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Chugai's ALK Inhibitor "Alectinib," New Drug Application Submitted for ALK Positive Advanced Non-Small Cell Lung Cancer in the United States

TOKYO, September 9, 2015 -- Chugai Pharmaceutical Co., Ltd. [Main Office: Chuo-ku, Tokyo. Chairman & CEO: Osamu Nagayama] (Chugai) (TOKYO: 4519) and F. Hoffmann-La Roche Ltd. [Head Office: Basel, Switzerland. CEO: Severin Schwan] (Roche) announced today that Genentech, Inc. [Head Office: California, U.S., CEO: Ian T. Clark], a member of the Roche Group, has filed a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) and the FDA has accepted the NDA, for ALK (Anaplastic Lymphoma Kinase) inhibitor "alectinib hydrochloride" (alectinib) for the treatment of patient with ALK positive advanced non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib in September.

Alectinib was granted Breakthrough Therapy Designation by FDA in June 2013 for patients with ALK positive NSCLC who have progressed on crizotinib.

Alectinib is a highly selective, CNS-active ALK inhibitor created by Chugai. Alectinib matches with the Personalized Healthcare Strategy promoted by Chugai and Roche. It has been reported that 2 to 5 percent of patients with NSCLC express a chromosomal rearrangement which leads to fusion of the ALK gene with another gene[1]. ALK kinase signaling is constantly active in cells with such fusion genes, resulting in uncontrolled growth of tumor cells and transforming the cells into tumor cells[2, 3]. Alectinib exerts its anti-tumor effect by selectively inhibiting ALK kinase activity to inhibit tumor cell proliferation and induce cell death[4]. In addition, alectinib is not recognized by the transporter proteins in the blood brain barrier that actively pump molecules out of the brain. Alectinib is active in the central nervous system and has proven activity against brain metastases.

In Japan, alectinib [brand name; Alecensa® capsule 20mg and 40mg] was become available to patients with "*ALK* fusion gene positive unresectable, recurrent/advanced NSCLC" in September 2014 and is marketed by Chugai. The rights for Alecensa in overseas countries including Europe and the US were out-licensed to Roche, and clinical trials of Alecensa (Roche Development Code: RG7853) for patients with NSCLC who have *ALK* mutation are currently ongoing in the US, Europe and other countries.

Two pivotal clinical phase I/II trials formed the basis for the new drug application.

NP28673 study

- NP28673 is a phase I/II global, single arm, open-label, multicentre trial evaluating the safety and efficacy of alectinib in 138 people with ALK positive NSCLC whose disease progressed on crizotinib.
- The study showed by assessment of an independent review committee an ORR in 50.0% of people treated with alectinib, as measured by RECIST criteria.
  - An investigator assessment also showed tumours shrank in 47.8% of people who received alectinib.
  - CNS tumours shrank in response to alectinib in 57.1% of people whose disease had spread to the brain or other parts of the CNS.
  - In addition, the people whose tumours shrank in response to alectinib continued to respond for a median of 11.2 months (Duration of Response (DOR), immature data).
  - The median progression-free survival (PFS) for people who received alectinib was 8.9 months.
- Alectinib demonstrated a safety profile consistent with that observed in previous studies.
  - The most common (occurring in at least 2% of people) Grade 3 or higher adverse event was shortness of breath (dyspnoea; 4%).

NP28761 study

- NP28761 is a phase I/II North American, single arm, open-label, multicentre trial evaluating the safety and efficacy of alectinib in 87 people with ALK positive NSCLC whose disease progressed on crizotinib.
- The study showed by assessment of an independent review committee an ORR in 47.8% of people treated with alectinib, as measured by RECIST criteria.
  - An investigator assessment showed tumours shrank in 46.0% of people who received alectinib.
  - CNS tumours shrank in response to alectinib in 68.8% of people whose disease had spread to the brain or other parts of the CNS.
  - In addition, the people whose tumours shrank in response to alectinib continued to respond for a median of 7.5 months (DOR, immature data).
  - The immature median PFS was 6.3 months.
- Alectinib demonstrated a safety profile consistent with that observed in previous studies.
  - The most common (occurring in at least 2% of people) Grade 3 or higher adverse events were an increase in muscle enzymes (increased blood levels of creatine phosphokinase; 8%), increased liver enzymes (alanine aminotransferase; 6%, and aspartate aminotransferase; 5%) and shortness of breath (dysponea; 3%).

1) Biomarker committee of The Japan Lung Cancer Society, Guidelines for ALK gene tests in lung cancer patients
2) Soda et al., Nature. 448: 561-566 (2007)
3) Takeuchi et al., Clin Cancer Res. 15: 3143-3149 (2009)
4) Sakamoto et al., Cancer Cell. 19: 679-690 (2011)

About Chugai

Chugai Pharmaceutical is one of Japan's leading research-based pharmaceutical companies with strengths in biotechnology products. Chugai, based in Tokyo, specializes in prescription pharmaceuticals and is listed on the 1st section of the Tokyo Stock Exchange. As an important member of the Roche Group, Chugai is actively involved in R&D activities in Japan and abroad. Specifically, Chugai is working to develop innovative products which may satisfy the unmet medical needs, mainly focusing on the oncology area.

In Japan, Chugai's research facilities in Gotemba and Kamakura are collaborating to develop new pharmaceuticals and laboratories in Ukima are conducting research for technology development for industrial production. Overseas, Chugai Pharmabody Research based in Singapore is engaged in research focusing on the generation of novel antibody drugs by utilizing Chugai's proprietary innovative antibody engineering technologies. Chugai Pharma USA and Chugai Pharma Marketing are engaged in clinical development activities in the United States and Europe.

The consolidated revenue in 2014 of Chugai totaled 461.1 billion yen and the operating income was 77.3 billion yen (IFRS Core basis).

Additional information is available on the internet at http://www.chugai-pharm.co.jp/english.

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