HEMLIBRA®
Subcutaneous Injection
30 mg, 60 mg, 90 mg, 105 mg, 150 mg
Product Overview

Hiroshi Motegi
HEMLIBRA Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.
Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

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**Product Outline**

<table>
<thead>
<tr>
<th>Product</th>
<th>Anti-coagulation factor IXa/X humanized bispecific monoclonal antibody Coagulation factor VIII substitute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product name:</td>
<td>HEMLIBRA® Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg</td>
</tr>
<tr>
<td>Generic name:</td>
<td>emicizumab (genetical recombination)</td>
</tr>
</tbody>
</table>

**Package:**
Characteristics of HEMLIBRA

- Bispecific antibody created by Chugai Pharmaceutical
- HEMLIBRA binds to activated blood coagulation factor IX (FIXa) and blood coagulation factor X (FX) and maintains both factors in position on the phospholipid membrane. It is considered that the mechanism enables to replace the cofactor function of FVIIIa and to promote the downstream blood-clotting reaction.

FVIIIa and HEMLIBRA cofactor activity [conceptual illustration]

[Diagram showing the interaction of FVIIIa and HEMLIBRA with FIXa and FX on the phospholipid membrane.]

The authors include an employee of Chugai Pharmaceutical
Treatment that HEMLIBRA Aims to Contribute

Meet the unmet medical needs of hemophilia A with inhibitors

- Efficacy (inhibitory effect on bleeding)
- Administration technique (intravenous administration)
- Time and effort due to frequent administration

Advancement of inhibitory effect on bleeding
Subcutaneous injection
Once-weekly administration
HEMLIBRA: History of Development 1

Creation at Fuji Gotemba Research Laboratories

Lead identification

Multi-dimensional optimization

Improved
✓ FVIII mimetic activity
✓ pharmacokinetics (half-life and bioavailability)
✓ physicochemical properties
✓ immunogenicity (humanization and in silico deimmunization etc.)
✓ manufacturability of bispecific antibody


 Identified HEMLIBRA: humanized anti-FIXa / X asymmetric bispecific IgG4

• >40,000 bispecific antibodies were screened to obtain lead antibody
• >2,000 engineered antibodies were evaluated

Anti-FIXa antibody
~200

Anti-FX antibody
~200

FIXa binding region
FX binding region

combinations

~200

>40,000 bispecific antibodies were screened to obtain lead antibody
>2,000 engineered antibodies were evaluated
HEMLIBRA: History of Development 2

● Research and creation at Fuji Gotemba Research Laboratories (from 2001)

● Conduct clinical development in Japan (from 2012): from FIH to proving PoC (Ph1, Ph1/2)
  • Received BTD from U.S. FDA based on the phase 1 clinical study in Japan (Sep. 2015)

● Start of global development in collaboration with Roche (from Jul. 2014)
  • Global phase 3 studies were carried out (HAVEN 1 to HAVEN 4)

● Simultaneous application for the indication of hemophilia A with inhibitors in Europe, U.S. and Japan (Jun. to Jul. 2017)
  • U.S. (priority review), EU (fast-track review), Japan (priority review under orphan drug designation)


  Japan (Approved in Mar. 2018, Launched in May 2018)

*FIH : first in human, PoC: proof of concept, BTD: breakthrough therapy designation
**INDICATION**

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with congenital factor VIII deficiency with factor VIII inhibitors

**DOSAGE AND ADMINISTRATION**

The usual dosage is 4 once-weekly subcutaneous doses at 3 mg/kg (body weight) emicizumab (genetical recombination) per dose, followed by once-weekly subcutaneous doses at 1.5 mg/kg (body weight)

<Precautions related to DOSAGE AND ADMINISTRATION>

HEMLIBRA should be used in routine prophylaxis to prevent or reduce the frequency of bleeding episodes and should not be used for on-demand hemostatic treatment.
Illustration of HEMLIBRA administration

Discontinue BPA prophylaxis by the day before the start of HEMLIBRA treatment.

If HEMLIBRA treatment is discontinued, do not use BPA prophylaxis for six months thereafter.

Administration at specialized medical facilities are recommended for the first four administration until stable blood concentration is achieved.

