News Release

Takeda Unveil New Data from the PROPEL Study at ISTH 2019, Reinforcing the Potential Benefit for Personalized Prophylaxis with ADYNOVATE in Severe Hemophilia A

- ***Updated results from the Phase IIIb/IV PROPEL Study show that pharmacokinetic (PK)-driven dosing may be used to achieve FVIII target trough levels of 8–12%; and that selecting a patient-appropriate target FVIII level plus adjusting a dosing regimen to that patient's PK characteristics, can improve the overall PK profile and may enhance outcomes, with no adverse event profile change – thus reinforcing the importance of PK-guided dosing and the potential benefit of personalized prophylaxis with ADYNOVATE[1]***
- ***Data presented alongside 47 other ISTH 2019 presentations showcasing the latest developments from Takeda's hematology gene therapy pipeline and leading Factor portfolio***
- ***Takeda's robust presence at ISTH underscores its commitment to progressing scientific advancements for the bleeding disorders community***

Cambridge, Mass., and Osaka, Japan, July 8, 2019 – Takeda Pharmaceutical Company Limited (TSE:4502/NYSE:TAK) ("Takeda"), R&D-driven, global biopharmaceutical company with a leadership position in rare diseases, has today announced updated results from its phase IIIb/IV clinical trial for ADYNOVATE® [Antihemophilic Factor (Recombinant), PEGylated] at the 27th Annual International Society on Thrombosis and Haemostasis Congress (ISTH), in Melbourne, Australia. The PROPEL study is a **PRO**spective, randomized, multi-center study comparing the safety and efficacy of ADYNOVATE following **P**K-guided prophylaxis targeting two different Factor **E**ight (FVIII) trough activity **L**evels in subjects with severe hemophilia A.

The latest results of the landmark PROPEL study show that ADYNOVATE prophylaxis in severe hemophilia A patients may enhance a patient's PK profile - by targeting FVIII trough levels of 8–12% (elevated prophylaxis arm, ELE) as compared with 1–3% (reference prophylaxis arm, REF). This represents a clinically meaningful trend towards more patients experiencing zero bleeds [62% ELE versus 42% REF, respectively; p=0.0545].[1] Patients randomized to the 8-12% target group also saw a:

- Reduced mean total annualized bleed rate (ABR); (1.6 ELE versus 3.6 REF, respectively).
- Reduced mean spontaneous joint ABR (0.5 ELE versus 2.0 REF)

The data supports the view that patients may benefit from PK-driven dosing that targets FVIII trough levels of 8–12%. The safety findings from this latest update were also comparable and consistent with previous ADYNOVATE trials.[1,2] Ongoing analyses will further characterize the relationship between PK-tailored dosing of ADYNOVATE FVIII levels and bleeding events.

Adapting the dosing regimen for an individual patient, guided by that patient's individual PK characteristics, has great potential – for managing patients with hemophilia A, particularly those desiring greater bleed protection.[1]

"These results, for the first time, provide proof of concept that targeting higher FVIII troughs can benefit severe hemophilia A patients with no adverse event profile change. The next step will be to characterize the relationships between pharmacokinetic profiles, FVIII activity levels and bleeding events, so that we can understand more about the optimal approach for personalized prophylaxis in hemophilia A and help more patients reach zero bleeds," said PD Dr. med. Robert Klamroth, Head of the Department of Internal Medicine Angiology and Coagulation Disorders and Director of the Comprehensive Care Haemophilia Treatment Center and the Haemostasis and Thrombosis Unit at the Vivantes Klinikum in Berlin, Germany.

"The PROPEL data confirm the critical role of FVIII replacement therapy and demonstrate that with PK-guided prophylaxis with ADYNOVATE individualized FVIII levels of 8–12% can be reliably achieved to improve the outcomes for some patients. Hence, the study reinforces Takeda's leadership in advancing treatment for hemophilia A, which also includes a comprehensive gene therapy clinical trial program," said Dr. med. Wolfhard Erdlenbruch, Vice President Head of Global Medical Hematology, Takeda. "ISTH provides a great opportunity for us to demonstrate our ongoing commitment to the hemophilia community and we are excited to be sharing several important updates from our R&D portfolio this week."

