Sylentis initiates a Phase III study for the treatment of dry eye syndrome

- HELIX is a Phase III clinical trial started by Sylentis with the investigational new drug SYL1001, based on RNA interference technology (RNAi)
- The Company has agreed with the U.S. Food and Drug Administration (FDA) on plans for the Phase III clinical program, which is designed to support the submission of a New Drug Application (NDA). The Company has received final, End-of-Phase II meeting minutes from the FDA
- Sylentis is a global leader in investigating use of RNAi for dry eye syndrome and it is one of the few in Europe to take this development to the field of ophthalmology
- Dry eye syndrome occurs when the eye does not produce tears properly, or when the tears are not of the correct consistency and evaporate too quickly[1]. Affects both the tear and/or the ocular surface and between 10% and 20% of the population in Spain suffer from this illness, especially the above 40´s[2,3,] women and also almost 100% of the elderly[1]

Madrid, May, 30th, 2017. The pharmaceutical Company Sylentis (PharmaMar Group) has announced the start of the first Phase III study, HELIX, with the investigational new drug, SYL1001 for the indication of dry eye syndrome. The Company has agreed with the U.S. Food and Drug Administration (FDA) on plans for the Phase III clinical program, which is designed to support the submission of a New Drug Application (NDA). The Company has received final, End-of-Phase II meeting minutes from the FDA. SYL1001 is an advance in the development of innovative compounds in different therapeutic fields, through the novel technology of gene silencing, based on RNA interference (RNAi). In the HELIX study, more than 30 centers from 5 European countries, including Spain, will participate with the objective of evaluating the effect of the ophthalmological solution SYL1001 for improvements in the signs and symptoms of dry eye syndrome in about 300 patients an area in which few therapeutic options exist today. SYL1001 is a compound based on RNAi being administered in the form of eye drops that block the synthesis of a receptor implicated in the pathology of dry eye syndrome.

In Spain it is estimated that 1 in 5 people that visit the ophthalmologist do it for this reason. Patients with dry-eye syndrome suffer the chronic loss of lubrication

and hydration on the ocular surface. More than 5 million people in Spain suffer from this condition –this is between 10% and 20% of the population-[1,2], mainly women over 40 years of age. The risk of developing this disorder increases in 35% every decade thereafter[2]. Around the world, 344 million people suffer from this syndrome.

Dry eye syndrome is characteristic in people that live in developed countries and is caused by pollution, air conditioning, the use of contact lenses, refractive eye surgery or the continued use of computers. The most common symptoms of this pathology are burning, a constant itching, eye fatigue, dryness, blurred vision, the sensation of having a foreign body or eye pain[4], are some of the symptoms

As explained by Dr Ana Isabel Jimenez, COO and Director of R&D at Sylentis, *"the RNA interference on which we are working, could improve the signs and symptoms for patients that suffer from this syndrome, given that this compound could reduce the inflammatory parameters of the eye´s surface, could improve the quality of the tear and could reduce the ocular pain associated with dry eye syndrome. We consider that our molecule SYL1001 could be a very effective and important therapeutic alternative for these patients".*

The Company is working on the investigation of new treatments for ophthalmological and inflammatory illnesses. *"Up to today, the line of work in which we have more rapidly advanced in is in ophthalmology, for the treatment of illnesses such as dry eye syndrome, glaucoma, ocular allergies and illnesses of the retina",* added Dr Jimenez.

What is RNA interference?

RNA interference is an innovative technology that looks for a reduction in the anomalous production of protein, silencing the RNA Messenger. The RNAi provides a great step forward, as it provides a new mechanism of action to confront numerous pathologies[5]. Nowadays there are two marketed products based on this technology and there are several drugs in different phases of clinical development.

Pathologies, such as dry eye syndrome, are produced by an alteration in certain proteins. Through this technology, the production of proteins that take part in various pathologies could be decreased or very specifically controlled[6].

"This is very promising as a new treatment for eye illnesses because it permits confronting the illness with a novel mechanism of action. Moreover, in all the clinical studies in which we have participated, the efficacy of SYL1001 has been demonstrated in patients, along with a high tolerance and safety to the ocular

surface", explained **Dr Jose Manuel Benítez del Castillo Sánchez**, professor of ophthalmology and section head at the Clinical Hospital San Carlos' ocular surface and inflammation unit in Madrid.

