Hemophilia – next generation therapies

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1. Progress to date in hemophilia
2. Problems that remain
3. Next generation Factors
4. Developing therapies
5. Gene therapy
Progress in Hemophilia?

No other genetic disease has made the progress of hemophilia.

Cryoprecipitate 1970

New products

Why? Molecular structure of new stuff……
Zero to 186 mph in 16.7 seconds
Community Effort: Clinical trials in action

It takes a team = everyone at every level

Science
necessary, not sufficient

Enthusiasm
appreciate subjects on clinical trials

Simplicity = “focus on goal”
simple trial design with defined purpose

Regulatory Agencies
proper understanding

Hemophilia community is pretty wonderful
Progress in hemophilia

• Life expectancy in 1960 approx. **20 years**
• In 2013, almost **normal** life expectancy

• No other genetic disease has had that impressive track record of progress.
• What accounts for this progress?
Progress in hemophilia

Key reasons:
1. Science
2. Enthusiastic patients who demand progress
3. Profits to motivate the pharmaceutical companies

Track record of safety:
No patient harmed in 30 years of clinical trials in hemophilia
Next step for hemophilia

The half life of Factor VIII in cryoprecipitate is the same as the half life of current Factor VIII products

40 years without improvement in half life?

And now, profit has motivated scientists and pharmaceutical companies.....
New Products for hemophilia
December 2013

1. Factor X, supplement with FVIIa
2. Fusion Fc antibody: VIIa, VIII, IX
3. rFIX-albumin Fusion Protein
4. Single chain FVIII
5. Pegylated Factor VIII
6. Glycopegylated Factor IX-gp, phase I
7. TFPI inhibitors
8. Anti-sense RNA for antithrombin
9. Human cell line Factor VIII
10. Sialylated FVIII

Which product will win in the market place?
Which basketball team is better?
March Madness = Clinical trials in basketball

TFPI-I  KGN

GENE THERAPY

scFVIII  rFVIII-Fc

FIX-FP

FIX-GP

BAX 855

HEMOPHILIA

rFIX-Fc

CLINICAL TRIALS PRODUCE WINNERS
1. Progress to date in hemophilia
2. Problems that remain
3. Next generation Factors
4. Developing therapies
5. Gene therapy
What to fear in hemophilia in 2014?

Intracranial hemorrhage
occurs approximately 1 in 200 patients per year

Spontaneous bleeding
is a function of time with factor level < 1%

Central venous access devices
with associated medical complications

Life with hemophilia is not yet normal.....
Problems are due to “too low” Factor level

< 1 %

> 10 %

Near normal ?

To solve a problem, we should define the problem
Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylaxis for severe hemophilia A

For each additional hour below 1 IU dL\(^{-1}\) there was a 1.4\% increase in the annual bleed rate (CI 0.21–2.62\%).

what Factor VIII concentration is needed?

Problem = level needed for activity
Survival in men in the United Kingdom with hemophilia who were not infected with HIV and in the general male population of the United Kingdom in 1999.


Problem = level needed for survival
Clinical severity of hemophilia A: does the old classification still stand?

Problem = level needed to prevent joint bleeding

12 %

Haemophilia
simple equation for bleeding

Factor level × Activity level × Other genetic factors × Medical conditions = risk of bleeding

Each box is different for each individual
How long does factor last?
Time to 1%?

1. Some patients think factor lasts 100% for 2 days
2. Each individual is different

Problem = education

<table>
<thead>
<tr>
<th>Table 1. Observed factor (F)VIII half-life and recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
</tr>
<tr>
<td>Recovery (IU dL(^{-1}) per IU kg(^{-1}))</td>
</tr>
</tbody>
</table>
Figure 1. Effect of half-life on factor (FVIII) level following a bolus infusion

Collins et al. 2010

One size does not fit all
Speculation: will an individual have a different half life with a different product?
topics

1. Progress to date in hemophilia
   we’re pretty cool
1. Problems that remain
   but not perfect yet…..
2. Next generation Factors
3. Developing therapies
4. Gene therapy
March Madness = Clinical trials in basketball
Who missed this year’s dance?

CLINICAL TRIALS PRODUCE WINNERS
THIS SUMMER WE WILL.....phone our patients.....switch if they want to.......
B-LONG: Results from a Phase 3 Study of Safety, Efficacy, and Pharmacokinetics of Long-Lasting Recombinant Factor IX Fc Fusion Protein (rFIXFc) ALPROLIX

A-LONG: Results From a Phase 3 Study of Safety, Efficacy, and Pharmacokinetics of Long-Lasting Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) ELOCTATE

Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B.

Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A.
rFIXFc, a Monomeric Fc Fusion Protein

Fc fusion technology has been applied to FIX for the treatment of haemophilia B\textsuperscript{1,2}

- rFIXFc consists of a single molecule of FIX covalently attached to the dimeric Fc domain of human IgG\textsubscript{1,2}
- Produced in HEK 293 cells, enabling human glycosylation patterns

This technology leverages a natural pathway in which the Fc domain enables binding to the neonatal Fc receptor (FcRn)
- FcRn binding results in protection of IgG and Fc fusion proteins from degradation and facilitates their recycling.\textsuperscript{3}

rFIXFc, recombinant factor IX Fc fusion protein; rFIX, recombinant coagulation factor IX; IgG, immunoglobulin

rFVIII Fc Clinical Development Plan

**Phase 1/2a study**
Completed

**Phase 3 pivotal trial**
Completed

**Phase 3 paediatric study**

**Phase 3 extension study**

**Key inclusion criteria**
- Male ≥12 years old
- <1 IU/dL endogenous FVIII
- ≥150 previous EDs to FVIII
- No prior history of FVIII inhibitor

A-LONG

Kids A-LONG

ASPIRE

EDs, exposure days
A-LONG Study Objectives

Primary objectives

• To evaluate the safety and tolerability of rFVIIIFc
  — Inhibitor formation, adverse events
• To evaluate the efficacy of rFVIIIFc for prophylaxis, for episodic treatment, and during surgery
  — Annualised bleeding rate (ABR)

Secondary objectives

• To characterise the pharmacokinetic (PK) profile of rFVIIIFc in comparison with rFVIII (Advate®)
• To characterise the range of doses and schedules required to adequately prevent bleeding in a prophylaxis regimen and in a surgical setting, and to treat bleeding episodes in all treatment arms

Advate (Baxter Healthcare, Westlake Village, CA, USA) is an antihaemophilic factor (recombinant) plasma/albumin-free method
A-LONG Study Design

**Sequential PK**
(Advate® vs rFVIIIFc @ 50 IU/kg)

**Individualised prophylaxis**
rFVIIIFc, 25–65 IU/kg, 3- to 5-day interval
N=118

**Weekly prophylaxis**
rFVIIIFc, 65 IU/kg
N=24

**Episodic treatment**
rFVIIIFc 10–50 IU/kg as required
N=23

Arm 1
Current prophylaxis or episodic regimen

Arm 2
Current episodic regimen

Arm 3
Randomisation
Study Subjects

- Participating countries: 19
- Enrolling centres: 60
- Overall, 92.7% of subjects completed study
- 111 subjects had ≥50 EDs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>30 (24–43)</td>
</tr>
<tr>
<td>Age category, n (%)</td>
<td></td>
</tr>
<tr>
<td>12–17 years</td>
<td>13 (7.9)</td>
</tr>
<tr>
<td>18–64 years</td>
<td>151 (91.5)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>107 (64.8)</td>
</tr>
<tr>
<td>Black</td>
<td>10 (6.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>43 (26.1)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>41 (24.8)</td>
</tr>
<tr>
<td>North America</td>
<td>56 (33.9)</td>
</tr>
<tr>
<td>Other</td>
<td>68 (41.2)</td>
</tr>
</tbody>
</table>

IQR, interquartile range
### PK Comparison of rFVIIIFc and Advate®

**Sequential PK Subgroup, N=28**

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>rFVIIIFc geometric mean (95% CI)</th>
<th>Advate® geometric mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elimination</strong> $t_{1/2}$ (h)</td>
<td>19 (17.0, 21.1)</td>
<td>12.4 (11.1, 13.9)</td>
</tr>
<tr>
<td><strong>Time to 1% @ 50 IU/kg (d)</strong></td>
<td>4.9 (4.4, 5.5)</td>
<td>3.3 (3.0, 3.7)</td>
</tr>
<tr>
<td><strong>Clearance</strong> (mL/h/kg)</td>
<td>2.0 (1.7, 2.2)</td>
<td>3.0 (2.7, 3.4)</td>
</tr>
</tbody>
</table>

- Consistent improvement in PK parameters with rFVIIIFc compared with Advate®
- Prolongation of half-life predicted from nonclinical studies and consistent with limitations imposed by von Willebrand factor
  - Regardless of VWF level, rFVIIIFc offered improved half life and decreased clearance compared to Advate®
- PK parameters were comparable to those reported in the phase 1/2a trial

$P<0.001$ for rFVIIIFc / Advate ratio

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**One-stage clotting assay**

![Corrected plasma FVIII activity, IU/dl](chart)

- **rFVIIIFc (n=28)**
- **Advate® (n=28)**

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$t_{1/2}$, half-life; CI, confidence interval. $P<0.001$ for rFVIIIFc / Advate ratio
What did he just say?

