National Securities Market Commission
Markets Directorate General
C/ Edison núm. 4
28006 Madrid

Colmenar Viejo (Madrid), January 31, 2019

Pursuant to Article 17 of Regulation (EU) nº 596/2014 on market abuse and Article 226 of the consolidated text of the Spanish Securities Market Act, approved by Royal Legislative Decree 4/2015, of 23 October, we hereby make the following **REGULATORY ANNOUNCEMENT**:

"Sylentis, a PharmaMar Group company, announces the results of the HELIX exploratory clinical trial; a Phase 3 efficacy and safety study with tivanisiran compared against artificial tears for the treatment of dry eye disease. Tivanisiran has shown an improvement ($p=0.035$) compared to the comparator in reducing central corneal staining in patients with moderate to severe dry eye disease after one month of treatment with tivanisiran. This endpoint was established as secondary in the clinical trial protocol. In addition, an improvement in ocular pain symptoms and sign of corneal staining has been demonstrated in patients, with respect to baseline ($p<0.0001$). A clinically relevant improvement in the primary endpoint of total corneal staining has also been demonstrated. Nevertheless, the primary endpoints of ocular pain and total corneal staining have not been met, because no statistically significant difference compared to the comparator in total population has been demonstrated. In the HELIX trial, several biomarkers of the disease were also determined. The results indicate a superiority of tivanisiran over the comparator with a 125% increase in mucin, which is related to an improvement in tear film, and a 13% decrease in the inflammation marker (HLA-DR). As for safety, no serious adverse effects associated with the use of tivanisiran have been reported. After 28 days of treatment, no differences between reported adverse effects for tivanisiran and artificial tears have been seen.

The complete results and additional analysis from the HELIX clinical trial will be presented at the Annual Congress of the Association for Research in Vision and Ophthalmology (ARVO), to be held in Vancouver in April 2019. In addition, these data will be presented to the FDA and other regulatory authorities during the second quarter of 2019 to define the future strategy.

Please find attached press release that will be distribute to the media today".

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Sylentis announces results of Phase 3 HELIX trial with tivanisiran for the treatment of Dry Eye Disease

- **The HELIX trial has shown improvement (p=0.035) in the reduction of central corneal staining**
- **Data will be presented to the FDA and other regulatory authorities during the second quarter of 2019 to define the regulatory strategy**
- **The results of the HELIX trial will be presented at the Annual Congress of the Association for Research in Vision and Ophthalmology, ARVO 2019**

Madrid, 31 of January, 2019.- Sylentis, a PharmaMar Group company (MSE:PHM), has announced today the results of the HELIX [i]exploratory clinical trial; a Phase 3 efficacy and safety study with tivanisiran compared against artificial tears for the treatment of dry eye disease[ii].

Tivanisiran has shown an improvement (p=0.035) compared to the comparator in reducing central corneal staining in patients with moderate to severe dry eye disease after one month of treatment with tivanisiran. This endpoint was established as secondary in the clinical trial protocol.

In addition, an improvement in ocular pain symptoms and sign of corneal staining has been demonstrated in patients, with respect to baseline (p<0.0001).

A clinically relevant improvement in the primary endpoint of total corneal staining has also been demonstrated. Nevertheless, the primary endpoints of ocular pain and total corneal staining have not been met, because no statistically significant difference compared to the comparator in total population has been demonstrated.

In the HELIX trial, several biomarkers of the disease were also determined. The results indicate a superiority of tivanisiran over the comparator with a 125% increase in mucin, which is related to an improvement in tear film, and a 13% decrease in the inflammation marker (HLA-DR).

According to **Jesús Merayo, PhD, MD,** of the Fernández-Vega University Institute of the University of Oviedo: *"the importance of finding a treatment for a specific area of the eye, severely damaged, is very relevant in the care of these patients, as they suffer more aggressively the symptoms of the disease than those who have less serious damage but more spread over the ocular surface of the eye."*

As for safety, no serious adverse effects associated with the use of tivanisiran have been reported. After 28 days of treatment, no differences between reported adverse effects for tivanisiran and artificial tears have been seen.