Start self-administration at home after training at medical facilities

Source: HEMLIBRA® Subcutaneous Injection Appropriate Use Guide (as of May 2018)
Conditions for Approval

1. A risk management plan should be created and appropriately implemented.

2. Because the number of participants in Japanese clinical trials was very limited, post-marketing drug use surveillance of all patients receiving HEMLIBRA treatment should be conducted until data for a certain number of patients have been accumulated, in order to understand background information on people using HEMLIBRA as well as to collect safety and efficacy data on HEMLIBRA promptly, and take necessary measures for the appropriate use of HEMLIBRA.

3. Early phase post-marketing vigilance should be conducted.

Source: HEMLIBRA® Package insert (version 3 as of May 2018)
Overview of HEMLIBRA RMP

Overview of RMP Regarding HEMLIBRA® Subcutaneous Injection 30 mg, 60 mg, 90 mg, 105 mg, 150 mg

<table>
<thead>
<tr>
<th>Product name</th>
<th>HEMLIBRA® Subcutaneous Injection</th>
<th>Active ingredient</th>
<th>emicizumab (genetical recombination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company</td>
<td>Chugai pharmaceutical Co., Ltd.</td>
<td>Therapeutic classification</td>
<td>876349</td>
</tr>
</tbody>
</table>

1.1. Safety concerns

**[Important identified risks]**
- Thromboembolic events (associated with emicizumab and aPCC)
- Thrombotic microangiopathy (associated with emicizumab and aPCC)

**[Important potential risks]**
- Thromboembolic events (associated with emicizumab and FVIIa/FX)
- Thrombotic microangiopathy (associated with emicizumab and FVIIa/FX)
- Serious bleeding due to inadequate control of bleeds based on coagulation test interference by emicizumab
- Shock, Anaphylaxis
- Immunogenicity

**[Important missing information]**
- Not applicable

1.2. Efficacy concerns

Inhibitory effect on bleeding of long-term use in hemophilia A with inhibitors to FVIII

aPCC : Activated prothrombin complex concentrate
FVIIa/FX : Freeze-dried activated human blood coagulation Factor VII concentrate containing Factor X

Source: HEMLIBRA® Subcutaneous Injection Appropriate Use Guide (as of May 2018)
A structure to ensure safety has been established through the nationwide assignment of MRs specialized in HEMLIBRA and collaboration with safety experts and medical science liaisons.

- Introduction of HEMLIBRA
- Regular visit (Confirm courses of treatment)
- Referral to a follow-up facility
- Consultation on hemostatic therapy
- Doctor visit/prescription (Daily medical practice)
- Follow-up at general medical facilities

Patients with hemophilia A/their families

Specialized medical facilities

Specialized MRs and General MRs

Medical Science Liaisons

Innovation all for the patients

Safety Experts

Specialized MRs

Medical Science Liaisons
Current Status of Hemophilia Treatment and Expectations for HEMLIBRA

Professor Midori Shima, M.D., PhD.
Department of Pediatrics

Nara Medical University
Conflicts of Interest

Presenter: Midori Shima
Affiliation: Nara Medical University

- Lecture fees etc.
  Roche, Chugai, Bayer, Bioverativ Japan, CSL Behring, Novo Nordisk, Baxalta, Pfizer

- Research expenses
  Chugai, Bayer, CSL Behring, Novo Nordisk, Baxalta, Pfizer
“If the first son is circumcised and bleeds, and the second son does similarly, the third son must not be circumcised.”

Nashim (Laws on marriage, divorce, and vows)
## Numbers and Inheritance Modes of Surviving Patients with Congenital Coagulation Disorders in Japan

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of pts</th>
<th>Inheritance mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>5,326</td>
<td>XLR</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>1,129</td>
<td>XLR</td>
</tr>
<tr>
<td>Hemophilia AB</td>
<td>2</td>
<td>XLR</td>
</tr>
<tr>
<td>Von Willebrand disease</td>
<td>1,283</td>
<td>AD, AR</td>
</tr>
<tr>
<td>Congenital fibrinogen deficiency, low or impaired</td>
<td>75</td>
<td>AD, AR</td>
</tr>
<tr>
<td>Congenital prothrombin deficiency, low or impaired</td>
<td>7</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital Factor V deficiency, low or impaired</td>
<td>45</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital Factor VII deficiency, low or impaired</td>
<td>106</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital Factor X deficiency, low or impaired</td>
<td>23</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital Factor XI deficiency, low or impaired</td>
<td>39</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital Factor XII deficiency, low or impaired</td>
<td>31</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital Factor XIII deficiency, low or impaired</td>
<td>72</td>
<td>AR</td>
</tr>
<tr>
<td>Congenital Factor V/VIII deficiency, low or impaired</td>
<td>7</td>
<td>AR</td>
</tr>
</tbody>
</table>