Every subject experienced a significant increase in his personal FVIII half life, none had a marginal increase in half life.

The shortest 5% half life with FVIII-Fc subjects had longer half life than the longest 5% half life with Advate.
Prophylactic Dosing Summary

**Arm 1**
Individualised interval prophylaxis (25-65 IU/kg, q3–5 days)

- Dose adjusted based on PK to maintain factor levels
- Interval adjusted based on PK to maintain factor levels

- Median (min, max)** weekly dose (IU/kg)
  - Overall (n=117): 77.9
  - Last 3 months* (n=112): 77.7

- Median (min, max)** dosing interval (days)
  - Overall (n=117): 3.5
  - Last 3 months* (n=112): 3.5

- ~30% of Arm 1 subjects achieved a mean dosing interval of 5 days over last 3 months on study**

**Arm 2**
Weekly prophylaxis (65 IU/kg q7 days)

- Constant dose and interval throughout study

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*Based on last 3 months on study, for subjects with ≥6 months on study
**The “box” and “whiskers” represent 25%-75% range, and min/max, respectively
Primary Endpoint
Annualised Bleeding Rates

Arm 1: Individualised prophylaxis (N=117) - ABR, median (IQR) 1.6 (0.0–4.7)

Arm 2: Weekly prophylaxis (N=23) - ABR, median (IQR) 3.6 (1.9–8.4)

Arm 3: Episodic treatment (N=23) - ABR, median (IQR) 33.6 (21.1–48.7)
ABR Subgroup Analyses
Individualised Prophylaxis (Arm 1)

Results of subgroup analyses were consistent with that of primary analysis.

Pre-study regimen, prior bleeding episodes, and number of target joints did not affect ABR of subjects in the prophylaxis arm.

* Only Arm 1 had sufficient subjects for subgroup analyses
Additional Efficacy Results

Control of bleeding

- 87.3% of bleeding episodes controlled by 1 injection of rFVIIIIFc
- 97.8% of bleeding episodes controlled by ≤2 injections
- Median dose per injection to control a bleeding episode was 27.35 IU/kg
- Median total dose per bleeding episode was similar at 28.23 IU/kg

Perioperative management

- Assessed in 9 patients undergoing 9 major surgical procedures, most of which were orthopaedic surgeries
- Haemostatic efficacy of rFVIIIIFc rated excellent or good in 100% of surgeries
A-LONG Safety Summary

- No serious adverse events were assessed to be related to rFVIIIFc
- Most common adverse events (incidence of ≥5%) that occurred outside of the perioperative management arm were nasopharyngitis, arthralgia, headache, and upper respiratory tract infection
- There was 1 death secondary to polysubstance overdose (suicide) in a patient with prior history of depression, which was assessed as unrelated to rFVIIIFc by the investigator

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>None</td>
</tr>
<tr>
<td>Serious vascular thrombosis</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune Responses</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitors to rFVIIIFc</td>
<td>None*</td>
</tr>
<tr>
<td>Non-neutralising antibodies (NNAs)</td>
<td>5 patients tested positive at baseline; 6 tested positive on study† All low titre and had no discernible clinical impact</td>
</tr>
</tbody>
</table>

* The presence of inhibitors was assessed by the Nijmegen modification of the Bethesda assay. An inhibitor test result of ≥0.6 BU/mL was considered positive. Inhibitor incidence rate was 0% (95% CI: 0%, 3.3%) based on 110 subjects who had >50 EDs and a valid inhibitor test.
†At the final visit, NNAs were no longer detected in 2 of the 5 subjects who tested positive at baseline; 4 of the 6 subjects who tested positive on study had a following negative result.