Prof. Elisabeth Messmer, MD, of the Augenklinik der Universität München commented: *"The treatment of patients with tivanisiran in the German study sites has shown a statistically significant improvement (p=0.043) of ocular pain and demonstrated an excellent safety and tolerability profile."*

In the words of **Prof. José Manuel Benítez del Castillo, MD**, from the Hospital San Carlos in Madrid, and principal investigator of this study: "*The need to find a solution to this disease is very high, in Spain alone, 1 out of 5 visits to the consultants are motivated by this pathology. Symptoms manifested by patients include pain, dry eyes, stinging, burning, a sensation of having a foreign body in the eye and could also include episodes of blurred vision. Tivanisiran could be a therapeutic alternative for these patients as it is a drug with a new mechanism of action."*

In the words of **Ana Isabel Jiménez, PhD**, COO and R&D Director of Sylentis: *"HELIX is part of a Phase 3 clinical program in both Europe and the United States and we look forward to present the data from this study to the FDA and other regulatory authorities. Improving one area of the corneal staining has been recognized by agencies for the approval of other products."*

For this study, 330 patients[iii] with dry eye disease were recruited at 39 centers in 6 European countries: Spain, Germany, Estonia, Portugal, Slovakia, and Italy. In HELIX, treatment with tivanisiran was compared to artificial tears after its administration once a day during 4 weeks in patients with moderate to severe dry eye.

According to data from Global Data[iv], in the 8 main markets (USA, Spain, Italy, France, Germany, Great Britain, China and Japan), in 2016 this disease affected more than 267 million people and is estimated to increase to more than 286 million in 2026. The dry eye market in these countries in 2016 was 2.2 billion US dollars. Global Data estimates that by 2026 the market could reach 5.6 billion US dollars. This increase is explained by the appearance of new drugs and the increase in the global prevalence of the disease.

The complete results and additional analysis from the HELIX clinical trial will be presented at the Annual Congress of the Association for Research in Vision and Ophthalmology (ARVO), to be held in Vancouver in April 2019. In addition, these data will be presented to the FDA and other regulatory authorities during the second quarter of 2019 to define the future strategy.

About dry eye disease

Dry eye disease is [v]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.

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.

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

Explanatory videos:

What is RNA interference?: https://youtu.be/T21N_dPM0_k

Dry Eye Disease: https://youtu.be/R-h_4_Yyq2g

About PharmaMar

Headquartered in Madrid, PharmaMar is a biopharmaceutical company, focused on oncology and committed to research and development which takes its inspiration from the sea to discover molecules with antitumor activity. It is a company that seeks innovative products to provide healthcare professionals with new tools to treat cancer. Its commitment to patients and to research has made it one of the world leaders in the discovery of antitumor drugs of marine origin.
PharmaMar has a pipeline of drug candidates and a robust R&D oncology program. It develops and commercializes Yondelis® in Europe and has other clinical-stage programs under development for several types of solid cancers: lurbinectedin (PM1183), PM184 and PM14. With subsidiaries in Germany, Italy, France, Switzerland, Belgium, Austria and the United States. PharmaMar wholly owns other companies: GENOMICA, a molecular diagnostics company; Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi); and a chemical enterprise, Zelnova Zeltia. To learn more about PharmaMar, please visit us at: www.pharmamar.com

About Sylentis

Sylentis 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 and III studies for glaucoma (bamosiran) and ocular pain (SYL1001), respectively. 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.

About tivanisiran (SYL1001)

Tivanisiran 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. Tivanisiran 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.

Tivanisiran is a product under development for the treatment of signs and symptoms related to dry eye syndrome and has the potential to be developed for other pathologies that cause ocular pain (corneal lesions, refractive surgery, etc.).

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 animals 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.

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[i] https://clinicaltrials.gov/ct2/show/NCT03108664?term=helix&rank=5

[ii] The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (DEWS) (2007). Ocul Surf, 2007. 5(2): p. 75-92

[iii] https://www.sylentis.com/index.php/es/noticias/noticias-generales/142-sylentis-grupo-pharmamar-anuncia-el-fin-del-reclutamiento-de-pacientes-para-su-ensayo-helix#_edn5

[iv] https://www.globaldata.com/store/report/gdhcer186-18--dry-eye-syndrome-epidemiology-forecast-to-2026/

[v] https://www.market-scope.com/pages/reports/61/2018-dry-eye-products-report-a-global-market-analysis-for-2017-to-2023-november-2018