Within the framework of the ARVO 2019 congress,

Sylentis (PharmaMar Group) presents its new drug for retinal diseases at ARVO

- The application of SYL1801 in eye drops could be a new therapeutic option for the treatment of retinal diseases characterized by neovascular processes, as opposed to the ocular injection used in current treatments.
- SYL1801 administered in eye drops reduces angiogenesis (blood vessel formation) in an animal model of laser-induced neovascularization, similar to intravitreally injected anti-VEGF agents.

Madrid, 3rd of May, 2019. Sylentis, a pharmaceutical company belonging to the PharmaMar Group (MSE:PHM), has presented the results of the preclinical development of its new compound, SYL1801, administered in eye drops for the prevention, treatment and control of the progression of retinal diseases characterized by neovascular processes. The results were presented at the Annual Congress of the Association for Research in Vision and Ophthalmology (ARVO), held from 28th April to 2nd May in Vancouver, Canada.

The ARVO Congress is the world's principal meeting of ophthalmologists, bringing together more than 11,000 experts from 75 countries each year. It is a unique venue 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 authorities with the aim of sharing knowledge, addressing new challenges and unmet medical needs in the treatment and prevention of eye diseases.

In the ARVO session that took place on May 1st, entitled "Age Associated Macular Degeneration and Anti-Angiogenic Agents", Sylentis presented the following poster:

- SYL1801: Preclinical Efficacy and Safety of a siRNA-based eye drops treatment for Age Related Macular Degeneration (Panel: 5389 - B0085).

The efficacy studies performed on an animal model of laser-induced choroidal neovascularization have shown that the reduction of NRARP protein expression in the retina by SYL1801, administered in drops, is associated with a regression of angiogenic lesions. Furthermore, the regressions observed are equivalent to those observed in the group of animals treated with intravitreally injected anti-VEGF agents (current standard treatment for diseases of the retina).

In addition, toxicology studies conducted on globally accepted animal models support that, at the tested concentrations and exposure times, SYL1801 local and systemically well tolerated.

Ana Isabel Jiménez, COO and Sylentis R&D director, comments that *"The drugs traditionally used to treat retinal diseases are antibodies, large molecules that cannot reach the retina from the ocular surface. This is why they are administered by intravitreal injections. Patients with age-related macular degeneration or diabetic retinopathy should periodically visit the hospital, where this type of procedure is frequently associated with a negative emotional burden and a large expenditure of time[1]. In addition, intravitreal injections entail both a large economic investment and a great effort from the health systems".*

Ana Isabel Jiménez points out that *"siRNAs, such as SYL1801, are much smaller than antibodies, allowing them to penetrate the retina and inhibit the formation of new blood vessels after being applied eye drops on the ocular surface".*

"We are confident that we can begin the clinical development program of candidate SYL1801 throughout 2019 and that in the future SYL1801 will be an alternative in the treatment of diseases of the retina," continues Ana Isabel Jiménez.

Sylentis is a leading research company in gene silencing technology using RNA interference (RNAi) and is one of the few that applies this technology in the field of ophthalmology. It is estimated that the number of individuals with AMD will reach 196 million in 2020 and 288 million in 2040. AMD is the leading cause of irreversible visual impairment in the elderly population of developed countries, accounting for 8% of all cases of blindness worldwide. In fact, the overall prevalence of AMD among 45-85 years is 8.7%[2] [3].

Explanatory videos:

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

About Sylentis

Sylentis is a PharmaMar Group pharmaceutical company focused on the discovery and development of innovative therapies based on gene silencing technologies or RNAi. 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 tivanisiran for the treatment of dry eye[4] [5] and bamosiran for the treatment of glaucoma, these are 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 SYL1801

SYL1801 is a small interfering RNA (siRNA) in the non-clinical research phase. This siRNA, by means of mechanism of action based on RNA interference (RNAi), inhibits the synthesis of NRARP (Notch-regulated ankyrin repeat-containing protein).

NRARP is directly involved in the pathophysiology of choroidal neovascularization, i.e. the abnormal formation of new vessels from the choroid into the retina. It is a common hallmark of several retinal diseases such as age-related macular degeneration (AMD) or diabetic retinopathy (DR).

During angiogenesis (new vessel formation), NRARP integrates the Notch and Wnt signaling pathways by controlling stalk cell proliferation to stabilize new endothelial cell connections[6]. Activation of the Notch

pathway produces a reduction in the volume of laser-induced lesions in a murine model of choroidal neovascularization whereas inhibition of the Notch pathway promoted neovascularization[7]. Nrarp acts as a negative regulator of Notch and, therefore, its inhibition may contribute to preventing and/or slowing the progression of visual impairment due to choroidal neovascularization[8].
SYL1801 has been designed using the bioinformatics tool SIRFINDER, property of Sylentis and is formulated in the form of eye drops in solution.

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 by its 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[9] [10].

On age-related macular degeneration
AMD is a chronic, progressive disease affecting a central region of the retina known as the macula. AMD leads to a gradual loss of visual acuity and can even lead to blindness in the most severe cases.
Although AMD has a major negative impact on patients' quality of life, its exact pathophysiology is only partially understood. It is estimated that the number of individuals with AMD will reach 196 million by 2020 and 288 million by 2040. AMD is the leading cause of irreversible visual impairment in older people in developed countries, accounting for 8% of all cases of blindness worldwide. In fact, the global prevalence of AMD among 45-85 year olds is 8.7%.
Currently, AMD is treated by intravitreal administration of anti-VEGF (vascular endothelial growth factor) agents. These injections must be administered regularly, are uncomfortable for the patient and have a number of associated adverse effects[11].

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