The adverse event profile was generally consistent with that expected in patients with haemophilia A
PK Comparison Between rFVIIIFc and Advate®
Sequential PK Subgroup, N=28

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>rFVIIIFc geometric mean (95% CI)</th>
<th>rFVIII (Advate®) geometric mean (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC normalised to dose (IU*h/dL per IU/kg)</td>
<td>51.2 (45.0, 58.4)</td>
<td>32.9 (29.3, 36.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elimination $t_{1/2}$ (h)</td>
<td>19.0 (17.0, 21.1)</td>
<td>12.4 (11.1, 13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clearance (mL/h/kg)</td>
<td>2.0 (1.7, 2.2)</td>
<td>3.0 (2.7, 3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean residence time (h)</td>
<td>25.2 (22.7, 27.9)</td>
<td>16.8 (15.2, 18.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>49.1 (46.6, 51.7)</td>
<td>51.2 (47.2, 55.5)</td>
<td>0.197</td>
</tr>
<tr>
<td>Incremental recovery (IU/dL per IU/kg)</td>
<td>2.2 (2.1, 2.4)</td>
<td>2.4 (2.2, 2.5)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

- rFVIIIFc showed significantly improved clearance-related PK parameters versus rFVIII
- Baseline von Willebrand factor antigen concentration was positively correlated with rFVIIIFc half-life (n=155; r=0.67; $P<0.0001$), which is consistent with Phase 1/2a results

* P value for rFVIIIFc / Advate ratio; AUC, area under the curve
Non-Neutralising Antibodies

- Five patients tested positive for NNAs at baseline
- Six additional patients who tested negative at baseline had a positive test on study
- NNAs were observed in 11 (6.7%) patients, which is consistent with or lower than previously reported rates in the inhibitor-negative haemophilia A population
- All NNAs were low titer and directed against FVIII, not Fc
- In 1 patient, NNA presence resulted in a transient effect on clearance at the week 14 PK assessment but did not impact clinical outcome. This patient continued on to the extension study
- Overall, NNAs had no discernible clinical impact
rFIXFc, a Monomeric Fc Fusion Protein

- Fc fusion technology has been applied to FIX for the treatment of haemophilia B\(^1,2\)
  - rFIXFc consists of a single molecule of FIX covalently attached to the dimeric Fc domain of human IgG\(_1\)\(^1,2\)
  - Produced in HEK 293 cells, enabling human glycosylation patterns
- This technology leverages a natural pathway in which the Fc domain enables binding to the neonatal Fc receptor (FcRn)
  - FcRn binding results in protection of IgG and Fc fusion proteins from degradation and facilitates their recycling\(^3\)

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rFIXFc, recombinant factor IX Fc fusion protein; rFIX, recombinant coagulation factor IX; IgG, immunoglobin

rFIXFc Clinical Development Plan

Key Inclusion Criteria
- Male ≥12 years old
- ≤2 IU/dL endogenous FIX
- ≥100 previous EDs to FIX
- No history of FIX inhibitor

B-LONG

Phase 1/2a*
Completed

Phase 3
Pivotal Trial
Completed

Phase 3 Paediatric Study

Phase 3 Extension Study

Kids
B-LONG

B-YOND

rFIXFc; recombinant factor IX Fc fusion protein; FIX, human coagulation factor IX; EDs, exposure days
B-LONG Study Objectives

**Primary Objectives**

- Safety and tolerability of rFIXFc
  - Inhibitors, adverse events
- Efficacy of rFIXFc in all treatment arms
  - Annualised bleeding rate (ABR), prophylaxis vs episodic treatment

**Secondary Objectives**

- Characterise pharmacokinetic parameters of rFIXFc
- Compare rFIXFc pharmacokinetics with rFIX (BeneFIX®)

rFIXFc; recombinant factor IX Fc fusion protein

B-LONG Study Design

**Arm 1**
Weekly Prophylaxis
50 IU/kg q7 days, dose adjusted to maintain factor levels

N=63

**Arm 2**
Individualised Interval Prophylaxis
100 IU/kg starting q10 days, interval adjusted to maintain factor levels

N=29

**Arm 3**
Episodic (On-Demand) Treatment

N=27

**Arm 4**
Perioperative Management

N=12*

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rFIX, recombinant factor IX; rFIXFc, recombinant factor IX Fc fusion protein; PK, pharmacokinetics

†PK Subgroup; dosed with 50 IU/kg rFIX then crossover to 50IU/kg rFIXFc

*Arm 4 only (n=4); initially in Arm 4, then Arm 1 (n=2); joined from Arms 1 or 3 (n=6)
Study Subjects’ Demographics and Disposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (min–max)</td>
<td>30 (12–71)</td>
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<tr>
<td>Age category, n (%)</td>
<td></td>
</tr>
<tr>
<td>12–17 years</td>
<td>11 (8.9)</td>
</tr>
<tr>
<td>18–64 years</td>
<td>110 (89.4)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>73 (59.3)</td>
</tr>
<tr>
<td>Black</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>29 (23.6)</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>36 (29.3)</td>
</tr>
<tr>
<td>North America</td>
<td>38 (30.9)</td>
</tr>
<tr>
<td>Other</td>
<td>49 (39.8)</td>
</tr>
</tbody>
</table>