XLR: X-linked recessive; AD: autosomal dominant; AR: autosomal recessive

Number of Bleeds and Differences in FVIII Activity

Severe

Moderate

Mild

<table>
<thead>
<tr>
<th>FVIII, FIX activity</th>
<th>classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>Severe</td>
</tr>
<tr>
<td>1% to 5%</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;5% to 30%</td>
<td>Mild</td>
</tr>
</tbody>
</table>

Uijl et al. Haemophilia 2011
### Number of Treated Bleeds by Bleeding Site in Hemophilia

<table>
<thead>
<tr>
<th>Type of bleed</th>
<th>No. of bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint bleed</td>
<td>1,776 (60.8%)</td>
</tr>
<tr>
<td>Muscle bleed</td>
<td>446 (15.3%)</td>
</tr>
<tr>
<td>Subcutaneous bleed</td>
<td>328 (11.2%)</td>
</tr>
<tr>
<td>Nosebleed</td>
<td>68 (2.3%)</td>
</tr>
<tr>
<td>Blood in urine</td>
<td>45 (1.5%)</td>
</tr>
<tr>
<td>Mouth bleed</td>
<td>41 (1.4%)</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>8 (0.3%)</td>
</tr>
<tr>
<td>Others</td>
<td>159 (5.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (0.6%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,920 (100%)</strong></td>
</tr>
</tbody>
</table>

Joint Bleeding and Hemophilic Arthropathy
Severe Bleedings

- Intra-cranial
- Cervical
- Gastrointestinal
- Spine
Hemostatic Treatment and Drug Products for Hemophilia

- Replacement therapies
  - Hemophilia A: Factor VIII products
    - Recombinant products
    - Plasma-derived products
  - Hemophilia B: Factor IX products
    - Recombinant products
    - Plasma-derived products

- Other hemostatic therapies
  - Desmopressin acetate (DDAVP)
  - Tranexamic acid
Advances in Treatment for Hemophilia

**Advances in treatment**

- Recombinant factor VIII agent (1993)
- Extended half-life recombinant factor VIII agent (2015)
- Recombinant factor IX agent (2010)
- Extended half-life recombinant factor IX agent (2014)
- Monoclonal purified product (1988)
- Plasma-derived concentrates (70s)
- Cryoprecipitate (1964)
- Whole blood or Fresh frozen plasma (40s-50s)

**Advances in drugs**

- HIV and HCV Infection (early 80s)

Principle of Hemophilia Treatment

On demand

Regular prophylaxis

Improve FVIII activity from severe to moderate

Uijl et al. Haemophilia 2011
Types of Regular Prophylaxis

- Primary regular prophylaxis
  - <2 years of age or >1 joint bleed
  - Severe disease
  - 25 – 40 U/kg, 3 times a week or every other day

- Secondary regular prophylaxis
Patient: MS
Severe hemophilia A
Age at onset: 6 years

250 U, twice a week  250 U, 3 times a week

Weight: 18 kg  Weight: 20 kg

Head injury  Marathon  Head injury  Head injury  Head injury

Source: Clinical case at Nara Medical University, Department of Pediatrics. This is an example of one clinical case. The clinical result does not apply to all cases.
Ratio of Patients with Severe Hemophilia Receiving Regular Prophylaxis

 Executing Rate

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients with Severe Hemophilia A</th>
<th>Patients with Severe Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>65 (1,464) (262)</td>
<td>48 (1,524) (266)</td>
</tr>
<tr>
<td>2013</td>
<td>72 (1,518) (268)</td>
<td>54 (1,664) (288)</td>
</tr>
<tr>
<td>2014</td>
<td>75 (1,664) (288)</td>
<td>60 (1,681) (302)</td>
</tr>
<tr>
<td>2015</td>
<td>79 (1,681) (302)</td>
<td>65 (1,681) (302)</td>
</tr>
<tr>
<td>2016</td>
<td>81 (1,537) (273)</td>
<td>68 (1,537) (273)</td>
</tr>
<tr>
<td>2017</td>
<td>83 (1,537) (273)</td>
<td>88 (1,537) (273)</td>
</tr>
</tbody>
</table>

