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Chugai Presents Results of Two Pivotal Phase lll Studies for its Bispecific Antibody HEMLIBRA® at WFH 2018

TOKYO, May 21, 2018 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) today announced that full results from HAVEN 3 study (NCT02847637) and HAVEN 4 study (NCT03020160) evaluating Chugai's hemophilia A treatment HEMLIBRA® [generic name: emicizumab (genetical recombination)] are being presented at the World Federation of Hemophilia 2018 World Congress held in Glasgow, Scotland from May 20 to 24. HAVEN 3 study is conducted in people with hemophilia A without inhibitors, and HAVEN 4 study is conducted in people with hemophilia A with or without inhibitors. Results from both studies will be presented as late-breaking abstracts.

"The results from HAVEN 3 study demonstrate that HEMLIBRA, which was created with Chugai's proprietary antibody engineering technologies, can reduce the bleeding risk in people with hemophilia A without inhibitors. The intra-patient comparison in this study also shows a statistically significant reduction in bleeding by HEMLIBRA prophylaxis compared to factor VIII therapy, the current standard treatment," said Chugai's President & CEO, Tatsuro Kosaka. "In addition, HAVEN 4 data indicates that regardless of the presence of inhibitors, HEMLIBRA administration once every four weeks can reduce the risk of bleeding in people with hemophilia A compared with existing treatments. We will closely work with Roche to obtain approval of HEMLIBRA for the treatment of hemophilia A without inhibitors as early as possible."

HAVEN 3 Study

Study description

HAVEN 3 study is a randomized, multicentre, open-label phase III study evaluating the efficacy, safety and pharmacokinetics of HEMLIBRA prophylaxis subcutaneous injection once a week and once every two weeks. The study enrolled 152 patients with hemophilia A, 12 years of age or older without inhibitors to factor VIII, who were previously treated with episodic or prophylactic factor VIII therapy.

- Primary endpoint: number of treated bleeds over time with HEMLIBRA prophylaxis (Arm A and Arm B) versus no prophylaxis (Arm C).
- Secondary endpoints: all bleed rate, treated spontaneous bleed rate, treated joint bleed rate, treated target joint bleed rate, health-related quality of life (HRQoL) / health status with HEMLIBRA prophylaxis (Arm A and Arm B) versus no prophylaxis (Arm C); intra-patient comparison of bleed rate and safety on their prior prophylactic factor VIII therapy (Arm D); and safety etc.

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Study design n=152

- Patients previously treated with episodic factor VIII therapy were randomized in a 2:2:1 fashion to either Arm A, B or C

Arm A (n=36)	Received HEMLIBRA prophylaxis at 3 mg/kg by once-weekly subcutaneous injection for 4 weeks, followed by 1.5 mg/kg once-weekly subcutaneous injection
Arm B (n=35)	Received HEMLIBRA prophylaxis at 3 mg/kg by once-weekly subcutaneous injection for 4 weeks, followed by 3 mg/kg once every two weeks subcutaneous injection
Arm C (n=18)	No prophylaxis control arm

- Patients previously treated with factor VIII prophylactic were enrolled in:

Arm D (n=63)	Received HEMLIBRA prophylaxis at 3 mg/kg by once-weekly subcutaneous injection for 4 weeks, followed by 1.5 mg/kg once-weekly subcutaneous injection

Episodic treatment of breakthrough bleeds with factor VIII therapy was allowed per protocol.

Summary of results

- HEMLIBRA achieved a statistically significant reduction in treated bleeds by 96% (Wald test, p <0.0001) with once-weekly prophylaxis of HEMLIBRA (Arm A) and 97% (p <0.0001) with once every two weeks prophylaxis respectively, compared with no prophylaxis control arm (Arm C).

[Major secondary endpoints and reduction rate (%)] (Wald test)

	Arm A	Arm B
All bleeds	95% (p <0.0001)	94% (p <0.0001)
Treated spontaneous bleeds	94% (p <0.0001)	98% (p <0.0001)
Treated joint bleeds	96% (p <0.0001)	97% (p <0.0001)
Treated target joint bleeds	95% (p <0.0001)	95% (p <0.0001)

- 55.6% (95% CI: 38.1, 72.1) of patients receiving once-weekly prophylaxis of HEMLIBRA (Arm A) experienced zero treated bleeds and 60% (95% CI: 42.1, 76.1) of patients receiving once every two weeks prophylaxis of HEMLIBRA (Arm B) compared to 0% (95% CI: 0.0, 18.5) of those not receiving prophylaxis treatment (Arm C).
- An intra-patient comparison (n=48) in patients who had previously treated with factor VIII prophylaxis prior to the study (Arm D) and participated in the foregoing non-interventional study (NIS) showed that 68% (RR=0.32, p <0.0001) reduction of treated bleeds with once-

weekly prophylaxis of HEMLIBRA.

- Adverse events (AEs) occurring in 5% or more of patients treated with HEMLIBRA were injection site reactions, joint pain (arthralgia), common cold symptoms (nasopharyngitis), headache, upper respiratory tract infection and influenza.
- There were no unexpected or serious adverse events (AEs) related to HEMLIBRA and most common AE profiles appeared consistent with the known safety profile of the medicine.

HAVEN 4 Study

Study Description

HAVEN 4 study is a single-arm, multicentre, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of subcutaneous administration of HEMLIBRA 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.

