15 de noviembre de 2022

MP-004, the new standard for the treatment of Retinitis pigmentosa (RP)

Pablo Ferrón

Content

1. The Institution

2. The Product

   a) Target Indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered

3. Partnering Opportunities

Executive Summary

- **Spin-off** of the University of the Basque Country and Biodonostia Health Research Institute founded in 2019.
- Focused on developing **First in Class drugs for Neurodegenerative and Rare Diseases.**
- First program in **lead optimisation for Retinitis Pigmentosa (RP)**, and four programs in **lead nomination for DMD, DM1, ALS and AD.**
- The **lead compounds bind an isomerase protein to allosterically modulate intracellular calcium channel**. They restore the activity of "leaky" calcium channels normalizing intracellular calcium levels.
- Since the creation of the company, **Miramoon has raised a total of more than €1.8 Million.** Recent **capital increase by** founding partners.
- **Solid IP Position**:1st Patent Granted in EU, US, Australia, Japan, Russia, Chile and Mexico. **2nd Patent Application filled** covers backup compounds and ocular diseases.
- **First rate management team** with many years of experience in the field of Neurodegenerative and Rare diseases, from basic research to clinical practice. Supported by a **high-level advisory board**.
- **Market Access and Pricing Strategy** defined, complemented with a Willingness To Pay study in the US, UK, Spain, France and Germany (€2,250 per patient and year).

Management Team

Pablo Ferrón (CEO)

Master's degree in Synthetic and Industrial Chemistry. He participated in the design and synthesis of the first MP compound. He has previous entrepreneur experience (in 2010, founded an industrial start-up: Gomavial Solutions). He is now leader of Miramoon Pharma.

Prof. Dr. Jesús María Aizpurua (CSO)

Expert in drug synthesis and click chemistry. He leads the research group Sustainable Catalysis: Methods and Computation in San Sebastián. He is the author of 120 scientific publications (H = 32), 5 patents and supervised 20 doctoral theses, and directed 19 research projects. He ensures the rapid synthesis of MPs compounds libraries when required.

Dr. MD Adolfo López de Munain (CMO)

Expert in neurodegenerative diseases and has permanent contact with patients affected by such conditions. He is author or co-author of 225 reviewed articles, and 26 book chapters. He provides medical and clinical expertise and, as a national authority in the area of neuroscience, facilitates access to national pharmaceutical companies and institutions.

Glória Martín (Regulatory Aff.)

Regulatory Affairs with +25 years of experience in the pharmaceutical industry R&D and +5 as a Regulatory Affairs consultant to start-up and biotech companies. Expertise encompasses EU and US regulations and procedures in different therapeutic areas and including small molecules, biologic and advanced therapies products.

Inveniam Group (Biz Dev. Manager)

An expert team of consultants from the Inveniam Group will take care of all the activities related to market access, such as health economics analysis and market research. Inveniam will also provide support on public and private funding strategy and execution.

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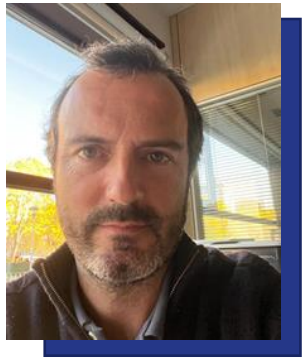
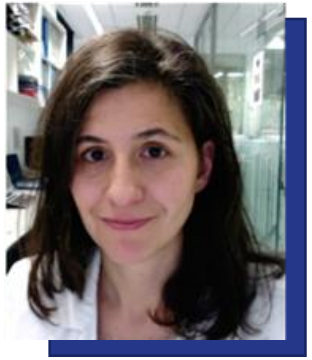
R&D Team



Dr. Javier Ruiz (Biology Director)

PhD in Biological Sciences with 5 years of Postdoctoral experience at the University of California, San Francisco and >20 years of experience in ocular diseases. He led the sensory neurodegeneration group at Biodonostia Health Research Institute (2010-2020); 14 research projects; 25 publications in indexed journals and 4 doctoral theses. Accredited with Excellence in Research (I3 Program, I3/2019/384) and in Human Genetics (AEGH). In 2021 he was hired by Miramoon Pharma through a Torres Quevedo contract (PTQ2019-010412) to lead the biology area of the company.



Dr. Ainara Vallejo (Pharmacology Director)

PhD in Neurosciences, expert in bioactivity evaluation. Demonstrated experience in the biomedical area with 26 scientific publications, 3 international patents and has supervised 4 doctoral theses. She has directed several national and international competitive research projects, many of them in muscular dystrophies. She provides the project with access to test laboratories with biological materials, cell and animal models, and various mass testing methods for the selection of "Hit" and "Lead" molecules, etc.

Dr. J. Ignacio Miranda (Medical Chemistry Director)

Expert in the design of in silico molecules against biological targets. The different cooperation activity with many groups with the result of 45 publications (H = 15). He has co-supervised 1 doctoral thesis. Provides the project with technical knowledge of structural and bioinformatic analysis of molecules and targets.

Prof. Dr. Jesús María Aizpurua (CSO)

Expert in drug synthesis and click chemistry. He leads the research group Sustainable Catalysis: Methods and Computation in San Sebastián. He is the author of 120 scientific publications (H = 32), 5 patents and supervised 20 doctoral theses, and directed 19 research projects. He ensures the rapid synthesis of MPs compounds libraries when required.

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High-Level Advisory Board

Advisory Board composed of **international renowned experts in Medicinal Chemistry, Computational Chemistry, Pharmaceutical Technology and Pharmacology of Neurodegenerative, Rare Diseases and Retinal disorders**. Combined expertise in basic research and clinical practice.

