Within the framework of the ARVO 2019 congress,

Sylentis (PharmaMar Group) presents new results of tivanisiran for the treatment of dry eye disease

- In patients with Sjögren's Syndrome, where the inflammatory component of the disease is more exacerbated, there is a statistically significant improvement in both signs and symptoms ($p<0.05$).
- Patients with dry eye disease treated with tivanisiran showed a statistically significant reduction in the central corneal damage ($p<0.05$).
- Sylentis has met at ARVO with recognized experts in ocular surface to agree on the following steps in its clinical development.

Madrid, 6th of May, 2019. Sylentis, a pharmaceutical company of the PharmaMar Group (MSE:PHM), has presented new results from its clinical trial HELIX with tivanisiran for the treatment of dry eye disease during the Annual Congress of the Association for Research in Vision and Ophthalmology (ARVO), which is being held from 28th April to 2nd May in Vancouver (Canada).

During the session entitled: "Cornea, dry eye clinical treatment" Sylentis presents the new results: "Clinical results of tivanisiran, a siRNA for the treatment of dry eye disease (Panel: 6738 - B0262)". Tivanisirán shows statistically significant results in:

- Statistically significant improvement in both signs and symptoms of dry eye syndrome in patients with Sjögren's syndrome ($p<0.05$).
- Reduction of central corneal damage in patients with dry eye disease ($p<0.05$).

In the new data obtained from HELIX clinical trial, it has been identified that in patients with Sjögren's Syndrome showing a more exacerbated pathology in which the inflammatory component plays a major role, a statistically significant improvement was observed both in signs and symptoms.

Sjögren's Syndrome is an autoimmune disorder in which the glands that produce tears and saliva are destroyed, causing dryness in the mouth and eyes.

In addition, patients treated with tivanisiran showed a reduction in central corneal damage compared to the comparator. This fact is of great clinical relevance since the central area of the cornea is densely innervated and participates in visual performance[1].

In the HELIX clinical trial[2], the safety and efficacy of tivanisiran eye drops were evaluated in a population of 289 patients with persistent signs and symptoms of moderate to severe dry eye disease.

The safety profile observed in animal model studies correlates with that of the HELIX trial, where good local and systemic tolerance of tivanisiran was showed.

According to **Ana Isabel Jiménez, COO and Sylentis R&D director**, *"These results support the potential of tivanisiran in the treatment of dry eye signs and symptoms. We trust in on our technology and hope that this investigational drug may soon become a real alternative for treating the millions of dry eye sufferers around the world."*

ARVO Congress, which annually brings together more than 11,000 experts from 75 countries, provides a unique setting to showcase the most innovative research and technological advances in the field of vision care. This congress is attended by basic researchers and ophthalmologists, as well as members of the pharmaceutical industry and regulatory agencies with the aim of sharing knowledge, addressing new challenges and unmet medical needs in the treatment and prevention of eye diseases.

During the congress, Sylentis has taken this opportunity to organize a meeting with experts and renowned American ophthalmologists, specialized in the treatment of dry eye disease to evaluate in detail the results of its clinical trial with tivanisiran and agree on the steps to follow in clinical development.

Sylentis is a leading research company in gene silencing technology using interference RNA (RNAi) and is a pioneer in applying this technology to develop new drugs in the field of ophthalmology. It should be noted that dry eye disease affects more than 5 million people in Spain - between 10% and 20% of the population, mostly women, and almost 100% in the elderly[3] [4].

Explanatory videos:

What is RNA interference? https://www.youtube.com/watch?v=iXvSitR5184

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About Sylentis

Sylentis is a PharmaMar Group pharmaceutical company focused on the discovery and development of innovative therapies based on gene silencing or RNAi technologies. This technology allows the targeted design of drugs whose mechanism of action focuses on the selective inhibition of the synthesis of abnormal proteins or whose overproduction is linked to the appearance of a disease.

Sylentis has a solid drug development program in the field of ophthalmology, with tivanisirán for the treatment of dry eye[5] [6] and bamosiran for the treatment of glaucoma, the two candidates in the most advanced clinical phases. Sylentis' product portfolio also includes candidates in the non-clinical development phase for the treatment and prevention of ocular allergies and various retinal diseases. For more information visit www.sylentis.com.

About tivanisiran

Tivanisiran (formerly SYL1001) is a small interfering RNA (siRNA) in the clinical research phase. This siRNA, through a mechanism of actionbased on the RNA of interference, inhibits the synthesis of the Transient Potential Receptor V1, also known as TRPV1.

TRPV1 is directly involved in the pathophysiology of Dry Eye Disease by having a dual function on the ocular surface. TRPV1 is involved in both the detection, transmission and regulation of the sensation of pain in the eye and in the mediation of the innate inflammatory response. The role of TRPV1 in tear quality is also being studied. The regulation of these mechanisms is key in the treatment and prevention of Dry Eye disease.

Tivanisiran has been designed using the bioinformatics tool SIRFINDER, property of Sylentis and is formulated in the form of eye drops in a preservative-free solution (eye drops) for study in clinical trials. Tivanisirán is an investigational drug to treat the signs and symptoms of dry eye disease. Due to its

mechanism of action, this drug has the potential to be developed for other pathologies with eye pain (corneal wound, refractive surgery, etc.)[7] [8] [9] [10].

About interference RNA (RNAi)

RNAi is a natural cellular mechanism that occurs in plants, animals and humans. It is mediated by small fragments of double-stranded RNA called siRNAs that play a key role in gene regulation during development and in the immune response to viral infections.

Biotechnology takes advantage of this cellular process that allows the rational design of specific therapies based on RNAi. RNAi drugs use cellular machinery to silence genes, or more precisely, eliminate genetic products called messenger RNA (mRNA), the molecular precursors of proteins.

Some diseases are caused by protein malfunctioning or by tis excessive production. The use of drugs based on RNAi allows to decrease or control in a very specific way the production of these proteins that are involved in a pathology.

In 2006 the Nobel Prize in Physiology or Medicine was awarded jointly to Andrew Z. Fire and Craig C. Mello for their discovery of RNAi mediated by siRNAs. Twelve years later the first drug based on this technology has been approved for the treatment of hereditary amyloidosis by transthyretin, demonstrating the high potential of this technology in drug development[11] [12].

Dry eye is a multifactorial disease of the tears and ocular surface. It is a very heterogeneous pathology whose diagnosis is made based on symptoms such as pain, eye discomfort, dryness, itching, sensation of foreign body or photophobia, which are reported by patients during medical consultations. In addition, there are a series of signs such as the presence of hyperemia (redness) in the conjunctiva, corneal staining or some parameters related to the quality of the tear and which can be evaluated objectively by health professionals.

About Dry Eye Disease

Dry Eye Disease is chronic and is associated with an inflammatory component, which can cause damage to the surface of the eye and even defects in vision. In addition, it also has a negative effect on patients' quality of life by altering the performance of activities of daily living such as reading, driving, working, watching television or spending time outdoors in bright light, cold or windy conditions.

The prevalence is 5-30% in the population aged 50 years or older and is more frequent in women[13].

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