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Chugai's Emicizumab Every Four Weeks Showed Positive Interim Results in Phase III Study

- emicizumab prophylaxis controlled bleeds in patients with and without inhibitors -

TOKYO, December 7, 2017 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced today that positive interim results have been reported from the global phase III HAVEN 4 study (NCT03020160) for emicizumab (ACE910) subcutaneous injection, every four weeks, in patients with hemophilia A (12 years of age or older) with and without inhibitors to factor VIII. This study aims to evaluate the efficacy, safety and pharmacokinetics (PK) of emicizumab prophylaxis. At this interim analysis after a median of 17 weeks of treatment, emicizumab prophylaxis demonstrated a clinically meaningful control of bleeding over time.

These results from HAVEN 4 are consistent with previous studies of emicizumab dosed once weekly or every two weeks to evaluate the reduction of bleed rate, including the pivotal studies in hemophilia A with inhibitors, phase III HAVEN 1 study (NCT02622321) in adults and adolescents and phase III HAVEN 2 study (NCT02795767) in children, as well as the phase III HAVEN 3 study (NCT02847637) in adults and adolescents (12 years of age or older) with hemophilia A without inhibitors. The most common adverse events with emicizumab were injection site reactions, with no new safety signals observed. No thrombotic microangiopathy or thrombotic events have been reported in this study. Further details will be presented at a future medical meeting. These results will be submitted to health authorities around the world for approval consideration.

"If emicizumab prophylaxis once every four weeks is proven to be effective in controlling bleeding regardless of the inhibitor status to factor VIII, it would advance the possibility to further prolong the administration interval of emicizumab," said Chugai's Senior Vice President, Head of Project & Lifecycle Management Unit, Dr. Yasushi Ito. "These interim results represent the potential to ease the burden surrounding hemophilia treatment experienced by patients or their family in their daily life and to increase the medical value of emicizumab."

Emicizumab is an investigational bispecific monoclonal antibody, which was developed using Chugai's proprietary antibody engineering technologies. The drug is designed to bind factor IXa and factor X. In doing so, emicizumab provides the cofactor function of factor VIII in people with hemophilia A, who either lack or have impaired coagulation function of factor VIII[1,2]. In November this year, the drug (US product name: HEMLIBRA®; Genentech) was approved by the U.S. Food and Drug Administration "for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors". An EU marketing authorization application was submitted in June 2017 and is being reviewed under Accelerated Assessment by the European Medicines Agency.

CHUGAI PHARMACEUTICAL CO., LTD. Corporate Communications Dept.
1-1, Nihonbashi-Muromachi 2-chome, Chuo-ku Tokyo, 103-8324 Japan
Media Relations Group TEL: +81-(0)3-3273-0881 E-mail: pr@chugai-pharm.co.jp
Investor Relations Group TEL: +81-(0)3-3273-0554 E-mail: ir@chugai-pharm.co.jp

In Japan, emicizumab obtained an orphan drug designation in August 2016 from the Ministry of Health, Labour and Welfare for the prevention and reduction of bleeding episodes in patients with congenital factor VIII deficiency (hemophilia A) who developed inhibitors to FVIII, followed by an application for regulatory approval filed in July 2017.

About HAVEN 4 study (NCT03020160)

HAVEN 4 study is a single-arm, multicentre, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of subcutaneous administration of emicizumab dosed every four weeks. The study included 48 patients (12 years of age or older) with hemophilia A with or without inhibitors to factor VIII who were previously treated with either on-demand or prophylactic factor VIII or bypassing agents, depending on their inhibitor status. The primary endpoint of the study is the bleed rate with emicizumab prophylaxis and secondary endpoints include joint bleed rate, target joint bleed rate, health-related quality of life (HRQoL)/ health status, and safety.

<Study Design>

Patients with or without inhibitors to factor VIII previously treated with either on-demand or prophylactic factor VIII or bypassing agents were enrolled in two cohorts. The study was conducted in two stages as follows;

Patients	Objective	Treatment Regimen
Pharmacokinetic (PK) run-in cohort (n=7)	Evaluate pharmacokinetics	Received emicizumab prophylaxis at 6mg/kg once every 4 weeks
Expansion cohort (n=41)	Evaluate efficacy and safety	Received emicizumab prophylaxis at 3mg/kg once every week for 4 weeks, followed by 6mg/kg once every 4 weeks

The evaluation of pharmacokinetics was conducted after monitoring all seven patients in a PK run-in cohort at least six weeks since they had initiated the administration of emicizumab, and followed by an expansion cohort study. Episodic treatment of breakthrough bleeds with factor VIII therapy was allowed per protocol.

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 Europe are engaged in clinical development activities in the United States and Europe.
The consolidated revenue in 2016 of Chugai totaled 491.8 billion yen and the operating income was 80.6 billion yen (IFRS Core basis).
Additional information is available on the internet at https://www.chugai-pharm.co.jp/english.

References

1) Kitazawa, et al. Nature Medicine 2012; 18(10): 1570
2) Sampei, et al. PLoS ONE 2013; 8: e57479

Contact:

For Media
Chugai Pharmaceutical Co., Ltd.
Media Relations Group, Corporate Communications Dept.,
Koki Harada
Tel: +81-3-3273-0881
E-mail: pr@chugai-pharm.co.jp

For US media
Chugai Pharma USA Inc.
Paul Mignone
Tel: +1-908-516-1350
E-mail: pr@chugai-pharm.com

For European media
Chugai Pharma France SAS
Nathalie Leroy
Tel: +33-1-56-37-05-21
E-mail: pr@chugai.eu

For Taiwanese media
Chugai Pharma Taiwan Ltd.
Susan Chou, Osamu Kagawa
Tel: +886-2-2715-2000
E-mail: pr@chugai.com.tw

For Investors
Chugai Pharmaceutical Co., Ltd.
Investor Relations Group, Corporate Communications Dept.,
Toshiya Sasai

Tel: +81-3-3273-0554
E-mail: ir@chugai-pharm.co.jp