Dr. MD. Cristina Irigoyen (Retinal Disorders-Clinician)

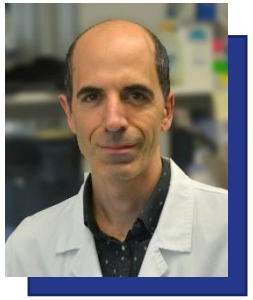
Medicine and Surgery, specialized in Ophthalmology and retina (Hospital Universitario Donostia). Published 22 articles and participated in 10 clinical trials and obtained several grants for clinical studies in Retinitis Pigmentosa.

Dr. Helmut Buschmann (MedChemi)

Chemist with + 20 years' experience in drug discovery and development, guided 15 novel drug classes into clinical phases and was appointed as inventor in over 200 patents.

Dr. MD. Pedro de la Villa (Retinal Disorders-R&D)

Author of +75 papers, Director of 15 PhD theses and Principal Investigator of 15 national and international research projects. Research in neurophysiology of the visual system, retinal physiology, and neuromuscular physiology.



Dr. Francisco J. Gil-Bea (Rare Diseases)

Principal Investigator from 2010 to 2014 at CIMA of the University of Navarra, with funding from the Alzheimer's Association of the USA. Since 2015 principal investigator at the Biodonostia Institute.+15 years of experience in the study of neurodegeneration, published more than 40 publications (H=23), and supervised 2 PhDs and several master students.

Dr. Virginia Arechavala - Gomeza (Pharmaceutical Technology)

She leads the Neuromuscular Research group at Biobizkaia Health Research Institute as an Ikerbasque Research Professor.
She has over 20 years' experience in research in neuromuscular disorders, has participated in the development of several orphan drugs and chairs an international network of researchers in the field of nucleic acid therapeutics. She serves in several Spanish and International grant review panels and has collaborated as an expert with the European Medicines Agency.

Retinitis Pigmentosa (RP) – ORPHA 791

- Group of Inherited Retinal Dystrophies (IRDs) characterized by progressive degeneration of photoreceptors or retinal pigment epithelium, leading to night blindness, tunnel vision, and gradual reduction of central vision. **Retinitis Pigmentosa (RP) is the most common cause of IRDs.**
- Reported prevalence of **1 in 3,000-5,000 individuals worldwide**, although higher frequencies have been reported in some Asia populations (1 in 930 in South India, 1 in 1,000 in China).
- **Leading cause of visual disability** and first cause of irreversible blindness in developed countries for people under 70 years of age.
- **Highly heterogenous genetic basis.** Most cases of RP are monogenic, with mutations in more than 80 genes identifies to date.
- Most RP cases are referred to as **"non-syndromic"** when the disease involved vision loss alone (70-80% of cases). However, RP can occur in cojunction with systemic disease, being referred as **"syndromic"**.

Inheritance of RP (Groups)	Estimate prevalence worldwide	RP-causative mutated genes
Autosomal Dominant (adRP)	15 to 25%	24 genes associated
Autosomal Recessive (arRP)	5 to 20%	46 genes associated
X-linked Recessive (xlRP)	7 to 15%	6 genes associated
Non-Mandelian Inheritance	No data available	Exceptional rare cases
Simplex or Isolated (sRP)	40-50%	Non-consanguineous affected individuals

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Current SoC is not adequate for managing RP patients

DIAGNOSIS: RP symptoms significantly differ in terms of severity and rate of progression. Thus, it is difficult to establish a standard diagnosis, counselling, and therapeutic strategy to all RP patients. **RP clinical diagnosis relies upon a complex combination of clinical history examinations, visual field testing and retinal imaging to evaluate photoreceptor function, and molecular genetic resting.**

TREATMENT & MANAGEMENT: Current care attempts to slow down the degenerative process with Vitamin A supplementation and psychological support.

- ***Symptomatic treatment***: There are some approved treatments for RP, although they are highly genericized and cannot cure RP (vitamin A as a standard of care, and anti-inflammatories such as betamethasone and cortisone).
- ***Curative treatment:*** The first ocular gene therapy and the only marketed treatment is **Luxturna** (approved in the US in 2017 and in the EU in 2018), indicated for RPEG5 mutation (around 1% of all RP patients). In addition, its administration required invasive retinal surgery, and only suitable if the retina has not degenerated much. Common severe side effects associated to intraretinal injections include cataract (up to 20%), increased intraocular pressure (up to 17%), macular holes (up to 10%), among others. Several economic studies have been conducted on Luxturna, albeit with differing results (some studies found Luxturna a non-cost-effective therapy).

