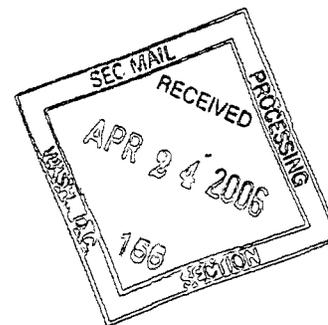


# Investor Update



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## SUPPL

Basel, 21 April 2006

### Chugai files innovative cancer medicine Avastin for fast approval in Japan

Faster approval process aims to make Avastin available to patients as soon as possible

Roche today announced that Chugai Pharmaceutical Co., Ltd. has submitted a New Drug Application (NDA) with the Japanese Ministry of Health, Labour and Welfare (MHLW) for the use of Avastin (bevacizumab) in patients with advanced or recurrent colorectal cancer.

Avastin has been filed under a new 'fast regulatory' scheme that has been established by the Investigational Committee for Usage of Unapproved Drugs (a body established by the MHLW). The system has been set up to enable faster regulatory approval of certain medicines with proven efficacy which are approved in the US and/or Europe but that are not yet available in Japan. Avastin is the first medicine to be filed under this scheme for an indication as significant as colorectal cancer.

"Today's submission comes just after Tarceva's initial filing in advanced or recurrent non-small cell lung cancer and represents a further significant milestone for oncologists and patients in Japan. The Japanese authorities have recognized that Avastin is a breakthrough drug which addresses an unmet medical need for patients suffering with advanced colorectal cancer" said Ed Holdener, Head of Roche's Global Pharma Development. "We will continue to work closely with the Investigational Committee to ensure that this groundbreaking treatment becomes available to colorectal cancer patients as quickly as possible."

The Avastin filing is based on local Phase I data, along with supporting US and European Phase II and pivotal Phase III data<sup>1,2,3</sup>. At the same time, Chugai is conducting a Safety Confirmation Study in order to provide data on Japanese patients during the review procedure.

In Japan, the incidence of colorectal cancer has increased significantly in the last 50 years and research interest in this cancer has grown rapidly among Japanese clinicians and pathologists<sup>4</sup>. In

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2005, colorectal cancer was one of the most commonly reported cancer with an estimated incidence of 115,000 people in Japan<sup>5</sup>.

Avastin is the first and only anti-angiogenic agent to have demonstrated improved overall and/or progression-free survival in the three major types of cancer leading to death: colorectal cancer, non-small cell lung cancer and breast cancer. In Europe, Avastin was approved early 2005 for first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with the chemotherapy regimens of intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan. Avastin received approval by the US Food and Drug Administration (FDA) in February 2004. In addition, filing occurred in the US on April 10, 2006, for use of Avastin in previously untreated advanced non-squamous, non-small cell lung cancer.

#### Data used for filing

The local Phase I study was conducted in 18 patients with metastatic carcinoma of the colon or rectum to investigate the pharmacokinetics and safety of Avastin in Japanese patients when used in combination with 5-fluorouracil/folinic acid.

A Phase II study (AVF2192) demonstrated that Avastin, when added to a combination of 5-fluorouracil/folinic acid, prolonged the time until disease progression or death by an extra four months compared to chemotherapy alone (a 67% increase in progression-free survival).

In the Phase III pivotal trial (AVF2107), patients with previously untreated metastatic carcinoma of the colon or rectum (mCRC) who received Avastin in combination with intravenous 5-fluorouracil/folinic acid/irinotecan lived significantly longer than patients receiving the same chemotherapy without Avastin- on average by nearly five months (20.3 months versus 15.6 months). Also, the addition of Avastin increased the amount of time that patients were without disease progression, on average four months, compared to patients receiving chemotherapy alone (10.6 months versus 6.2 months).

In a second Phase III study (E3200), conducted by the Eastern Cooperative Oncology Group (ECOG), Avastin was also shown to significantly improve survival when added to another widely prescribed chemotherapy regimen (oxaliplatin/5-fluorouracil/leucovorin). With Avastin, patients who had failed previous irinotecan or 5-FU containing chemotherapy for their disease, lived nearly two months longer, on average, compared to those who received chemotherapy alone (12.9 months vs. 10.8 months).

### **About Avastin**

Avastin is the first treatment that inhibits angiogenesis, which is defined as the growth of a network of blood vessels that supply nutrients and oxygen to cancerous tissues. Avastin targets a naturally occurring protein called VEGF (Vascular Endothelial Growth Factor), a key mediator of angiogenesis, thus choking off the blood supply that is essential for the growth of the tumour and its spread throughout the body (metastasis).

Roche and Genentech are pursuing a comprehensive clinical programme investigating the use of Avastin in various tumour types (including colorectal, breast, lung, pancreatic, ovarian cancer, renal cell carcinoma and others) and different settings (advanced, adjuvant and neoadjuvant) The total development program is expected to include over 25'000 patients worldwide.

