FOR IMMEDIATE RELEASE

Peretinoin reduces recurrence risk of hepatocellular carcinoma
after curative therapy

The results of a Phase II/III trial presented
at the International Liver Cancer Association Fourth Annual Conference

TOKYO, Japan, September 13, 2010 --- Kowa Company, Ltd. (Headquaters: Nagoya, Japan, President & CEO: Yoshihiro Miwa, “Kowa”) announced today that the results of a Phase II/III trial showed that high dose peretinoin (NIK-333) given daily for up to 96 weeks reduced the recurrence of hepatocellular carcinoma (HCC) after surgical resection or ablation in hepatitis C virus (HCV) positive patients when compared to placebo. The study was presented at the Plenary General Session of International Liver Cancer Association Fourth Annual Conference (ILCA2010) on September 11, 2010 (Presentation number O-014). Kowa plans to submit peretinoin to regulatory authorities in Japan for marketing authorization.

About the phase II/III trial

The study was the multicenter, double-blind, parallel, randomized controlled trial of 401 HCV positive HCC patients who underwent curative therapy (surgical resection or transcutaneous radiofrequency ablation) at 41 sites in Japan. Patients were randomized to one of three groups: 600 mg/day peretinoin, 300 mg/day peretinoin, or placebo. The primary endpoint was recurrence-free survival (RFS).

Three-year RFS rate was 43.7% for peretinoin 600 mg/day, 24.9% for pretinoin 300 mg/day, and 29.3% for placebo. RFS rate for the peretinoin 600 mg/day exceeded placebo. The dose-response analysis showed the effect started to increase at the 600 mg/day dose.
The risk of HCC recurrence or death throughout the study period with peretinoin 600 mg/day was reduced approximately 27% compared to placebo. When focused on recurrence and survival after two years of randomization, peretinoin 600 mg/day group showed a 73% reduction in the risk of HCC recurrence and death compared to placebo [HR=0.27 (95% CI: 0.07-0.96)].

Adverse events considered related to peretinoin were mainly albumin urine present, hypertension, and headache, although all of these were within tolerable levels.

Based on the results of this trial, Kowa is moving forward to obtain regulatory approval to produce and market peretinoin.

Expert comments on this trial

Dr. Kiwamu Okita (superintendent at Shimonoseki Kohsei Hospital, and professor emeritus at Yamaguchi University), the chairperson of the coordinating committee for the trial, presented the trial findings at the conference. He said, “It was extremely meaningful to present the results of the peretinoin Phase II/III trial, which was conducted in Japan where liver cancer is prevalent, to the world’s liver cancer experts at ILCA2010.” Recurrent HCC are generally divided into two types: Within two years of curative therapy, metastases may occur within the liver. After two years, recurrences include more de novo (multicentric) carcinogenesis, which are new HCC that occur separately from the primary lesion. Dr. Okita also said, “In our trial, we observed a significantly reduced risk of recurrence and death after two years of randomization with peretinoin 600 mg/day, suggesting that the peretinoin inhibited de novo carcinogenesis. This indicates that peretinoin not only inhibits HCC recurrence but also possibly inhibits de novo carcinogenesis of HCC from liver cirrhosis etc., which is a very exciting result. Since there currently is no established treatment to inhibit the recurrence of HCC, we think peretinoin will become a great hope for those patients who are at risk for HCC recurrence. On behalf of the investigators, I would like to thank all of the patients who participated in the trial.”

Professor Yasuo Ohashi (Department of Biostatistics, School of Public Health, the University of Tokyo), the statistician for the trial, said, “This study reproduced the results of the clinical trial published in New England Journal of Medicine in 1996¹, and I think the reliability of the result is high. The low dose group was designed to reflect the suggestions from Japanese regulatory authority. We analyzed the result with the consideration for false-positive error (multiplicity) due to the comparison between

multiple groups, and the high-dose group demonstrated statistical difference. We expect the validation results on the primary preventive effects for HCC from liver cirrhosis in HCV positive patients.”

**About Peretinoin**

Peretinoin is the oral acyclic retinoid with vitamin A-like structure, and its main targeting molecule is the retinoid nuclear receptor.

**About Liver Cancer and HCC**

Liver cancer is the sixth most common cancer in the world, and more than six hundred thousand patients are newly diagnosed every year. In Japan, liver cancer is the third leading cause of death from cancer. The newly diagnosed patients are about 40,000, and about 35,000 patients die every year. Primary liver cancer is classified into HCC and cholangiocellular carcinoma, and about 94% is HCC. HCC are mainly caused by the infections of hepatitis B virus or HCV, and in Japan about 67% of HCC are caused by the HCV. HCV positive HCC is known to have a high recurrence rate after curative resection, and the recurrence rates are 24%, 76%, 92% within 1, 3, 5 years, respectively.

**About Kowa**

Kowa Company, Ltd. “Kowa” is a privately held multinational company headquartered in Nagoya, Japan. Established in 1894, Kowa is actively engaged in various manufacturing and commercial activities in the fields of pharmaceutical, life science, information technology, textiles, machinery and various consumer products. In its ethical pharmaceutical business section, the company offers the hypercholesterolemia drug Livalo (pitavastatin), among other products, to the Japanese, US and other markets worldwide, and is in the process of global expansion of Livalo. Other drugs in the pipeline for global development include the DPP-IV inhibitor SK-0403, the antiplatelet agent K-134, and the ACAT-1 inhibitor K-604.

Kowa’s US subsidiaries include Kowa Research Institute, Inc., for the research and development of pharmaceutical products, and Kowa Pharmaceuticals America, Inc., which markets their pharmaceutical products. European subsidiaries include Kowa Research Europe, Ltd., for the research and development of pharmaceutical products, and Kowa Pharmaceutical Europe Co. Ltd., which markets their pharmaceutical products. Kowa is organizing its global network from Japan-Europe-US trilateral bases.
Contacts:
Kowa Company, Ltd.
Public Relations Department.2, +81·3·3279·7392 (Japanese inquiries only)
info-peretinoin@kowa.co.jp (Japanese and English inquiries)
Fax: +81·3·3279·7250