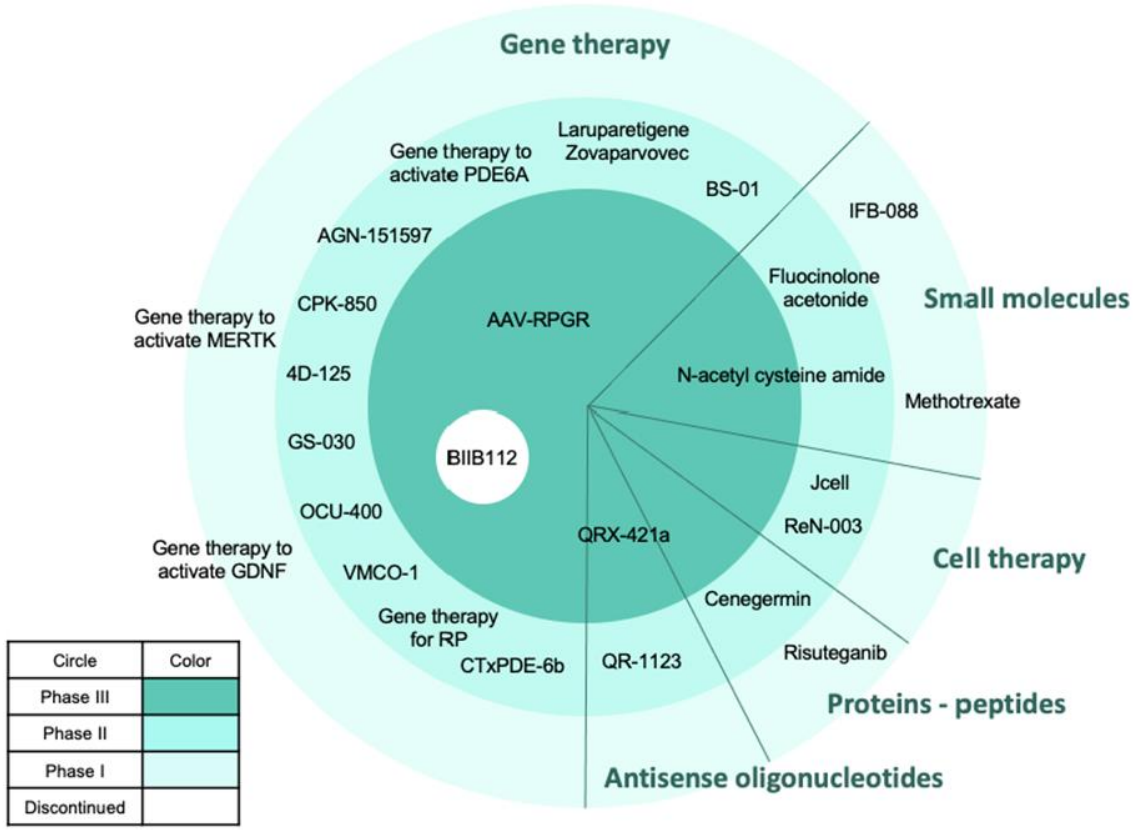
How does it start

How does it end

Competitive Landscape

- **Marketed Drugs:**
  - Luxturna (Spark Therapeutics/Novartis): Gene therapy for the treatment of patients with genetic mutation in RPE65 gene (approx. 1% all patients).

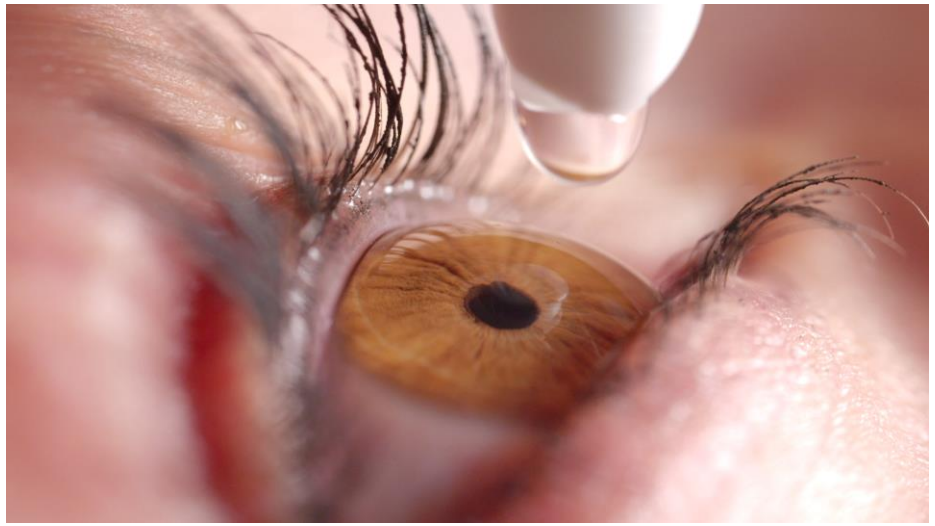
- **Novel therapeutics**
  - 23 pipeline agents under development for RP with just two products in Phase III development (both gene therapies). The remaining products are in Phase II.
  - In terms of drug class, 64% are gene therapies, 12% small molecules, and 8% are antisense, oligonucleotides, stem cell therapies, and recombinant proteins.



Pipeline products by type and pase (RP Market)

MP-004, the new standard for RP

- Potential therapy for **all RP patients** (agnostic to mutations).
- Stand alone therapy or combinable with other therapeutic approaches.
- **Reaches retina after topical administration.**
- Preliminary results in pigs confirm absence of MP-004 in untreated contralateral eye
- Optimized physicochemical and ADME properties
- **Easily scalable synthesis and low manufacture cost**
- **Improves rods and cones' structure and function**
- **Low toxicity** due to specific mechanism of receptor defects (does not alter physiological function)