### **About Roche**

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. As a supplier of innovative products and services for the early detection, prevention, diagnosis and treatment of disease, the Group contributes on a broad range of fronts to improving people's health and quality of life. Roche is a world leader in diagnostics, the leading supplier of medicines for cancer and transplantation and a market leader in virology. In 2005 sales by the Pharmaceuticals Division totalled 27.3 billion Swiss francs, and the Diagnostics Division posted sales of 8.2 billion Swiss francs. Roche employs roughly 70,000 people in 150 countries and has R&D agreements and strategic alliances with numerous partners, including majority ownership interests in Genentech and Chugai. Additional information about the Roche Group is available on the Internet ([www.roche.com](http://www.roche.com)).

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### **Further information:**

About Chugai: [www.chugai-pharm.co.jp](http://www.chugai-pharm.co.jp)

About cancer: [www.health-kiosk.ch](http://www.health-kiosk.ch)

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# Media Release



Basel, 20 April 2006

## **Roche submits application to FDA to market CERA for the treatment of renal anaemia**

**Submission Based On Full Phase III Program Including Four Maintenance and Two Correction Trials with Dialysis and Non-Dialysis Chronic Kidney Disease Patients**

Roche a world leader in biotechnology today announced it has submitted a Biological License Application (BLA) to the U.S. Food and Drug Administration (FDA) to market CERA for the treatment of anaemia associated with chronic kidney disease (CKD) including patients on dialysis and not on dialysis.

CERA, an innovative investigational anti-anaemia agent, is the first and only continuous erythropoietin receptor activator. This means that the activity of CERA at the receptor sites involved in stimulating red blood cell production is different from that observed with traditional epoetins. This distinct molecular interaction is believed to have a role in providing targeted, stable and sustained control of anaemia. CERA is the only anti-anaemia treatment to have been studied with long dosing intervals, up to once every four weeks, for its initial filing.

"The US filing for CERA is the next step along the path to making this important therapy available," said Eduard Holdener, Global Head Pharmaceutical Development, Roche. "One of the primary endpoints we investigated was haemoglobin response and levels over time as we know that physicians find it challenging to keep patients' haemoglobin in a recommended target range despite their best efforts."<sup>iii</sup> We believe CERA's clinical profile is able to address this issue."

The BLA submission is based on the largest clinical programme ever undertaken for a drug treating renal anaemia. It included six Phase III trials conducted in 29 countries and involved 2,400 patients. The studies investigated the efficacy of both intravenous and subcutaneous CERA administered up to once every four weeks.

Last December the four maintenance studies from Phase III were successfully completed and very recently Roche completed the last two studies to treat (correct) anaemia. The studies met their primary endpoints and showed that both intravenous and subcutaneous CERA, when given at extended dosing intervals, were effective in correcting anaemia according to best practice guidelines, and in maintaining Hb levels following correction. Overall, the safety profile was characteristic of the population under study.

#### About Anaemia

There are approximately 530'000 US CKD patients not on dialysis and 324'000 US patients on dialysis who suffer from anaemia. Anaemia refers to patients experiencing a lower than normal level of red blood cells or the haemoglobin in them. Haemoglobin enables red blood cells to carry oxygen throughout the body and therefore, when the body is starved of the oxygen it requires, extreme fatigue sets in along with dizziness, pale skin and other symptoms. Other serious clinical complications will appear as the body – in particular, the heart - works harder to compensate for the lack of oxygen.

Normally, when the body senses a decrease in the oxygen available to the body, more erythropoietin (a protein produced by the kidneys) is created. This protein stimulates the production of oxygen-carrying red blood cells in the bone marrow which raises the red blood cell count. When this natural mechanism is hindered (as in patients with kidney disease), it is necessary to stimulate the receptors to produce red blood cells which is what CERA is designed to do. The goal of treatment is to increase haemoglobin back to a desirable level and maintain that level over time.

#### About Roche

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**Notes to the Editor:**

The Phase III study program consisted of two correction and four maintenance studies. Correction is a term that is used to describe the initial phase of treatment for renal patients who have been diagnosed with anemia but who have not previously received treatment with an agent to increase their Hb level. Maintenance refers to keeping Hb levels in a defined range over time in patients whose Hb levels have been corrected.

The first correction study in a 182 dialysis patients examined the Hb response rate to intravenous administration of CERA in patients who were treated once every two weeks during the first 24 weeks. Thereafter, the patients were maintained on the same schedule or provided with a once every-four-week dosing regimen for the remaining 28 weeks. These CERA patients were compared to patients who were treated with epoetin at the approved three-times-weekly schedule.

The second correction study in 324 chronic kidney disease patients not on dialysis, evaluated the Hb response rate achieved during the first 28 weeks, and the change in Hb concentration between the baseline and the 10-week evaluation period. Patients' anaemia was corrected with subcutaneous (SC) CERA given once every two weeks. Then during the 24-week maintenance phase two dosing intervals of C.E.R.A were provided: once every two weeks or once every four weeks. These patients were compared to patients treated with darbepoetin alfa given once a week or once every two weeks according to its label.

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<sup>1</sup> Lascon E et al: Effect of Variability in Anemia Management on Hemoglobin Outcomes in ESRD. *Am J Kidney Dis*;41:111-124, 2003.

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