News Release

Bayer Yakuhin, Ltd.
Santen Pharmaceutical Co., Ltd.

Intravitreal VEGF Inhibitor “EYLEA” Obtains Additional Indication of Macular Edema Secondary to Central Retinal Vein Occlusion (CRVO)

Osaka, November 22, 2013 – Bayer Yakuhin, Ltd. (Osaka, hereinafter Bayer Yakuhin) and Santen Pharmaceutical Co., Ltd. (Osaka, hereinafter Santen) announced today that Bayer Yakuhin has received approval for the additional indication of macular edema secondary to central retinal vein occlusion (CRVO) for the intravitreal VEGF* inhibitor EYLEA® solution for intravitreal injection 40 mg/mL and EYLEA® intravitreal injection KIT 40mg/mL (aflibercept [genetical recombination], hereinafter EYLEA). The marketing of EYLEA started in November 2012 as treatment for “age-related macular degeneration with subfoveal choroidal neovascularization (wet AMD)”, and “macular edema secondary to CRVO” is the second indication the drug obtained this time.

* VEGF = vascular endothelial growth factor

CRVO is caused by obstruction of the central retinal vein, which increases the VEGF concentration in the eye. VEGF is thought to contribute to the increased vascular permeability and abnormal angiogenesis in CRVO, which may cause leakage of blood and fluid, resulting in macular edema. EYLEA has a high affinity for VEGF and inhibits the binding of VEGF to the VEGF receptor, thereby inhibiting the activation of the signaling pathway. In clinical trials, reduction of macular edema secondary to CRVO and improved visual acuity were observed.

The approval is based on data from the Phase III trials COPERNICUS and GALILEO. In both studies, the primary efficacy endpoint was the proportion of patients who gained at least 15 letters – as measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart – of best corrected visual acuity at 24 weeks compared to baseline on the ETDRS visual acuity charts. In the GALILEO trial, in which Japan participated, 60.2% of patients who received 6 monthly doses

of EYLEA gained at least 15 letters in visual acuity with a mean 18 letters. Though the number of patients investigated was limited, a similar tendency was observed in the ischemic patients whose VEGF concentration is known to be higher and who have a poorer prognosis in terms of visual acuity as well as a higher risk of progression to neovascular glaucoma in comparison with non-ischemic patients.

Dr. Yuichiro Ogura, Professor of Ophthalmology and Visual Science at Nagoya City University Graduate School of Medical Sciences and Medical School and a member of the steering committee of the GALILEO trial said, "Macular edema secondary to CRVO is a serious clinical condition that often progresses rapidly and decreases the central vision of patients. In the GALILEO trial, the proportion of patients who gained at least 15 letters in visual acuity tended to be higher in the patients with shorter duration of disease, indicating the importance treating the disease early. The introduction of EYLEA, which has demonstrated a high therapeutic effect in the treatment of wet AMD, as a new treatment option for patients with macular edema secondary to CRVO is expected to be great news for those patients."

Based on the co-promotion agreement for EYLEA in Japan concluded on May 7, 2012, Santen distributes the product. Bayer Yakuhin and Santen both provide EYLEA drug information to healthcare professionals.

<Overview of EYLEA® solution for intravitreal (IVT) injection (inj.) 40 mg/mL>
(The addition is indicated in **Bold** letters.)

Product name	EYLEA® solution for IVT inj. 40 mg/mL
Non-proprietary name	Aflibercept (genetical recombination)
Indication	Age-related macular degeneration with subfoveal choroidal neovascularization **Macular edema secondary to central retinal vein occlusion**
Dosage & Administration	Age-related macular degeneration with subfoveal choroidal neovascularization 2 mg of Aflibercept (Genetical Recombination) (0.05 mL) is administered by intravitreal injection once every month for three times consecutively (initiation phase). In the following maintenance phase, usually, it is administered by intravitreal injection once every 2 months. The dosing interval may be adjusted according to the patient's symptoms and conditions

	<u>Macular edema secondary to central retinal vein occlusion</u> **The injection dose is 2 mg Aflibercept (Genetical Recombination) [equivalent to 0.05mL Eylea solution] per injection, administered by intravitreal injection. The dosing interval should be one month or longer.**
Package	EYLEA® solution for IVT inj. 40 mg/mL One vial (with one needle to collect solution attached with a dedicated filter)
Date of marketing authorization	September 28, 2012
Date of listing in the NHI reimbursement price	November 22, 2012
NHI drug price	(2 mg 0.05 mL 1 vial) 159,289 yen
Date of launch	November 27, 2012
Date of additional approval	**<u>Macular edema secondary to central retinal vein occlusion</u>** **November 22, 2013**
Marketing authrorization held by	Bayer Yakuhin, Ltd.
Distributed by	Santen Pharmaceutical Co., Ltd.

About the Phase III CRVO Program

Patients in the COPERNICUS (**CO**ntrolled **P**hase III **E**valuation of **R**epeated i**N**travitreal administration of EYLEA **I**n **C**entral retinal vein occlusion: **U**tility and **S**afety) and the GALILEO (**G**eneral **A**ssessment **L**imiting **I**nfi**L**tration of **E**xudates in central retinal vein **O**cclusion with EYLEA) studies received six monthly injections of either EYLEA at a dose of 2 mg or sham injections.

