Málaga (coleccionmuseoruso.es)

La Colección del Museo Ruso celebra un almuerzo benéfico en apoyo a la lucha contra la enfermedad de Menkes (101tv.es)

Amount raised:	€19,180
Amount spent:	€8,466, including: €6,416.29 (catering) and €2,050 (lighting)

ANNEX II

Menkes International Boards

Members of MIa Executive Board

Aurora Mateos (Executive Secretary)	Menkes relative
Tote Portillo (Secretary)	Menkes relative
Vicente Mateos (treasurer)	Menkes relative

Members of MIa Advisory Board *(in their personal capacity)*

Denis Broun (pharmaceutical adviser)	non Menkes relative
Leonardo Cervera Navas (data-policy adviser)	non Menkes relative
Andrey Galaev (adviser)	Menkes relative
Jorge A. López (IT manager)	Menkes relative
Juan Mateos (adviser)	Menkes relative
Irene Melo (communications manager)	Menkes relative
Vinay Saldahna (policy adviser)	Menkes relative

Copper(les) Committee *(in their personal capacity)*

Pr PALAU MARTINEZ, Francesc
Director of Copper (Less) Committee. Director, Servei de Medicina Genètica i Molecular. Institut Pediàtric de Malalties Minoritàries – IPER. Director, Institut de Recerca Sant Joan de Déu, Barcelona, Spain.

***

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CEO, Givopax pharmaceutical company, Geneva, Switzerland.

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Pr GOHIL, Vishal
Associate Professor, Biochemistry & Biophysics. A&M University, Texas

Dr GODOY, Elena
Complex Chronic Children and Palliative Care Unit, Department of Pediatrics, Regional University Hospital, Málaga, Spain;

Pr HORN, Nina
Menkes researcher, Pharmacist director (rtd), Professor(rtd) Kennedy Center-Copenhagen University Hospital.

Pr LUTSENKO, Svetlana
Professor of Physiology. Director for Basic Science and Clinical Relations, Institute for Basic Biomedical Sciences, Johns Hopkins University School of Medicine, Baltimore, USA.

MATEOS, Aurora
Leader of Menkes International Association (MIA). Mother of Marco, the first treated patient with Elesclomol-Copper.

Pr MANGAS, Victor
Assistant professor, University of Valencia. Specialist in Pharmacometrics, pharmacokinetics, Bioequivalence, Pharmacometrics, Modeling, Absorption.

Pr. PETRIS, Michael
Professor of Biochemistry, University of Missouri-School of Medicine, Columbia, USA. Menkes researcher

Pr SACCHETTINI, James
Rodger J. Wolfe-Welch Foundation Chair, Science. Professor | Biochemistry & Biophysics, Chemistry. Menkes researcher. A&M University, Texas, USA.

Pr STANDING, Joseph
Professor of Pharmacometrics, UCL Institute of Child Health. Honorary Research Pharmacist Pharmacist, Great Ormond Street Hospital. Honorary Senior Lecturer, St George's, University of London.

Dr SERRANO, Natalia
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