- Primary endpoint: treated bleed rate with HEMLIBRA prophylaxis
- Secondary endpoints: all bleed rate, treated spontaneous bleed rate, treated joint bleed rate, treated target joint bleed rate, health-related quality of life (HRQoL) / health status, and safety etc.

Study design n=48

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;

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

All patients in the PK run-in cohort (n=7) were previously treated with on-demand treatment and then received HEMLIBRA prophylaxis in the study. The evaluation of pharmacokinetics was conducted after monitoring all seven patients in the PK run-in cohort for at least six weeks since they had initiated the administration of HEMLIBRA, followed by an expansion cohort study. Episodic treatment of breakthrough bleeds with factor VIII therapy was allowed per protocol.

Summary of results

- Patients receiving HEMLIBRA prophylaxis in Expansion cohort had a median annualized bleeding rate (ABR) for treated bleeds of 0.0 (IQR: 0.0; 2.1).
- 56.1% (95% CI: 39.7, 71.5) of patients in Expansion cohort achieved zero treated bleeds

and 90.2% (95% CI: 76.9, 97.3) of patients experienced three or fewer treated bleeds.

[Major secondary endpoints and achievement rate (%) of zero bleeds]

All bleeds:	29.3% (95% CI: 16.1, 45.5)
Treated spontaneous bleeds:	82.9% (95% CI: 67.9, 92.8)
Treated joint bleeds:	70.7% (95% CI: 54.5, 83.9)
Treated target joint bleeds:	85.4% (95% CI: 70.8, 94.4)

- Results from HAVEN 4 study is consistent with results obtained from other phase III studies of HEMLIBRA. These data show that once every 4 weeks prophylaxis of HEMLIBRA can provide clinically meaningful control of bleeding in patients with hemophilia A with or without factor VIII inhibitors.
- There were no unexpected or serious adverse events (AEs) related to HEMLIBRA and the most common AEs were consistent with previous studies.
- Injection site reaction was the most common AE, occurring in nine people.

Summary of the HAVEN 3 (NCT02847637) study results presented at WFH

Study Description	A randomized, multicentre, open-label phase III study evaluating the efficacy, safety and pharmacokinetics of HEMLIBRA prophylaxis subcutaneous injection once a week and once every two weeks.		
Patients	Patients with hemophilia A, 12 years of age or older without inhibitors to factor VIII, who were previously treated with episodic or prophylactic factor VIII therapy. N=152		
Primary endpoint	Number of bleeds over time with HEMLIBRA prophylaxis (Arm A and Arm B) versus no prophylaxis (Arm C)		
Study group	No prophylaxis (Arm C; n=18)	Once weekly HEMLIBRA prophylaxis (Arm A; n=36)	Once every 2 weeks HEMLIBRA prophylaxis (Arm B; n=35)
Treated bleeds (primary endpoint)			
Median efficacy period, weeks (min–max)	24.0 (14.4–25.0)	29.6 (17.3–49.6)	31.3 (7.3–50.6)
Model-based ABR (95% CI)*	38.2 (22.9; 63.8)	1.5 (0.9; 2.5)	1.3 (0.8; 2.3)
% reduction vs arm C (RR, Wald test; p-value)	N/A	96% reduction (0.04, p <0.0001)	97% reduction (0.03, p <0.0001)
Median ABR (Interquartile range; IQR)	40.4 (25.3; 56.7)	0.0 (0.0; 2.5)	0.0 (0.0; 1.9)

% patients with zero bleeds (95% CI)	0.0 (0.0; 18.5)	55.6 (38.1; 72.1)	60 (42.1; 76.1)
% patients with zero to three bleeds (95% CI)	5.6 (0.1; 27.3)	91.7 (77.5; 98.2)	94.3 (80.8; 99.3)

Treated bleeds ABR intra-patient comparison (Arm D patients who participated in NIS, n=48; secondary endpoint)		
Study group	Prior factor VIII prophylaxis (Arm C; n=48)	Once-weekly HEMLIBRA prophylaxis (Arm D; n=48)
Median efficacy period, weeks (min–max)	30.1 (5.0–45.1)	33.7 (20.1–48.6)
Model-based ABR* (95% CI)	4.8 (3.2; 7.1)	1.5 (1.0; 2.3)
% reduction vs NIS Factor VIII (RR, p-value)	68% reduction (0.32, p <0.0001)	
Median ABR (IQR)	1.8 (0.0; 7.6)	0.0 (0.0; 2.1]
% patients with zero bleeds	39.6 (25.8; 54.7)	54.2 (39.2; 68.6)
% patients with zero to three bleeds	72.9 (58.2; 84.7)	91.7 (80.0; 97.7)

*Negative binomial regression model

Summary of the HAVEN 4 (NCT03020160) study results presented at WFH

Study Description	A single-arm, multicentre, open-label, phase III study evaluating the efficacy, safety, and pharmacokinetics of subcutaneous administration of HEMLIBRA dosed every four weeks.
Patients	12 years of age or older patients 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. N=48
Primary endpoint	bleed rate with HEMLIBRA prophylaxis
Study group	HEMLIBRA prophylaxis (n=48 total; n=41 included in efficacy analyses)
Treated bleeds (primary endpoint)	
ABR, model based (95% CI)	2.4 (1.4; 4.3)
Median ABR,	0.0

calculated (IQR)	(0.0; 2.1)
% patients with zero bleeds (95% CI)	56.1 (39.7; 71.5)
% patients with zero to three bleeds (95% CI)	90.2 (76.9; 97.3)

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.

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