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Chugai's Bispecific Antibody Emicizumab to Present Results of Two Pivotal Phase III Studies at ISTH

TOKYO, June 26, 2017 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced results from two global phase III studies for Chugai's bispecific antibody emicizumab (ACE910): the primary analysis of HAVEN 1 study (NCT02622321) and the interim analysis of HAVEN 2 study (NCT02795767). The data will be presented on July 10 at the upcoming 26th International Society on Thrombosis and Haemostasis (ISTH) Meeting in Berlin, Germany (July 8 to 13). Both studies were conducted in haemophilia A with inhibitors, while HAVEN 1 is for adult and adolescent patients and HAVEN 2 is for paediatric patients.

HAVEN 1 Study

Study description

HAVEN 1 is a randomised, multicentre, open-label, global phase III study evaluating the efficacy, safety, and pharmacokinetics of emicizumab once-weekly subcutaneous injection for 24 weeks or longer in adults and adolescents (12 years of age or older) with haemophilia A with inhibitors to factor VIII.

Study design n=109

- Patients previously treated with on-demand bypassing agents (BPAs) were randomised in a 2:1 fashion to Arm A or B
  - Arm A (n=35): emicizumab once-weekly dosing
  - Arm B (n=18): no prophylaxis (on-demand BPA)
- Patients previously treated with prophylactic BPA
  - Arm C (n=49): emicizumab once-weekly dosing
- Patients who participated in a forgoing Non-Interventional Study (NIS) and previously on BPA (on-demand or prophylactic)
  - Arm D: emicizumab once-weekly dosing

On-demand use of BPAs was allowed to treat breakthrough bleeds per protocol in all arms.

Summary of results

- The primary endpoint was achieved with a statistically significant reduction in bleed rate of 87% (risk rate [RR]=0.13, $p<0.0001$) in treated bleeds with emicizumab (Arm A) compared with on-demand treatment with BPAs (Arm B). All secondary endpoints were also achieved with consistent reductions in bleed rates.

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

[Major secondary endpoints and reduction rate (%) compared with on-demand BPAs]

All bleeds:	(80%, RR=0.20, p<0.0001)
Treated spontaneous bleeds:	(92%, RR=0.08, p≤0.0001)
Treated joint bleeds:	(89%, RR=0.11, p=0.0050)
Treated target joint bleeds:	(95%, RR=0.05, p=0.0002)

- After a median observation time of 31 weeks, 62.9% of patients receiving emicizumab experienced zero treated bleeds (Arm A) compared to 5.6% of those receiving on-demand BPAs (Arm B).
- Results also showed a statistically significant improvement in health-related quality of life (HRQoL) measured at 25 weeks with emicizumab (Arm A) compared to on-demand BPAs (Arm B).
- Among patients who had previously received prophylactic use of BPAs and then received emicizumab (Arm C), 24 patients had participated in the foregoing NIS, which was conducted without emicizumab. An intra-patient analysis in this group showed a 79% (RR=0.21, p=0.0003) reduction in treated bleeds receiving emicizumab compared to their prior prophylaxis with BPAs.
- Adverse events (AEs) occurring in 5% or more of patients treated with emicizumab were injection site reactions, headache, fatigue, upper respiratory tract infection and arthralgia.
- Serious adverse events were reported with thromboembolic events (TE) in two patients and thrombotic microangiopathy (TMA) in three patients (one patient experienced TMA after the clinical data cut off for primary analysis) while receiving emicizumab prophylaxis. The TE and TMA events were associated with repeated high doses of a BPA, activated prothrombin complex concentrate, when used to treat breakthrough bleeds.

HAVEN 2 Study

Study Description

HAVEN 2 is a single-arm, multicentre, open-label, global phase III study evaluating the efficacy, safety, and pharmacokinetics of emicizumab once weekly subcutaneous injection in paediatric patients with haemophilia A with inhibitors to factor VIII.

Interim analysis

The interim analysis was conducted with 19 children younger than 12 years of age with haemophilia A with inhibitors who require treatment with BPAs. The median observation time was 12 weeks.

Summary of results

- Only one of 19 children receiving emicizumab reported a treated bleed. There were no reported joint or muscle bleeds.
- An intra-patient comparison (n=8) in patients who were previously enrolled in the NIS showed that all patients experienced zero treated bleeds or a 100% reduction after

emicizumab treatment (previous annualized bleeding rate ranged from 0 to 34.24); this included seven children who had received prior BPA prophylaxis, and one who had received prior on-demand BPA.

- Data indicated that the same dose of emicizumab is appropriate for children as for adults and adolescents, based on the levels of emicizumab in the blood (pharmacokinetics) of the children compared with the level of emicizumab in the blood of adults and adolescents.
- The most common AEs with emicizumab in the HAVEN 2 study were mild injection site reactions and common cold symptoms (nasopharyngitis).

Summary of the HAVEN 1 (NCT02622321) study results to be presented at ISTH

Study Description	Phase III randomised, multicenter, open-label study evaluating the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis versus no prophylaxis in people with haemophilia A with inhibitors to factor VIII.	
Patients	Patients with haemophilia A with inhibitors aged ≥12 years on episodic or prophylactic treatment with bypassing agent(s) N=109	
Study group	No prophylaxis (prior episodic BPAs) (Arm B; n=18)	Emicizumab prophylaxis (prior episodic BPAs) (Arm A; n=35)
Treated bleeds ABR (primary endpoint)		
Annualized bleeding rate [ABR]* (95% CI)	23.3 (12.33; 43.89)	2.9 (1.69; 5.02)
% reduction (RR, p-value)	87% reduction (RR= 0.13, p<0.0001)	
Median ABR (Interquartile range; IQR)	18.8 (12.97; 35.08)	0.0 (0.00; 3.73)
% patients with zero bleeds (95% CI)	5.6 (0.1; 27.3)	62.9 (44.9; 78.5)

Treated bleeds ABR intra-patient comparison (Arm C patients who participated in NIS n=24; secondary endpoint)		
Study group	Prior prophylaxis with BPAs	Emicizumab prophylaxis
ABR* (95% CI)	15.7 (11.08; 22.29)	3.3 (1.33; 8.08)
% reduction (RR, p-value)	79% reduction (RR= 0.21, p=0.0003)	
Median ABR (IQR)	12.0 [5.73; 24.22]	0.0 [0.00; 2.23]
% patients with zero bleeds	12.5 (2.7; 32.4)	70.8 (48.9; 87.4)

*Negative binomial regression model

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 totalled 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.

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.
Casey Astringer
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
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