Patients in both trials were randomized in a 3:2 ratio with 114 patients receiving EYLEA and 74 randomized to the control arm in COPERNICUS and 104 patients randomized and treated with EYLEA and 68 randomized and treated in the control arm in GALILEO. At the end of the initial six months, all patients randomized to EYLEA were dosed on the basis of the retreatment criteria for another six months. In the COPERNICUS trial, patients randomized to sham injections in the first six months were eligible to cross over to EYLEA dosing on as needed basis in the second six months. Anytime of the studies, all patients were eligible for rescue laser treatment for their neovascularization in the eye. Visual acuity was measured as a score based on the total number

of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, a standard chart used in research to measure visual acuity.

About Central Retinal Vein Occlusion (CRVO)

Over 66,000 people in major European countries and more than 100,000 people in the United States are estimated to suffer from CRVO. CRVO is caused by obstruction of the central retinal vein that leads to an accumulation of deoxygenated blood and fluid in the retina. Macular edema secondary to CRVO causes retinal damage and loss of vision. Release of vascular endothelial growth factor (VEGF) contributes to increased vascular permeability in the eye and macular edema. It has been shown that anti-VEGF treatment may help decrease vascular permeability and edema in the retina in patients with CRVO.

The research conducted in 1998 in residents in Hisayama, Japan, showed that 0.2% of residents over the age of 40 had CRVO*. Extrapolating from this study, the number of CRVO patients in Japan is estimated to be approximately 140,000.

*References:

Investigative Ophthalmology & Visual Science, June 2010, Vol. 51, No. 6

“Prevalence and Systemic Risk Factors for Retinal Vein Occlusion in a General Japanese Population: The Hisayama Study” Miho Yasuda, Yutaka Kiyohara, Satoshi Arakawa, Yasuaki Hata, Koji Yonemoto, Yasufumi Doi, Mitsuo Iida, and Tatsuro Ishibashi

About EYLEA® (aflibercept solution for injection)

EYLEA is a novel intravitreal VEGF inhibitor co-developed by Bayer HealthCare in Germany and Regeneron Pharmaceuticals, Inc., in the United States for the treatment of retinal disorders. It is a recombinant fusion protein consisting of portions of the extracellular domains of human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1 and formulated as an iso-osmotic solution for intravitreal administration. EYLEA acts as a soluble decoy receptor for various members of the VEGF family including VEGF-A and placental growth factor (PlGF) and binds with them with high affinity and thus can inhibit the binding and activation of these cognate VEGF receptors. EYLEA thus inhibits abnormal vascularization and leakage.

EYLEA has been approved for the indication of wet AMD in more than 50 countries including the United States and in Europe and for the indication of macular edema secondary to CRVO in more than 30 countries including the United States and in Europe.

About Santen
Founded in 1890, Santen is a global company headquartered in Osaka, Japan. Santen researches, develops and markets ophthalmic products for physicians worldwide. Among prescription ophthalmic pharmaceuticals, Santen holds the top share within the Japanese market and is one of the leading ophthalmic companies worldwide. For more information, visit
http://www.santen.co.jp/

About Bayer Yakuhin
Bayer Yakuhin Ltd., headquartered in Osaka, is a healthcare company which combines business activities of Pharmaceuticals, Radiology & Interventional and Animal Health (companion and food animal products). Pharmaceuticals business is focused on the following areas: Cardiovascular & Neurology, Oncology & Hematology, Women's Health & Dermatology and Ophthalmology.Bayer Yakuhin aims to be one of leading pharmaceutical companies, which responds to Japanese patients' unmet medical needs, with the spirit of Bayer's corporate slogan "Science For A Better Life".
Bayer Yakuhin homepage: http://www.bayer.co.jp/byl

About Bayer HealthCare
The Bayer Group is a global enterprise with core competencies in the fields of health care, nutrition and high-tech materials. Bayer HealthCare, a subgroup of Bayer AG with annual sales of EUR 17.2 billion (2011), is one of the world's leading, innovative companies in the healthcare and medical products industry and is based in Leverkusen, Germany. The company combines the global activities of the Animal Health, Consumer Care, Medical Care and Pharmaceuticals divisions. Bayer HealthCare's aim is to discover, develop, manufacture and market products that will improve human and animal health worldwide. Bayer HealthCare has a global workforce of 54,900 employees
(Dec 31, 2011) and is represented in more than 100 countries. Find more information at www.bayerhealthcare.com.

About Regeneron Pharmaceuticals
Regeneron is a leading science-based biopharmaceutical company based in Tarrytown, New York that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron markets medicines for eye diseases, colorectal cancer, and a rare inflammatory condition and has product candidates in development in other areas of high unmet medical need, including hypercholesterolemia, oncology, rheumatoid arthritis, asthma, and atopic dermatitis. For additional information about the company, please visit www.regeneron.com.

Bayer Forward-Looking Statements
This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Santen Forward-looking Statements
Information provided in this press release contains forward-looking statements. The achievement of these forecasts is subject to risk and uncertainty from various sources. Therefore, please note that the actual results may differ significantly from the forecasts. Business performance and financial conditions are subject to the effects of changes in regulations made by the governments of Japan and other nations concerning medical insurance, drug pricing and other systems, and to fluctuations in market variables such as interest rates and foreign exchange rates.