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Results Presented from Primary Analysis of the Phase III HAVEN 2 Study with Chugai's HEMLIBRA® for Children with Hemophilia A with Inhibitors at the American Society of Hematology 2018

TOKYO, December 4, 2018 -- Chugai Pharmaceutical Co., Ltd. (TOKYO: 4519) announced that the primary analysis of the phase III HAVEN 2 study (NCT02795767), evaluating hemophilia A treatment HEMLIBRA® [generic name: emicizumab (genetical recombination)] in children with hemophilia A with factor VIII inhibitors, was reported in an Oral Presentation at the 60th American Society of Hematology (ASH) Annual Meeting held in San Diego, USA from December 1 to 4 2018. These data, including longer follow-up (median of 11 additional months of data for once weekly dosing) and new data for less frequent dosing schedules (every two weeks or every four weeks), demonstrated clinically meaningful control of bleeding.

"Bleeding control is important especially for children with hemophilia A. I am happy that HEMLIBRA showed positive data from a longer period of treatment in children younger than 12 years of age with hemophilia A with inhibitors," said Chugai's Executive Vice President, Co-Head of Project & Lifecycle Management Unit, Dr. Yasushi Ito. "HEMLIBRA has been approved in more than 50 countries. I hope that the new data will broaden the potential contribution of HEMLIBRA in people with hemophilia A with inhibitors who have limited treatment options."

HAVEN 2 Study

Study description

The HAVEN 2 study is a multicenter, open-label, clinical phase III study evaluating the efficacy, safety and pharmacokinetics of once weekly, every two weeks or every four weeks subcutaneous administration of HEMLIBRA prophylaxis in children younger than 12 years of age with hemophilia A with factor VIII inhibitors. The primary analysis on evaluation of efficacy included 85 children (once weekly dosing, Arm A, n=65; every two weeks dosing, Arm B, n=10; every four weeks dosing, Arm C, n=10) with hemophilia A with factor VIII inhibitors. The median follow-up period of Arm A, B and C was 58 (range 17.9–92.6), 21.3 (range 18.6–24.1), and 19.9 (range 8.9–24.1) weeks, respectively.

Study design n=85

- HEMLIBRA prophylaxis was administered as follows.

Arm A (n＝65)	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＝10)	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

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Arm C (n＝10)	Received HEMLIBRA prophylaxis at 3 mg/kg by once-weekly subcutaneous injection for 4 weeks, followed by 6 mg/kg once every four weeks subcutaneous injection

- The prospective intra-patient comparison included 18 patients from the once weekly cohort (Arm A) previously treated with bypassing agents (BPAs) either as prophylaxis (n=15) or on-demand (n=3) as part of a non-interventional study.

Summary of results

Arm A		
	Annualized bleeding rate [ABR] (95% CI)	**Median ABR (Interquartile range; IQR)**
Treated bleeds (primary endpoint)	0.3 (0.17; 0.50)	0.0 (0.00; 0.00)
All bleeds	3.2 (1.94; 5.22)	0.6 (0.00; 2.92)
Treated spontaneous bleeds	0.0 (0.01; 0.10)	0.0 (0.00; 0.00)
Treated joint bleeds	0.2 (0.08; 0.29)	0.0 (0.00; 0.00)
Treated target joint bleeds	Not estimable	0.0 (0.00; 0.00)

	Arm B	**Arm C**
ABR, treated bleeds (95% CI)	0.2 (0.03; 1.72)	2.2 (0.69; 6.81)
Median ABR, treated bleeds (IQR)	0.0 (0.00; 0.00)	0.0 (0.00; 3.26)
% patients with zero treated bleeds (95% CI)	90.0% (55.5; 99.7)	60.0% (26.2; 87.8)
% patients with 1-3 treated bleeds (95% CI)	10.0% (0.3; 44.5)	40.0% (12.2; 73.8)

- In patients receiving HEMLIBRA once weekly (Arm A), 76.9% (95% CI, 64.8; 86.5) experienced zero treated bleeds and 23.1% experienced 1–3 treated bleeds.
- Once-weekly HEMLIBRA dosing showed a 99% (95% CI: 97.7 - 99.4) reduction in treated

bleeds compared to prior treatment with bypassing agents (BPAs) as prophylaxis (n=15) or on-demand (n=3) in a prospective intra-patient comparison in Arm A.

- The most common adverse reactions occurring in 10% or more of children treated with HEMLIBRA were common cold symptoms (nasopharyngitis; 37.5%), injection site reactions (29.5%), fever (pyrexia; 23.9%), upper respiratory tract infection (23.9%), cough (23.9%), diarrhoea (15.9%), vomiting (15.9%), headache (14.8%), contusion (12.5%), fall (12.5%) and influenza (10.2%).
- No cases of thrombotic microangiopathy (TMA) or thrombotic events occurred.
- Four patients tested positive for anti-drug antibodies (ADAs) to HEMLIBRA. Of these patients, two had ADAs with neutralizing potential based on reduced HEMLIBRA levels. As previously reported, the ADA in one of these patients resulted in reduced efficacy of HEMLIBRA and led to discontinuation of treatment. The other patient had no bleeds as of the clinical cut-off date of the study.

Also, the data from HOHOEMI study (JapicCTI-173710) were reported as a Poster Presentation at the ASH Annual Meeting. The HOHOEMI study is conducted in Japan by Chugai to investigate the efficacy, safety and pharmacokinetics of every two weeks or every four weeks subcutaneous administration of HEMLIBRA prophylaxis in children younger than 12 years of age with hemophilia A without inhibitors including pediatric patients previously untreated with FVIII.

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 2017 of Chugai totalled 534.2 billion yen and the operating income was 103.2 billion yen (IFRS Core basis).

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

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