An Insight into Clinical Outcomes in Mild, Moderate, and Severe Hemophilia A (HA): A Preliminary Analysis of the CHESS II Study

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## Disclosures for Francis Nissen

- **Research Support/P.I.**
  - Received grants/research support from Novartis, GSK.

- **Employee**
  - F. Hoffmann-La Roche Ltd.

- **Consultant**
  - Received consultation fees from Actelion Pharmaceuticals Ltd.

- **Major Stockholder**
  - No relevant conflicts of interest to declare

- **Speakers Bureau**
  - No relevant conflicts of interest to declare

- **Honoraria**
  - No relevant conflicts of interest to declare

- **Scientific Advisory Board**
  - No relevant conflicts of interest to declare

- This study was supported by F. Hoffmann-La Roche Ltd.
The CHESS II study collected real-world data on the burden-of-illness in adult PwHA without FVIII inhibitors

- The previous CHESS I study captured the annualized economic and psychosocial burden of severe hemophilia\(^1\) and the CHESS PAEDS study assessed the burden-of-illness of moderate and severe hemophilia in the pediatric population\(^2\)
  - Both studies were conducted in five European countries (France, Germany, Italy, Spain, UK)\(^1,2\)

- However, there is a paucity of data on the clinical burden of HA across disease severity, especially in mild and moderate HA

- Aim of this interim analysis
  - To examine clinical outcomes by disease severity in adult PwHA without current FVIII inhibitors in relation to treatment strategy, in eight European countries (Denmark, France, Germany, Italy, Netherlands, Romania, Spain, and the UK)

CHESS, Cost of Haemophilia Across Europe: a Socioeconomic Survey; CHESS PAEDS, Cost of Haemophilia across Europe – a Socioeconomic Survey in a paediatric population; HA, hemophilia A; PwHA, persons with hemophilia A.

HA severity classification is based on the amount of FVIII clotting factor activity in the person’s blood

- HA, a congenital bleeding disorder caused by a deficiency in FVIII, is characterized by uncontrolled bleeding and musculoskeletal dysfunction

<table>
<thead>
<tr>
<th>HA severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td>23–30%</td>
<td>17–18%</td>
<td>51–59%</td>
</tr>
<tr>
<td>% FVIII level</td>
<td>5–&lt;40%</td>
<td>1–&lt;5%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Bleeding episodes
- Severe bleeding with major trauma or surgery
- Spontaneous bleeding is rare
- Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
- Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge

- Residual FVIII activity level accounts for ~70% of the bleeding phenotype, the remaining ~30% are potentially related to unexplained individual variables; thus some patients do not exhibit a bleed phenotype as traditionally expected based on their FVIII level

For this interim analysis, 12 months of retrospective data were captured from physicians and patients

1. Physician recruitment
   - 120 hematologists/hemophilia healthcare providers recruited from Denmark, France, Germany, Italy, Netherlands, Romania, Spain, UK

2. Physician profiling
   - Physicians completed workload survey and attitudinal profile online

3. Patient profiling
   - 787 web-based case report forms (CRFs) for treated patients ≥18 years old completed by physicians
     - This included patient’s medical history, consultations, clinical information, and healthcare resource utilization
     - 628 PwHA were recruited, 580 of which were included in the analysis; mild HA (n=97), moderate HA (n=199), severe HA (n=284)

4. Patient perspective
   - Paper-based PPIE questionnaire, covering non-medical costs, work impairment, and health status, was completed by the patients

HA, hemophilia A; PPIE, patient and public involvement and engagement; PwHA, persons with hemophilia A.
Baseline demographics and characteristics

- Bleed data were available for 580 PwHA without current FVIII inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Mild HA (n = 97)</th>
<th>Moderate HA (n = 199)</th>
<th>Severe HA (n = 284)</th>
<th>All (N = 580)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prophylactic</td>
<td>On-demand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>39.41 (14.8)</td>
<td>38.82 (15.1)</td>
<td>38.33 (14.5)</td>
<td>38.15 (14.4)</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>24.59 (2.4)</td>
<td>24.59 (3.0)</td>
<td>24.92 (2.9)</td>
<td>24.62 (2.8)</td>
</tr>
</tbody>
</table>

**Treatment strategy, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Prophylaxis*</th>
<th>On-demand†</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (2)</td>
<td>17 (9)</td>
<td>69 (71)</td>
</tr>
<tr>
<td></td>
<td>156 (55)</td>
<td>128 (45)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>175 (30)</td>
<td>216 (37)</td>
<td>189 (33)</td>
</tr>
</tbody>
</table>

*Includes both primary prophylaxis, where treatment has always been prophylactic, and secondary prophylaxis, where treatment was previously episodic or ‘on-demand’, and currently prophylactic;
†Includes both primary on-demand, where treatment has always been episodic or ‘on-demand’, and secondary on-demand, where treatment was previously prophylactic and is currently episodic or ‘on-demand’.