In addition to PROPEL, Takeda are presenting 47 other data updates across the hematology portfolio. Most notably, 14 presentations will unveil some of the foundational work being carried out within the Takeda Hematology gene therapy pipeline, looking at ways to help hemophilia patients naturally produce factor VIII or IX, in order to eliminate or experience fewer bleeding episodes.

About the PROPEL Study[1,2]

The PROPEL study evaluated the safety and efficacy of ADYNOVATE in PK-guided prophylaxis targeting two different FVIII trough levels in previously treated patients with severe hemophilia A.

Methods: Eligible subjects had FVIII activity <1%, annualized bleed rate (ABR) ≥2, and transitioned from a previous SHP660 (ADYNOVATE) study or were 12–65 years old with ≥150 exposure days to plasma-derived or recombinant FVIII. After initial PK assessments, subjects were randomized to receive 12 months of PK-guided prophylaxis targeting FVIII trough levels of 1–3% (REF) or 8–12% (ELE) (1st 6 months: dose adjustment period). Primary outcome was the % of subjects with a total ABR=0 (all bleeds) during the 2nd 6-month study period. Secondary outcomes included total ABR, spontaneous ABR and joint ABR (AJBR) (all bleeds), SHP660 consumption and adverse events (AEs). [1]

Results: Overall, 115 male subjects (57, REF; 58, ELE) received ≥1 prophylactic SHP660 dose. Median (range) age was 29 (12–61) years; 100 subjects (52, REF; 48, ELE) completed the study. During the 2nd 6 months, the multiple imputations (MI) estimate for REF vs ELE was 42% vs 62% (p=0.0545) for total ABR=0, 60% vs 76% (p=0.1006) for spontaneous ABR=0, and 65% vs 85% (p=0.0260) for spontaneous AJBR=0. Mean (SD), median (IQR) total ABRs for the 2nd 6-month period: 3.6 (7.5), 2.0 (4.0) REF; 1.6

(3.4), 0 (2.0) ELE. Overall AEs and SAEs occurred in REF vs ELE: 60% vs 62% and REF vs ELE: 5% vs 7% of the subjects, with 1 SAE in an 8–12% target subject considered related to SHP660: a transient 0.6 BU inhibitor without evidence of anti-FVIII binding, which resolved before study end. AE profiles were comparable and consistent with previous SHP660 trials.[1]

About ADYNOVATE/ADYNOVI

ADYNOVATE [Antihemophilic Factor (Recombinant), PEGylated] was first approved by the Food and Drug Administration (FDA) in the U.S. followed by approval in Japan, Canada, and Colombia, and is approved as ADYNOVI® in the 28 Member States of the European Union (EU) as well as Iceland, Liechtenstein, Norway and Switzerland. In Europe ADYNOVI is approved for the treatment and prophylaxis of bleeding in patients 12 years and above with hemophilia A.

ADYNOVI SAFETY INFORMATION FOR EUROPE[3]

Please consult the ADYNOVI Summary of Product Characteristics (SmPC) before prescribing, particularly in relation to dosing and treatment monitoring.

Contraindications

Hypersensitivity to the active substance, to the parent molecule octocog alfa or to any of the excipients listed in the SmPC. Known allergic reaction to mouse or hamster protein.

Special warnings and precautions for use

The medicinal product contains traces of mouse and hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

The formation of neutralising antibodies (inhibitors) against factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay.

In general, all patients treated with coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed.

After reconstitution this medicinal product contains 0.45 mmol sodium (10 mg) per vial.

Adverse Reactions

Common (Greater-than or equal to 1/100 to <1/10)	**Headache, Diarrhea, Nausea, Rash**
Uncommon (Greater-than or equal to 1/1000 to <1/100)	**Factor VIII inhibition in previously-treated patients (PTPs), Hypersensitivity, Flushing**

For more information, please refer to the ADYNOVI Summary of Product Characteristics **here**.
For US specific safety information, please refer to the ADYNOVATE US Prescribing Information **here**.