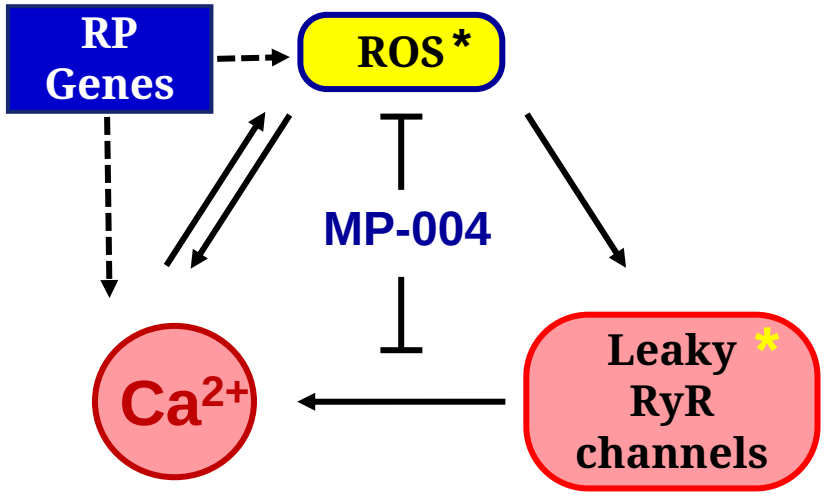


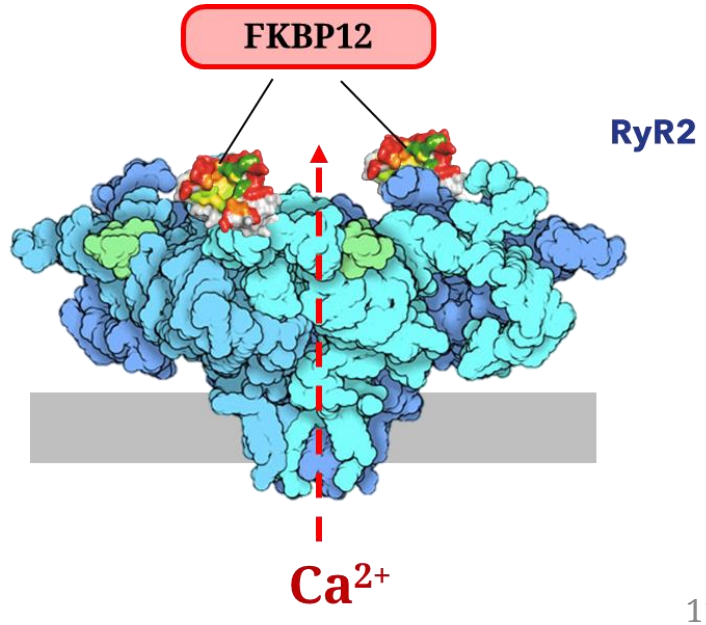
Mechanism of Action of MP-004

Calcium dysregulation and **oxidative stress** are pathogenic mechanisms contributing photoreceptor death in RP.

MP-004 is a novel FKBP12 ligand that modulates the **FKBP12-RyR2 interaction** preventing **calcium leakage** from RyR2 channels under pathological conditions.

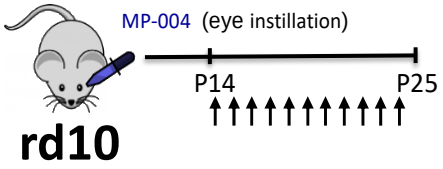
MP-004 can act as a **ROS scavenger**, reducing the formation of highly reactive deleterious species.





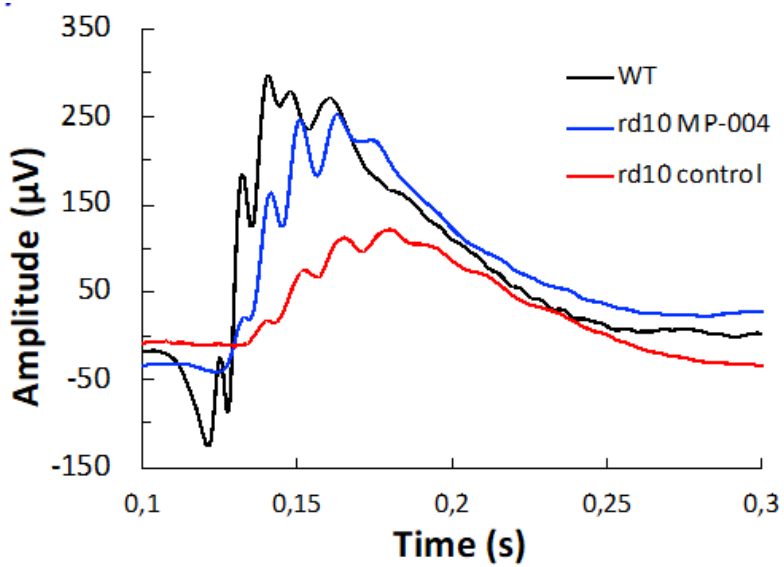
In-vivo : rd10 mouse model (eye drops)

MP-004 improves ERG response in rd10 & rd3 mice

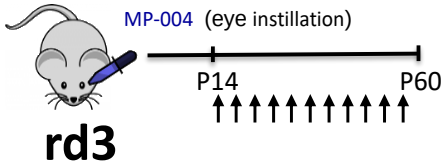


rd10

rd10 (retinitis pigmentosa)

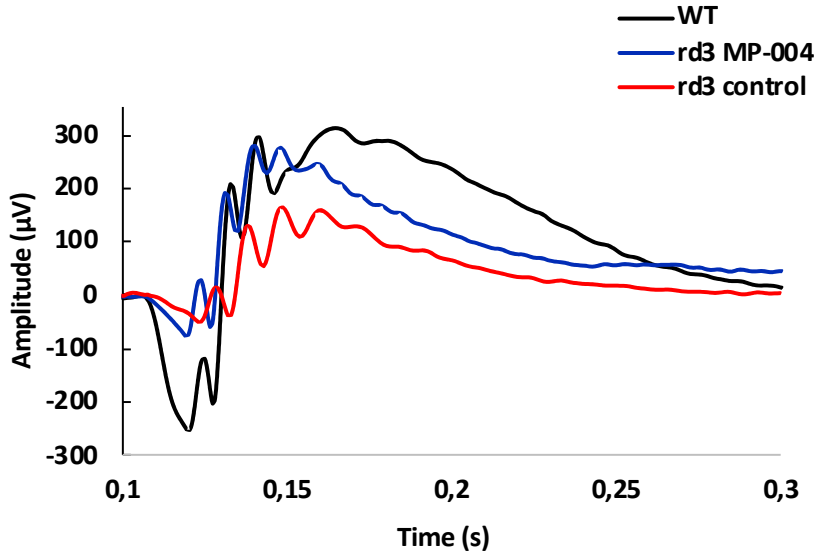


- **improved rod function** (rod b-wave) by 41% compared to untreated group (at 25 days).