BMI, body mass index; HA, hemophilia A; PwHA, persons with hemophilia A; SD, standard deviation.
The mean ABR was >2 in PwHA without FVIII inhibitors in all disease severity categories.

Mean (±SD) ABR

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mean ABR (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (n = 97)</td>
<td>2.12 ±10.1</td>
</tr>
<tr>
<td>Moderate (n = 199)</td>
<td>3.06 ±7.5</td>
</tr>
<tr>
<td>On-demand treatment (n = 128)</td>
<td>3.92 ±8.9</td>
</tr>
<tr>
<td>Prophylactic treatment (n = 156)</td>
<td>3.90 ±3.1</td>
</tr>
<tr>
<td>All (N = 580)</td>
<td>3.32 ±3.1</td>
</tr>
</tbody>
</table>

Median ABR (IQR)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Median ABR (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (n = 97)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Moderate (n = 199)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>On-demand treatment (n = 128)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Prophylactic treatment (n = 156)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>All (N = 580)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

ABR is for the past 12 months.
ABR, annualized bleed rate; IQR, interquartile range; PwHA, persons with hemophilia A; SD, standard deviation.
The majority of patients with moderate and severe HA had \( \geq 2 \) bleeds a year.

% of patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mild ((n = 97))</th>
<th>Moderate ((n = 199))</th>
<th>On-demand treatment ((n = 128))</th>
<th>Prophylactic treatment ((n = 156))</th>
<th>All ((N = 284))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 bleeds</td>
<td>45</td>
<td>29</td>
<td>7</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>1 bleed</td>
<td>26</td>
<td>15</td>
<td>20</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>( \geq 2 ) bleeds</td>
<td>29</td>
<td>29</td>
<td>73</td>
<td>76</td>
<td>61</td>
</tr>
</tbody>
</table>

Percentages may add up to >100% due to rounding.
HA, hemophilia A.
Patients with moderate and severe HA receiving on-demand treatment had similar incidences of problem joints and joint surgery.

Joint damage in persons with mild, moderate, and severe HA

- **Target joint**: any joint that has been permanently damaged as a result of patients bleeding disorder, with or without persistent bleeding; a problem joint can be defined as having chronic joint pain and/or limited range of movement due to compromised joint integrity (i.e. chronic synovitis and/or hemophilic arthropathy).
- **Problem joint**: a joint that has been permanently damaged as a result of patients bleeding disorder, with or without persistent bleeding.
- **Joint surgery**: includes: arthrocentesis (joint aspiration), arthrodesis (joint fusion), arthroplasty (joint reconstruction/replacement), arthroscopy (joint examination/repair via endoscope), and synovectomy (removal of synovium).

<table>
<thead>
<tr>
<th>Severe (n = 284)</th>
<th>Mild (n = 97)</th>
<th>Moderate (n = 199)</th>
<th>On-demand treatment (n = 128)</th>
<th>Prophylactic treatment (n = 156)</th>
<th>All (N = 580)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of patients (%)</strong></td>
<td>8</td>
<td>17</td>
<td>23</td>
<td>45</td>
<td>46</td>
</tr>
</tbody>
</table>

Conclusions

• The CHESS II study addresses the lack of available data on clinical outcomes across disease severity, and is one of the largest datasets in mild/moderate HA available to date; the data presented here are from an interim analysis, with further data on a larger sample to follow.

• These data demonstrate that all PwHA experience bleeds regardless of disease severity; they also highlight the unmet need in patients with mild and moderate disease severity.

• Persons with mild and moderate HA appear to exhibit a clinical burden indicated by their ABR and frequency of bleeds.
  – The majority of patients with moderate disease experienced ≥2 bleeds, which may lead to irreversible, long-term joint damage.

• In patients with severe disease, mean ABR and frequency of bleeds were similar, regardless of treatment regimen.

• The proportions of patients with problem joints and the incidence of surgeries to affected joints were similar in patients with moderate and severe HA receiving on-demand treatment, indicating that HA may have a similar impact on quality of life in these patients.

ABR, annualized bleed rate; HA, hemophilia A; PwHA, persons with hemophilia A.
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  – Study investigators, coordinators, and site personnel.

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• The CHESS II study was approved by the University of Chester Ethics committee and was conducted in collaboration with the UK Haemophilia Society and governed by a steering committee chaired by Prof. Brian O’Mahony, Chief Executive of the Irish Haemophilia Society.

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