- Overall 93.5% of subjects completed study
- At end of study, 55 subjects completed ≥50 EDs and had a valid inhibitor test
PK Comparison: rFIXFc versus BeneFIX®
Sequential PK Subgroup (n=22)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>rFIXFc Geometric Mean (95% CI)</th>
<th>BeneFIX® Geometric Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination $t_{1/2}$</td>
<td>82.12 hours* (71.39, 94.46)</td>
<td>33.77 hours† (29.13, 39.15)</td>
</tr>
<tr>
<td>Clearance (mL/h/kg)</td>
<td>3.19 (2.84, 3.59)</td>
<td>6.34 (5.64, 7.13)</td>
</tr>
<tr>
<td>Time to 1% @ 50 IU/kg</td>
<td>11.2 days (10.2, 12.4)</td>
<td>5.1 days (4.6, 5.7)</td>
</tr>
</tbody>
</table>

*Terminal half-life extension to 82 hours by 2-compartmental analysis
†Using 96-hour PK sampling schedule. Analysis using data up to 48 hours yielded median half-life (95% CI) of 17.04 (15.89, 18.26) hours for BeneFIX®, which is consistent with the mean half-life of 18.1 ± 5.1 hours stated in the Prescribing Information

P<0.001 for rFIXFc / BeneFIX® ratio for listed parameters
Prophylactic Dosing Summary

**Weekly Prophylaxis** (initially 50 IU/kg every 7 days)
*Dose adjusted based on PK and bleeding frequency*

**Arm 1**
- Overall (n=61)
  - Median (IQR) weekly dose (IU/kg): 45.2
  - Last 3 months (n=58)
    - Median (IQR) weekly dose (IU/kg): 40.5

**Arm 2**
- Individualised Interval Prophylaxis (initially: 100 IU/kg every 10 days)
  - Interval adjusted based on PK and bleeding frequency
- Overall (n=26)
  - Median (IQR) dosing interval (days): 12.5
  - Last 3 months (n=26)
    - Median (IQR) dosing interval (days): 14.0

~50% of Arm 2 subjects achieved ≥14 day dosing interval

*Based on last 3 months on study, for subjects with ≥ 6 months on study

**Data are presented as median, IQR, and min/max. The “box” and “whiskers” represent 25%-75% range (IQR), and min/max, respectively**
Primary Efficacy Endpoint
Annualised Bleeding Rate per Subject

**Arm 1**
Weekly Prophylaxis

**Arm 2**
Individualised Interval Prophylaxis

**Arm 3**
Episodic (On-Demand) Treatment

**Annualised Bleeding Rate, Median (IQR)**

- **Arm 1**: 2.95 (1.01, 4.35)
- **Arm 2**: 1.38 (0.0, 3.43)
- **Arm 3**: 17.69 (10.77, 23.24)

**23.0% of patients in arm 1 and 42.3% of patients in arm 2 experienced no bleeding episodes**

**IQR**, interquartile range
ABR Subgroup Analyses

Weekly Prophylaxis (Arm 1)

†Arm 1 was the only arm with a sufficient number of patients to display subgroup analyses graphically (Arm 1, n=63; Arm 2, n=29; Arm 3, n=27).
‡Includes all Arm 1 subjects, independent of whether pre-study regimen was prophylaxis or episodic treatment.

All prespecified subgroup analyses were consistent with the primary efficacy analysis, showing a reduction in ABR in all demographic and disease-based subgroups.

†Arm 1 was the only arm with a sufficient number of patients to display subgroup analyses graphically (Arm1, n=63; Arm 2, n=29; Arm 3, n=27).
‡Includes all Arm 1 subjects, independent of whether pre-study regimen was prophylaxis or episodic treatment.