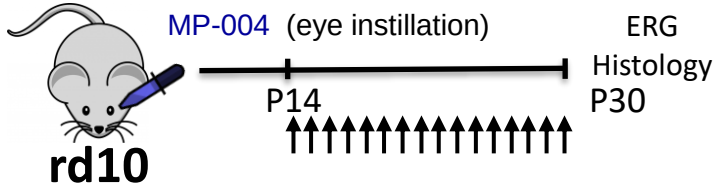
rd3

rd3 (Leber congenital amaurosis)

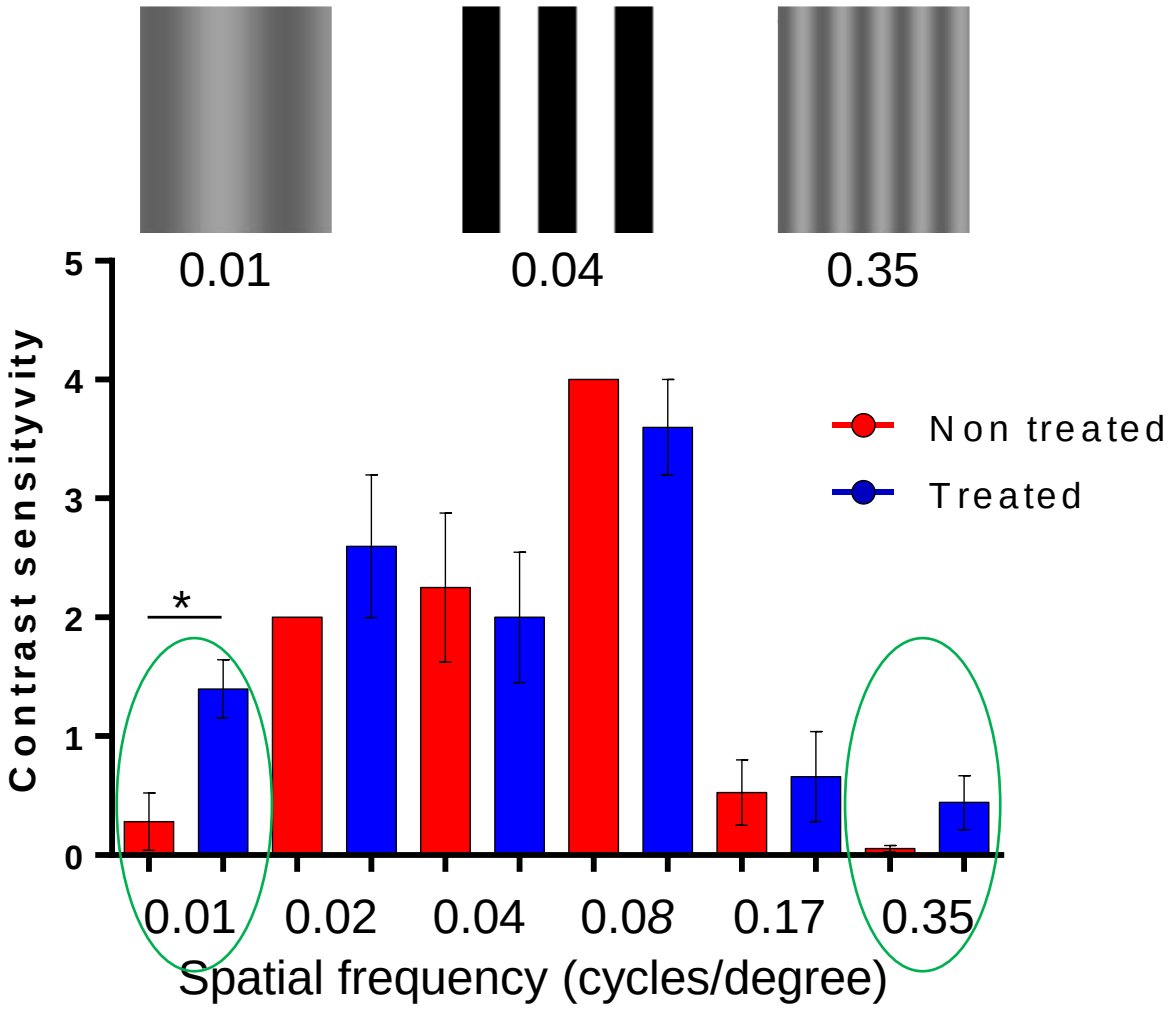


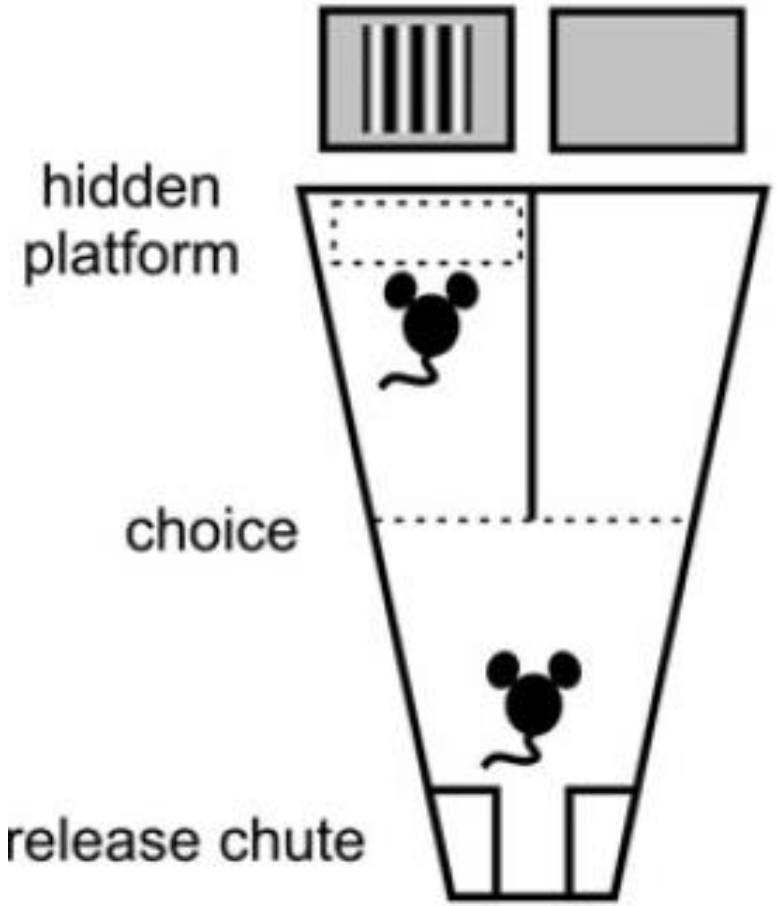
- **improved rod function** (rod b-wave) by 33% compared to untreated group (at 2 months).