The compounds based on RNAi usually have a prolonged effect in comparison with traditional drugs. *"This drug is particularly interesting in chronic diseases and areas in which patient compliance is a challenge because it may show an increased duration of effect*", said Dr Benitez del Castillo.

Spain leads the HELIX study

With the purpose of progressing in this field, Sylentis has begun the multicenter, random, controlled and double blind Phase III clinical trial in more than 30 hospitals in Spain, Germany, Estonia, Portugal and Italy. The trial, in which 300 patients are going to be enrolled, and begins with one Spanish patient, will evaluate the efficacy of the product patented by Sylentis, SYL1001, in the treatment of the signs and symptoms of dry eye disease[7].

"Nowadays that, with the knowledge obtained, we have an opportunity to develop therapies based on RNAi", concluded Dr Benitez del Castillo. *"The challenge now is to transform this powerful technology into marketable products".*

For more information about the clinical trial:
https://clinicaltrials.gov/ct2/show/NCT03108664?term=SYL1001&rank=2

For more information (only available in Spanish)
Whats is RNA interference? https://youtu.be/T21N_dPM0_k
Dry eye syndrome: https://youtu.be/R-h_4_Yyq2g

About SYL1001

SYL1001 is a drug based on RNAi that is administered as preservative-free eye drops; it selectively inhibits production of the transient receptor potential cation channel (TRPV1). These receptors are ion channels that mediate the transmission of ocular pain. SYL1001 is a small synthetic double-stranded RNA oligonucleotide (siRNA) with a novel and highly selective mechanism of action. Non-clinical studies conducted by Sylentis with SYL1001 have demonstrated it has high ability to inhibit this specific target and block the perception of ocular pain in animals[3].

SYL1001 is a product undergoing development for the signs and symptoms related to with dry eye syndrome, and has potential to be developed for other pathologies that cause ocular pain (corneal lesions, refractive surgery, etc.)[6,8,9,10].

About RNA interference (RNAi)

RNA interference (RNAi) is a natural cellular process that regulates the expression of certain genes, providing a role in innate defense and development in animal and plants. This process is used to specifically silence genetic transcripts that encode protein-causing diseases. The

therapeutic application of targeted siRNAs is booming given the specificity of gene silencing for a particular protein in a given tissue and the lack of side effects. This new approach to drug discovery is a promising technology that is rapidly moving in the translational research space[11,12].

About dry eye syndrome

Dry eye syndrome is a multifactorial disease of the tear film and ocular surface that produces symptoms of ocular discomfort, eyesight disorders, and tear film instability with potential damage to the ocular surface. Dry eye syndrome is accompanied by such symptoms as ocular pain, itching, stinging, and irritation of the eye tissues. It is a characteristic disease of developed countries, associated with pollution, air conditioning, the use of contact lenses, refractive surgery and continued use of computers. Moreover, the amount and quality of tears decrease with age. Prevalence is between 10% and 20% among people aged 50 or over, and it is more frequent in women[1,2].

Dry eye can be treated with cyclosporin drops or autologous serum, but there is as yet no specific product for chronic treatment of the ocular pain related to dry eye syndrome; oral analgesics or anaesthetics are used in general. However, the main treatment consists of artificial tears, in the form of drops, gel or creams. Preservative-free eye drops have generally been found to offer the best long-term response.

About Sylentis

Sylentis, a company of PharmaMar (MSE:PHM), is a biotechnology company fully owned that develops innovative therapies harnessing the technology of post-transcriptional gene silencing or RNA interference (RNAi). Sylentis has developed an approach to efficiently design RNAi-based therapeutics that can be used to silence numerous disease-causing genes. We currently have a robust therapeutic program in ophthalmology with two candidates under development in Phase II studies for glaucoma (bamosiran)[13] and ocular pain (SYL1001)[11]. Sylentis is also developing new products for the treatment of several eye diseases such as ocular allergies and retina diseases. To know more about us, please visit us at www.sylentis.com.

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