Sylentis announces top-line results from Phase II study SYLTAG for RNAi drug bamosiran (SYL040012) in Glaucoma

- *All bamosiran doses similarly reduced the intraocular pressure (IOP). In patients with a baseline IOP greater than or equal to 25 mm Hg, 1.125% bamosiran showed more efficacy*
- *The trial did not meet the secondary objective of demonstrating non-inferiority compared to timolol in the total patient population; however, bamosiran at dose 1.125% ((450 micrograms) showed non-inferiority in patients with baseline IOP greater than or equal to 25 mm Hg*
- *Bamosiran was very well-tolerated and treatment-related adverse events were more frequent in patients treated with timolol*

Madrid, October 2nd, 2015: Sylentis, a pharmaceutical company of Grupo Zeltia (MSE: ZEL), pioneer in research and development of new RNA interference (RNAi)-based therapies announced today top-line results of a dose-finding Phase II study, SYLTAG, for the novel RNAi therapeutic bamosiran in patients with open-angle glaucoma or ocular hypertension. The SYLTAG study, which includes 184 patients with a baseline IOP greater than or equal to 23 mm Hg, evaluates the efficacy and safety of four doses 0,375% (150 micrograms); 0,75% (300 micrograms); 1,125% (450 micrograms) y 1,5% (600 micrograms) given once a day for 28 days. The comparator group received timolol (0.5%), given twice a day.

After 28 days of treatment, the four groups treated with bamosiran (0.375%, 0.75%, 1.125% y 1.5%) showed a similar reduction in the IOP. Bamosiran did not meet the secondary objective of demonstrating non-inferiority compared to timolol for any of the doses in the total patient population; however, at dose 1.125% (450 micrograms) it showed non-inferiority in patients with baseline IOP greater than or equal to 25 mm Hg and it was non-inferior compared to timolol in this patient group. The results showed excellent tolerability of bamosiran in all the treated groups with a very low hyperhemia (less than 8%).

"All the bamosiran doses investigated in this study have shown a similar reduction in IOP, so that the identification of a dose in the whole study population could not be achieved. This is a frequent outcome of dose-finding studies with RNAi-based

drugs, where identifying the most effective dose is difficult," pointed out Ana Isabel Jiménez, Ph.D., Executive Operations Director, Sylentis, who added that "the results we have obtained in this study along with the good ocular tolerability of bamosiran given once a day as a preservative-free eye drop, will allow us to continue working on this approach to develop a novel and effective product for the treatment of glaucoma or ocular hypertension."

About the SYLTAG study (NCT02250612):

- SYLTAG is a multicenter, international, dose-finding Phase II, double masked, randomized and controlled study that investigated the efficacy and safety of bamosiran by measuring the IOP during the day after 28 days of treatment (one drop per day in each eye) in patients with open-angle glaucoma or ocular hypertension compared to the active control, timolol given twice a day.
- The study has enrolled 180 patients from 21 centers across Europe and the US, which were distributed in 5 groups of about 36 patients each to receive four different doses of bamosiran (0.375%, 0.75%, 1.125% and 1.5%) or timolol (0.5%), respectively.
- The primary efficacy endpoint of the study was to determine the most effective drug dose to reduce IOP during the day, at day 14 and 28. The secondary endpoints included comparison of efficacy against timolol and quality of life measurements (using the Glaucoma Quality of Life questionnaire (GQL-15).
- The trial also studied the safety profile and tolerability of the treatments by means of measuring ocular discomfort, clinical ophthalmological values, systemic tolerability and adverse events.

About bamosiran (SYL040012)

The investigational drug bamosiran (SYL040012) is an RNAi-based therapy administered as eye drops that selectively blocks the production of the β2-adrenergic receptors, which are directly involved in the IOP[i] through the regulation of the production and drainage of the aqueous humour. Bamosiran is a small interfering double-stranded RNA (siRNA) that specifically functions through a novel and highly specific mechanism. In preclinical studies, bamosiran has shown to be superior compared to glaucoma drugs dorzolamide and Xalatan (latanoprost) at preventing an increase in IOP in a relevant disease model[ii].

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 in biotechnology[iii] to specifically silence genetic transcripts that encode protein-causing diseases. The therapeutic application of targeted siRNAs[iv] is booming[v] 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

About open-angle glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide, characterized by a progressive loss of sight owing to optic nerve damage, which is often associated with intraocular pressure[vi]. In 2020, it is estimated more than 80 million people worldwide will have glaucoma and at least 6–8 million individuals will become bilaterally blind[vii]. Primary open-angle glaucoma (POAG) is the most prevalent form of this disease, accounting for approximately two-thirds of all diagnosed cases of glaucoma. Although risk factors include a history of intraocular pressure and age, many patients with POAG have a genetic basis[viii]. Reducing the intraocular pressure in the eye to prevent progressive loss of vision remains the mainstay of glaucoma treatment; however, more specific and long-lasting approaches are needed to improve patient management and increase therapeutic efficacy. Novel glaucoma treatments using RNAi therapeutics may help overcome the challenges faced by patients regarding treatment compliance.

About Sylentis

Sylentis, a company of Grupo Zeltia (Madrid Stock Exchange: ZEL) is a biotechnology company fully owned that develops innovative therapies harnessing the technology of post-transcriptional gene silencing or RNA interference (RNAi). The Company uses its own innovative RNAi platform called SIRFINDER®,for the development of new therapies. The technology allows for the optimized search of siRNAs that specifically target a gene causing of particular disease. Sylentis has developed an approach to efficiently turn these siRNA fragments into 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) and ocular pain (SYL1001). There are also other RNAi-based investigational drugs at the discovery and preclinical stage for ocular diseases, inflammatory diseases and disorders of the central nervous system (CNS). To know more about us, please visit us at www-sylentis.com.

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[i] http://iovs.arvojournals.org/article.aspx?articleid=2177563
[ii] http://www.nature.com/mt/journal/v22/n1/full/mt2013216a.html
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