In vivo efficacy of MP-004 – Visual response



MP-004 improves visual response. Adapted water-maze test at P30



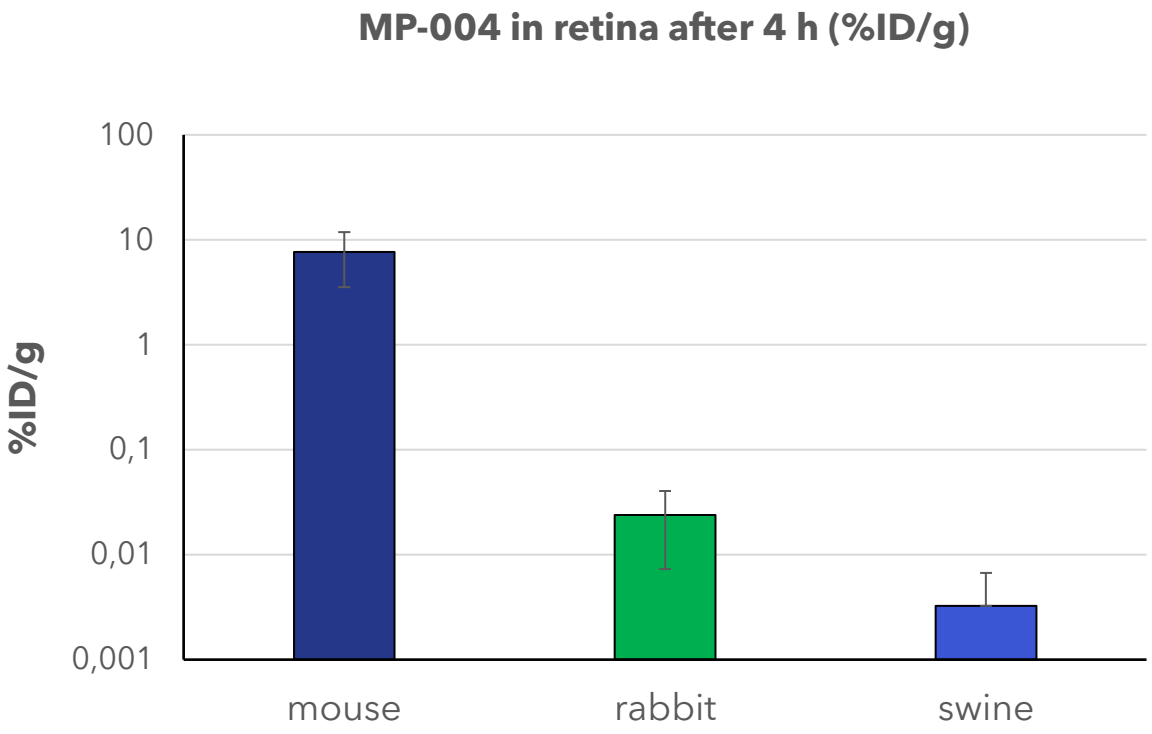


An improved contrast sensitivity is observed in mice treated with MP-004.