Unmet Needs in Hemophilia Treatment

- Need for frequent intravenous injections
- The problem of inhibitors (anti-FVIII, IX allo-antibodies)
- Progression of hemophilic arthropathy
- Prevention of microhemorrhage
- Maintain higher trough levels
- Problems of medical expenses
Changes in FVIII Concentrate
Regular Prophylaxis 25 IU/kg, 3/W Dosing

FVIII administration

Source: Clinical case at Nara Medical University, Department of Pediatrics. This is an example of one clinical case. The clinical result does not apply to all cases.
Problems of Inhibitors

- **Allo-antibodies**
  Antibodies that recognize Factor VIII or Factor IX in drug products as non-self

- **Inhibitor titer**
  High titer: $\geq 5$ BU/mL
  Low titer: $< 5$ BU/mL

- **Inhibitor responsiveness**
  Low responder
  High responder
  Transient
Why is the Development of Inhibitors a Problem?

- Reduction / disappearance of hemostatic effect of FVIII, the standard of care
- Increase in bleeding
- Increase in target joints
- Rapid progress in arthropathy
- Reduction of physical activity
- Reduction of quality of life

Clinical deterioration will have a significant impact on patient’s life, and make treatment more difficult
Hemostasis during acute bleeding episodes or surgery

- Inhibitor neutralization: replacement products
- Hemostasis with bypassing agents:
  - Activated prothrombin complex concentrate
  - Recombinant activated Factor VII

Treatment to prevent bleeding

Treatment to eliminate inhibitors

- Immune tolerance induction (ITI) therapy
  - The success rate of ITI therapy in the good risk group is about 70%
  - There are no effective inhibitor treatment options for patients in the bad risk group

*Source: Blood Products Research Organization "Survey on immune tolerance induction therapy for hemophilia with inhibitors" 57 sites, (2000 and beyond)
Without inhibitors

- 1000 IU (74,000 yen/unit)
  - 3 injections / week: approx. 10 million yen / year
  - 3.5 injections / week: approx. 12 million yen / year

- 2000 IU
  - 3 injections / week: approx. 21 million yen / year
  - 3.5 injections / week: approx. 25 million yen / year

With inhibitors

approx. 60～100 million yen/year
Traumatic six bone fractures in a patient with high responding inhibitors

Source: Clinical case at Nara Medical University, Department of Pediatrics. This is an example of one clinical case. The clinical result does not apply to all cases.
### Top 10 High Cost Medical Care in 2016

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cost (Yen) / Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Von Willebrand disease</td>
<td>106,941,690</td>
</tr>
<tr>
<td>2 Hemophilia A</td>
<td>102,379,460</td>
</tr>
<tr>
<td>3 Hemophilia A</td>
<td>70,229,710</td>
</tr>
<tr>
<td>4 Hemophilia A</td>
<td>50,427,470</td>
</tr>
<tr>
<td>5 Hemophilia A</td>
<td>49,941,080</td>
</tr>
<tr>
<td>6 Hemophilia A</td>
<td>45,902,330</td>
</tr>
<tr>
<td>7 Hemophilia A</td>
<td>41,049,330</td>
</tr>
<tr>
<td>8 Hemophilia A</td>
<td>41,049,330</td>
</tr>
<tr>
<td>9 Hemophilia A</td>
<td>40,780,090</td>
</tr>
<tr>
<td>10 Hemophilia A</td>
<td>37,268,590</td>
</tr>
</tbody>
</table>

**Top100:**
- Hemophilia A: 23
- Hemophilia B: 6
- Heart disease: 47

Source: National Federation of Health Insurance Societies “H28 overview of expensive receipts for reimbursement”

63.4 billion yen + / year

Million yen

- Plasma-derived FVIII
- Recombinant FVIII
- Total

- 2013: 5,452
- 2014: 5,539
- 2015: 5,540
- 2016: 5,323
- 2017: 5,458

Created based upon data from "H24-28 Draft plans for stable supply of blood derivatives"
What is the mechanism of expression of FVIII functions?
FVIIIa Function and Concept of FVIIIa-Mimetic Bispecific Antibodies