About Hemophilia

Hemophilia is a challenging chronic disease that causes longer-than-normal bleeding due to absent or deficient clotting factor in the blood.[4] Hemophilia A is more common than hemophilia B;[4] hemophilia A affects about 158,225 people, whereas hemophilia B affects about 31,247 people worldwide.[5]

People with hemophilia, working closely with their healthcare professionals, can live healthy lives with proper care and adequate treatment.[6] Treatment regimens typically include on-demand and/or regular prophylactic infusions of factor replacement therapy to control or prevent the risk of bleeding.[4,7]

About Takeda Hematology

Following its recent acquisition of Shire, Takeda is a leader in hemophilia with the longest heritage and market-leading portfolio, backed by established safety and efficacy profiles with decades of real world experience. We have 70+ years driving innovation for patients[8] and a broad portfolio of 11 products across nine hemophilia indications. Our experience as leaders in hematology means we are well prepared to meet today's needs as we pursue future developments in the care of bleeding disorders. Together with the hematology community, we are raising expectations for the future, including earlier diagnosis, earlier and full protection against bleeds, and more personalized patient care.

About Takeda Pharmaceutical Company Limited

Takeda Pharmaceutical Company Limited (TSE:4502/NYSE:TAK) is a global, values-based, R&D-driven biopharmaceutical leader headquartered in Japan, committed to bringing Better Health and a Brighter Future to patients by translating science into highly-innovative medicines.
Takeda focuses its R&D efforts on four therapeutic areas: Oncology, Gastroenterology (GI), Rare Diseases and Neuroscience. We also make targeted R&D investments in Plasma-Derived Therapies and Vaccines. We are focusing on developing highly innovative medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options and leveraging our enhanced collaborative R&D engine and capabilities to create a robust, modality diverse pipeline. Our employees are committed to improving quality of life for patients and to working with our partners in health care in approximately 80 countries and regions. For more information, visit https://www.takeda.com

Media Contacts:

Japanese Media	Media outside Japan	Media outside Japan
Kazumi Kobayashi	Tsuyoshi Tada	Linda Calandra
kazumi.kobayashi@takeda.com	tsuyoshi.tada@takeda.com	linda.calandra1@takeda.com
+81 (0) 3-3278-2095	+1 (617) 551-2933	+1 (617) 301-2092

References

1 Klamroth R, Windyga J, Radulescu V, *et al.*, PK-guided rurioctocog alfa pegol prophylaxis in patients with severe hemophilia A targeting two FVIII trough levels: results from the phase 3 PROPEL Study. Presented at ISTH 2019 (International Society on Thrombosis and Haemostasis (ISTH) Biennial Congress. July 6-10, 2019. Abstract #A-1052-0038-01311.

2 Klamroth R, Windyga J, Radulescu V, et al., Results of a phase 3, randomized, multicenter study of RURIOCTOCOG ALFA PEGOL PK-guided prophylaxis targeting 2 FVIII trough levels in patients with severe Hemophilia A (propel study). Presented at European Association of Haematology and Allied Disorders (EAHAD) February 2019. Abstract #255.

3 Shire Pharmaceuticals Group. Shire granted EU marketing authorization for ADYNOVI (Antihemophilic Factor
(Recombinant). PEGylated) for adults and adolescents with Hemophilia A. 2018. Available here: https://globenewswire.com/news-release/2018/01/15/1289070/0/en/Shire-granted-EU-marketingauthorization-for-ADYNOVI-Antihemophilic-Factor-Recombinant-PEGylated-for-adults-and-adolescents-withHemophilia-A.html Last accessed April 2019.

4 World Federation of Hemophilia. "What is hemophilia?" World Federation of Hemophilia website. http://www.wfh.org/en/page.aspx?pid=646. Last Accessed June 2019.

5 World Federation of Hemophilia. Report on the Annual Global Survey 2017. World Federation of Hemophilia website. http://www1.wfh.org/publications/files/pdf-1714.pdf. Last Accessed June 2019.

6 World Federation of Hemophilia. "About Bleeding Disorders: Treatment." World Federation of Hemophilia website. https://www.wfh.org/en/page.aspx?pid=642. Last Accessed June 2019.

7 National Hemophilia Foundation. "Hemophilia A". National Hemophilia Foundation website. https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Last Accessed June 2019.

8 Shire Website. Standards of Care for Hemophilia. Website: https://www.shire.com/who-we-are/how-weoperate/policies-and-positions/standards-of-care-for-hemophilia Last Accessed April 2019.