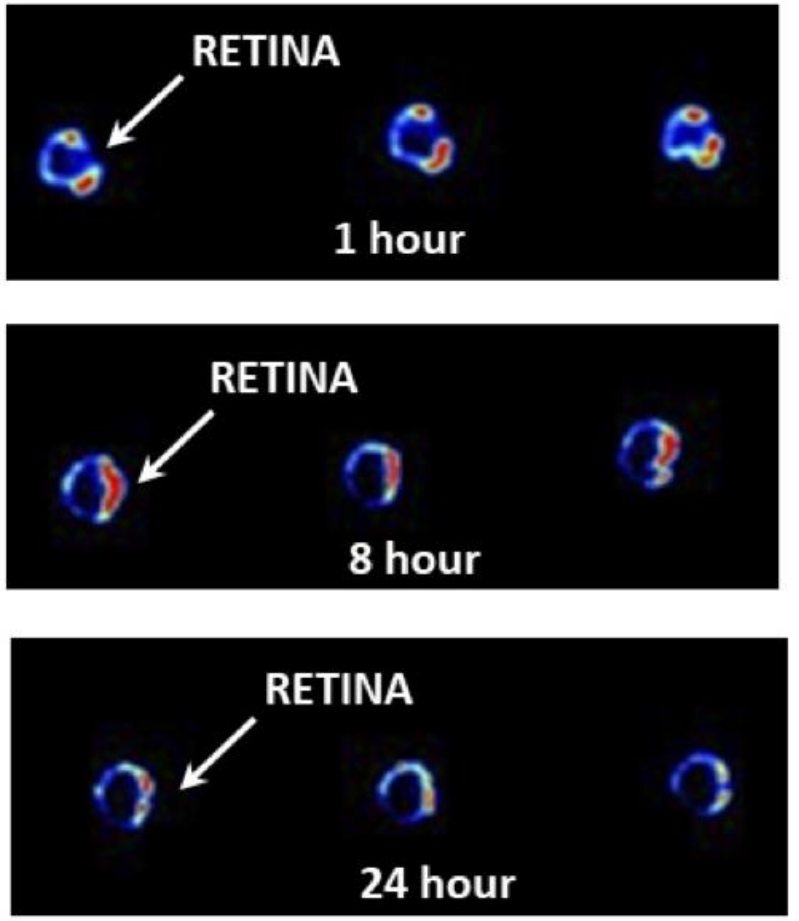
Bioavailability of MP-004 in 4 species

MP-004 reaches retina of mice, rats, rabbits and pigs after topical administration

Dose in Mouse: 17 µg/ eye
Dose in rabbit & Pig: 559 µg/ eye



Bioavailability of MP-004 in retina – 4h after ocular administration



Rat: PET autoradiography image

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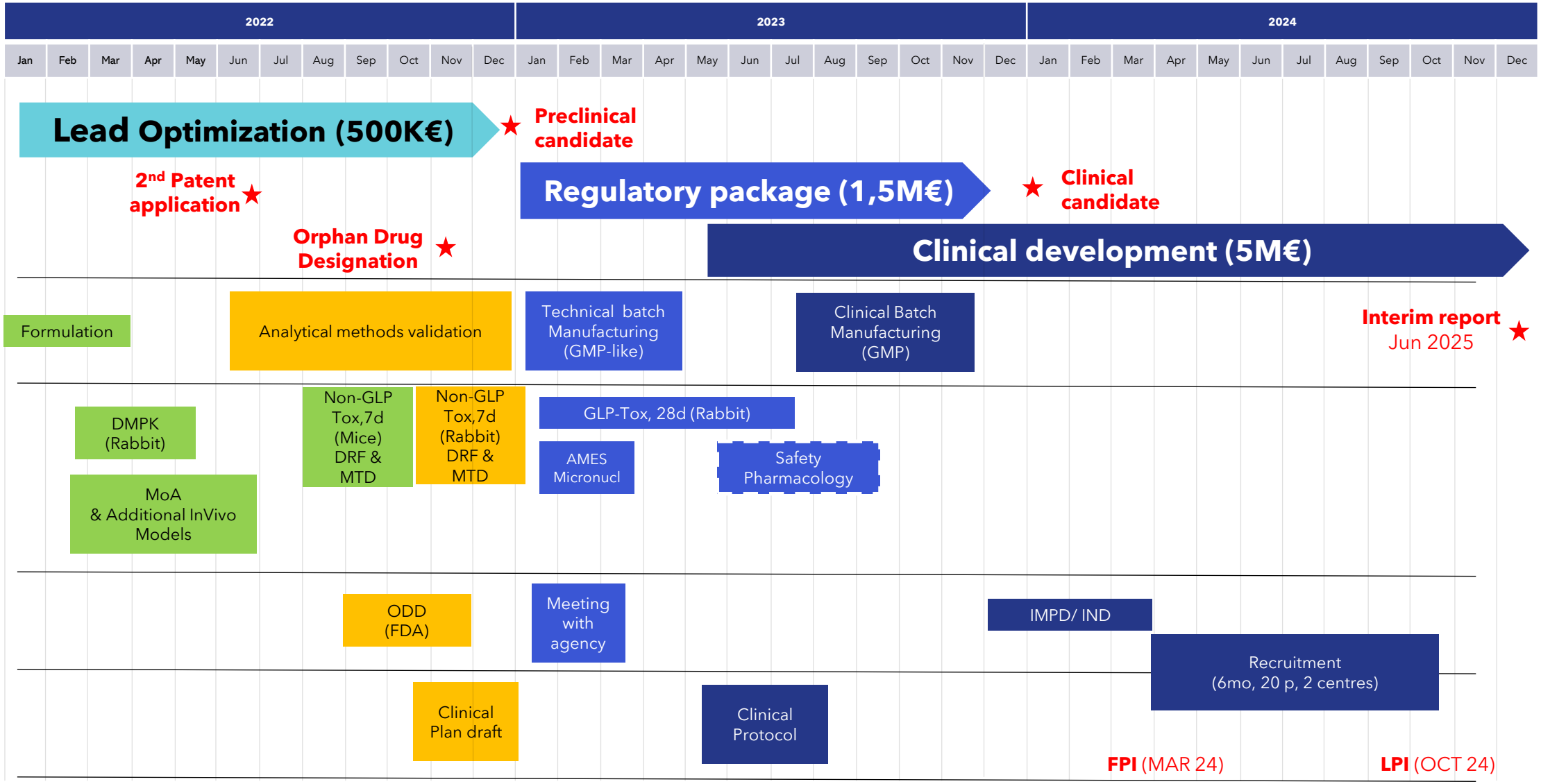
Competitive Landscape: TPP & Main Competitors

Product properties	MP-004	Luxturna	SPVN06
Primary indication	Retinitis pigmentosa	Retinitis pigmentosa	Retinitis pigmentosa
Patient population	**All patients**	RPE65 mutations (1% patients)	All patients
Treatment duration	Chronic	Single injection	Single injection
Delivery mode	**Ocular instillation (eye drop)**	Subretinal injection	Subretinal injection
Delivery form	Monodose	Prefilled vial	Prefilled vial
Regimen	1-2/ day	once	once
MoA	Calcium homeostasis	Replacement of defective gene	Introduction of neurotrophic factors (RdCVF and RdCVFL)
	Improves structure and function of rods and cones	Curative for target population	Slow or stop the degeneration of cone photoreceptors
Risk/ side effects	Unknown to date	Associated to delivery mode (Conjunctival hyperaemia, cataract and increased pressure in the eye)	Associated to delivery mode Unknown those associated with the product
Therapeutic Modality	**Small Molecule**	Gene therapy (AAV)	Gene therapy (AAV)
Stage	Preclinics	Approved	Preclinics
Cost of treatment	**€2,250 per patient and year**	450k€/ eye	Unknown