$K_D = 0.3 \, \mu M$
$K_D = 1-3 \, \mu M$
$K_D = 1.52 \, \mu M$
$K_D = 1.85 \, \mu M$

Benefit of treatment with FVIII-mimetic bispecific antibody

- Subcutaneous injection is possible
- Long-acting (half-life, 30 days)
- Effective also in inhibitor patients
- Inhibitors against factor VIII not produced

Development of HEMLIBRA for Hemophilia A with Inhibitors

2003

Dept. of pediatrics, NMU
FVIII mimicking function
Treatment of hemophilia
Experience of clinical studies

Chugai
Antibody engineering technology

2012 Phase 1: Healthy adults (in Japan, Chugai)
2013 Phase 1/2: Hemophilia A (in Japan, Chugai)
2015 Phase 3 (international, Roche, Genentech, Chugai)

2015 Breakthrough therapy designation by FDA

2017 (16th November) Approval from FDA
2018 (27th February) Approval from EMA
2018 (23rd March) Approval from MHLW
Clinical Development of HEMLIBRA

Phase 1: Healthy adults and patients
→ Phase 1/2 (continuing study): Patients

Non-interventional studies: Patients (Primary objective: real-world treatment data)

HAVEN 1
Phase 3: Adult or adolescent inhibitor patients
once weekly

HAVEN 2
Phase 3: Pediatric inhibitor patients
Injections once weekly

HAVEN 3
Phase 3: Non-inhibitor patients
Injections once weekly or every 2 weeks

HAVEN 4
Phase 3: Inhibitor/Non-inhibitor patients
Injections once every 4 weeks

Approved in March 2018 in Japan

Approved in March 2018 in Japan

US BTD obtained
Application pending in Japan

Application pending in Japan

Phase 1 and 1/2 studies conducted in Japan
Others were global studies conducted jointly with Roche
HAVEN 1: Study Design

Patients were enrolled from Arm A to C in accordance with how bypass agents were used prior to the study. Arm D enrolled those patients who were unable to register prior to the closure of the three arms.

Prior episodic
n=53

Prior prophylactic
n=49

PwHA with inhibitors aged ≥12 years

2:1

R*1

PwHA with inhibitors on episodic / prophylactic treatment with bypassing agent(s)*2

Primary efficacy evaluation period
24 weeks

Arm A

HEMLIBRA (n=35)

Arm B

No prophylaxis (n=18)

Arm C

HEMLIBRA (n=49)

Arm D

HEMLIBRA (n=7)

HEMLIBRA

Source: Evaluation dossier for new drug approval, phase 3 global study (BH29884)
HAVEN 1: Treated Bleeds
HEMLIBRA prophylaxis (Arm A) vs no prophylaxis (Arm B)

Annual Bleeding Rate (ABR) of Treated Bleeds

- Arm A (n=35) HEMLIBRA prophylaxis: 2.9 (times/year)
- Arm B (n=18) no prophylaxis: 23.3 (times/year)

ABR ratio: 0.13
[95%CI: 0.057-0.277]
p < 0.0001

Percentage of Treated Zero Bleeds

- Arm A (n=35) HEMLIBRA prophylaxis: 62.9%
- Arm B (n=18) no prophylaxis: 5.6%

Median evaluation period (duration):
- Arm A (n=35): 29.3 weeks (0.1~48.9)
- Arm B (n=18): 24.1 weeks (23.0~26.0)

Source: Evaluation dossier for new drug approval, phase 3 global study (BH29884)
HAVEN 1: Treated Bleeds
Intra-individual comparison vs prior BPA prophylaxis (Arm C)

ABR of Treated Bleeds

Prior BPA prophylaxis (n=24)  HEMLIBRA prophylaxis (n=24)

ABR ratio 0.21
[95%CI: 0.089-0.486]
p=0.0003

ABR of All Bleeds

Prior BPA prophylaxis (n=24)  HEMLIBRA prophylaxis (n=24)

ABR ratio 0.23
[95%CI: 0.119-0.435]
p<0.0001

Source: Evaluation dossier for new drug approval, phase 3 global study (BH29884)
HAVEN 1: Safety Summary

Patients who received HEMLIBRA

<table>
<thead>
<tr>
<th>Total (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of adverse events (AEs), n</td>
</tr>
<tr>
<td>Total patients ≥1 AE, n (%)</td>
</tr>
<tr>
<td>Serious AE*</td>
</tr>
<tr>
<td>Thrombotic microangiopathy (TMA)**</td>
</tr>
<tr>
<td>Thrombotic event</td>
</tr>
<tr>
<td>Death**</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
</tr>
<tr>
<td>Related AE</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
</tr>
</tbody>
</table>

- **Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal hemorrhage
- Thrombotic events were skin necrosis/superficial thrombophlebitis in one patient, and cavernous sinus thrombosis in a second patient
- No patients tested positive for anti-drug antibodies

*Additional serious AEs included one event each of: iron deficiency anemia, sepsis, hemorrhosis, muscle hemorrhage, gastric ulcer hemorrhage, headache and hematuria. Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision.

Source: Johannes Oldenburg et al. ISTH 2017
HAVEN 2: Study Design

The target number of patients was 20 to 60. Primary efficacy evaluation period is 52 weeks. This interim analysis reviewed 20 patients.

Pediatric PwHA with inhibitors aged <12 years*1,2

Screening N=20–60

HEMLIBRA prophylaxis (n=20) *3

Interim data review

Primary efficacy analysis 52 weeks after last patient enrolled

HEMLIBRA prophylaxis (or 24-week safety follow-up of study drug)

BPA were used to treat bleeds regardless of the use of HEMLIBRA

*1: Patients aged 2< were not included in the interim analysis as the patient registration was conducted in stages depending on the age category.

*2: Patients aged 12-17 were enrolled if body weight< 40 kg

*3: Number of patients registered at the time of the interim analysis

Source: Evaluation dossier for new drug approval, phase 3 global study (BH29992)
HAVEN 2: Intra-individual Comparison vs prior BPA prophylaxis

Data sorted by HEMLIBRA ABR in descending order and then by descending efficacy period duration. Intraindividual comparison performed for 13 NIS patients on HAVEN 2 study for ≥12 weeks.

Treated bleeds: 2 (2 patients, 1 per each) / 13 patients (observation period: 106 – 291 days)

Treated bleeds ABR reduced by 99%

Source: Young et al. ASH 2017
## HAVEN 2: Safety Summary

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>HEMLIBRA 1.5 mg/kg QW (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>43</td>
</tr>
<tr>
<td>Total patients experiencing ≥1 AE, n (%)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Related AE</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Local injection-site reaction</td>
<td>3 (15.0)</td>
</tr>
</tbody>
</table>

- Serious AEs: mouth hemorrhage, appendicitis, catheter-site infection
- **All related AEs were mild injection-site reactions (3 patients; 9 events)**
- No thromboembolic or thrombotic microangiopathy events observed
- No patients tested positive for anti-drug antibodies

Source: Guy Young et al. ISTH 2017
## Phase III Studies of HEMLIBRA for Hemophilia A without Inhibitors

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Interval</th>
<th>Initiation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVEN3 ≥ 12 years, Non-inhibitor</td>
<td>Weekly Every 2 wks</td>
<td>Sep, 2016</td>
<td>152</td>
</tr>
<tr>
<td>HAVEN4 ≥ 12 years, inhibitor, Non-inhibitor</td>
<td>Every 4 wks</td>
<td>Jan, 2017</td>
<td>48</td>
</tr>
<tr>
<td>HOHOEMI &lt;12 years Including PUPs Non-inhibitor</td>
<td>Every 2 wks Every 4 wks</td>
<td>Oct, 2017</td>
<td>13</td>
</tr>
</tbody>
</table>

PUPs: previously untreated patients

Source: NCT02847637, NCT03020160, JapicCTI-173710
Concept of Early Use of HEMLIBRA for Prophylaxis

- Zero bleeding
- Higher activity
- Intact joints
- Protect from subclinical bleeds
- Prevent intracerebral hemorrhage
- No induction of FVIII inhibitors
- No need of ITI
Paradigm Shift of Hemophilia A Treatment

- Zero Joint Bleeding
- Intact Joint
- Maintain Higher Trough Levels
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