Development plan

DONE

Ongoing



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Intellectual Property (2 Patents)

Priority: 2016

The patent covers new compounds that are capable of treating or preventing disorders or diseases associated with intracellular calcium dysregulation or Ryanodine receptor dysfunction. The invention also relates to methods for synthesizing said compounds, to pharmaceutical compositions containing them, and to the use thereof for preventing or treating skeletal muscle, heart and nervous system disorders

Current status:

- Granted in: US; EU (Austria, Belgium, Czech Republic, Croatia, Denmark, Finland, France, Germany, Greece, The Netherlands, Hungary, Ireland, Italy, Luxemburg, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Turkey, U.K.); Australia; Chile; Mexico; Russia; Japan.

- Pending in: Canada, China, India and Israel.

2nd Patent: A new patent has been filled at the European office with **priority date 06/2022.**

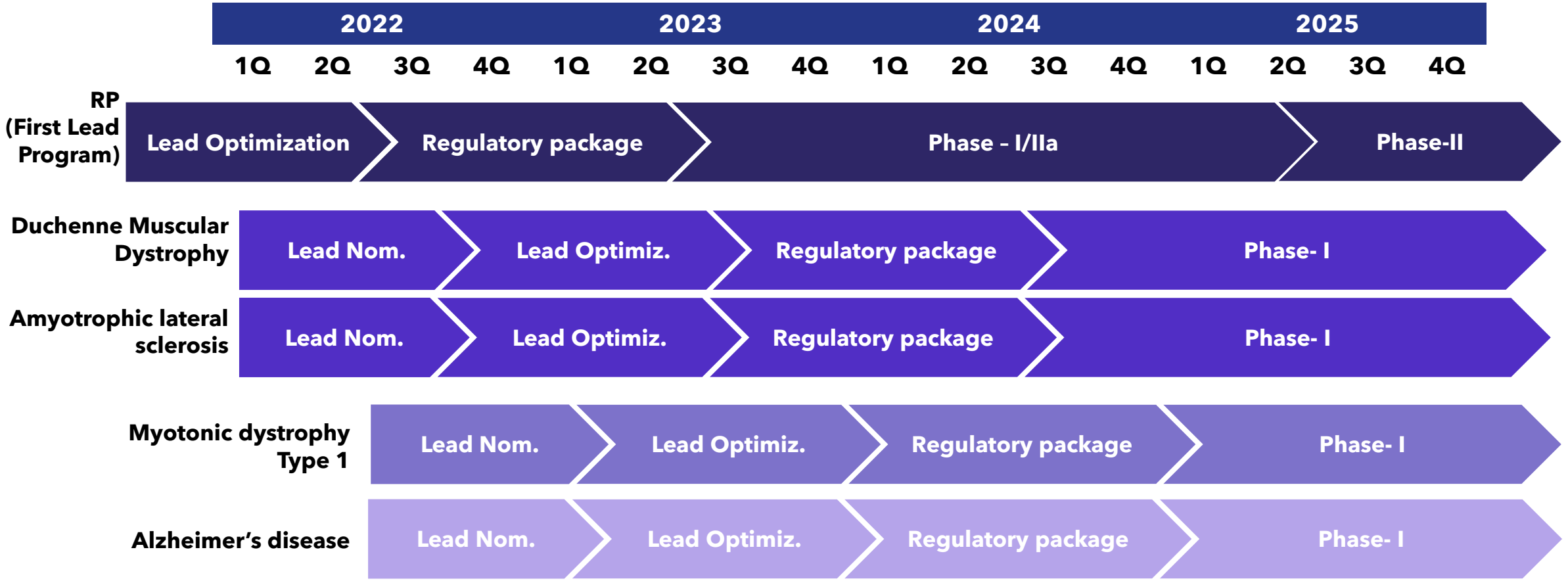
The patents has been licensed in exclusivity to Miramoon Pharma

Pitfalls & Risks to be considered

Pitfalls & Risks	Mitigation Strategy
Inability to reach the retina	-Positive results in pre-clinical studies with animal models. -Formulation of MP-004 reaches the retina x5 than our unformulated compound
Compound performance in RP (safety & efficacy)	-*In-vivo* studies supporting evidence -Inclusion of different RP group patients in planned Phase I/IIa clinical trial. -MP-004 can target other pathologies
Failure to synthesizer at big scale	-Easy to synthesize molecule – Click chemistry
New candidates for RP & other target pathologies	-Regulation of RyR channels is a novel approach (MoA target) -Strong IP and Orphan Drug Designation
Reluctancy from payers	-Collaborate and communicate with all stakeholders -Define economic endpoints in clinical trials -Health Technology Assessment

Pipeline: Targeting Neurodegenerative and Rare Diseases

MPs compounds stabilize the binding of a specific isomerase protein with intracellular calcium channels and normalize cytosolic calcium levels in cells suffering from oxidative stress. They have an enormous therapeutic potential in pathologies that present a primary or secondary dysfunction in underlying calcium mechanisms, which is not only present in RP, but also in dystrophinopathies and neurodegenerative diseases.



Partnering opportunities

We are open to share our **knowledge and structures** to explore other **targets & interactions** in collaboration

Always looking forward to develop our **projects in partnership** with the industry agents

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Miramoon Pharma in 2 minutes video

Video: Adapted water-maze test at P30

2022

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