ABR, annualised bleeding rate; IQR, interquartile range
Secondary Efficacy Results

Control of bleeding

• 90.4% of bleeding episodes controlled by 1 injection of rFIXFc
• 97.3% of bleeding episodes controlled by ≤2 injections of rFIXFc

Median dose per injection (Arms 1-3): 46.1 IU/kg
Total dose per bleeding episode (Arms 1-3): 47.0 IU/kg

Perioperative Management

▪ There were 14 major surgical procedures in 12 subjects, including knee arthroscopy (n=1), arthroscopic ankle fusion (n=1), knee replacement (n=5), and other (n=7)†

Haemostatic efficacy of rFIXFc rated ‘excellent’ or ‘good’ in 100% of surgeries

†Other types of surgery included finger amputation, closure of intestinal fistula; external fixation of “Ilizarov” in right knee; dental extractions, incision and drainage; pilonidal cyst, incision and drainage; tendon transfer/ulnar nerve release

51rFIXFc, recombinant factor IX Fc fusion protein
Safety summary

- The AE profile was consistent with that expected in the haemophilia B population
- The most common AEs (incidence of ≥5% in Arms 1, 2, and 3) were: nasopharyngitis, influenza, arthralgia, upper respiratory infection, hypertension, and headache
- There were no reports of vascular thrombotic events, serious hypersensitivity, or anaphylaxis
- One serious adverse event (SAE) was assessed as possibly related to rFIXFc treatment by the investigator: obstructive uropathy in the setting of haematuria
  - Patient continued treatment with study drug and event resolved with medical management
- Two subjects discontinued due to AEs: one subject required surgery for infected knee prosthesis and the other suffered injuries in a motorcycle accident (both assessed as unrelated to rFIXFc)
Safety summary

- No inhibitors† were detected in any patients.

- Low-titer or borderline-positive (maximum two-fold above lowest measurable titer) non-neutralizing antibodies (NNAs) were detected in four patients at screening/baseline:
  - Three subjects tested positive prior to study drug and reverted to negative on study; 1 tested borderline-positive during screening and pre dose, and remained borderline-positive throughout study.
  - These transient, low-titer NNAs did not affect rFIXFc pharmacokinetics and had no discernible clinical impact throughout the study.

†In 55 subjects with ≥50 rFIXFc exposure days, the incidence of inhibitors (95% CI) was 0% (0%, 6.49%)
Extended PK profile

Potential for less frequent infusions for prophylaxis, compared with BeneFIX®

Low ABRs with routine prophylaxis

Prophylactic dosing every 1 to 2 weeks with rFIXFc resulted in:

- 83% reduction in ABR† with Weekly Prophylaxis (Arm 1) vs. Episodic treatment (Arm 3)
- 87% reduction in ABR† with Individualised Interval Prophylaxis (Arm 2) vs. Episodic treatment (Arm 3)

Excellent control of bleeding

rFIXFc controlled nearly all bleeding events (97%) with 1 or 2 injections, 14 major surgeries

Favorable safety profile

No inhibitors were observed in any subjects; AE profile was consistent with the background characteristics of the haemophilia B population

†Based on analysis of bleeding rate ratios using a negative binomial regression model

rFIXFc, recombinant factor IX Fc fusion protein; PK, pharmacokinetic; ABR, Annualised Bleeding Rate; AE, adverse event
## PK Parameters of rFIXFc and rFIX

### Sequential PK Subgroup, N=22

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>rFIXFc PK Geometric Mean (95% CI)</th>
<th>rFIX PK Geometric Mean (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Terminal t½</strong></td>
<td>82.12 h* (71.39, 94.46)</td>
<td>33.77 h (29.13, 39.15) †</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Clearance (mL/h/kg)</strong></td>
<td>3.19 (2.84, 3.59)</td>
<td>6.34 (5.64, 7.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Vss (mL/kg)</strong></td>
<td>314.8 (277.8, 356.8)</td>
<td>261.1 (222.9, 305.9)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>DNAUC (IU*h/dL per IU/kg)</strong></td>
<td>31.32 (27.88, 35.18)</td>
<td>15.77 (14.02, 17.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MRT (h)</strong></td>
<td>98.60 (88.16, 110.29)</td>
<td>41.19 (35.98, 47.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Incremental recovery (IU/dL per IU/kg)</strong></td>
<td>0.92 (0.77, 1.10)</td>
<td>0.95 (0.81, 1.10)</td>
<td>0.713</td>
</tr>
</tbody>
</table>

**PK sampling schedule:**
- rFIX: 0, 10 minutes, 1, 3, 6, 24, 48, 72, 96 hours
- rFIXFc: 0, 10 minutes, 1, 3, 6, 24, 48, 96, 144,168,192, 240 hours

---

* Terminal half-life extension to 82 hours by 2-compartmental analysis
† Using 96-hour PK sampling schedule. Analysis using data up to 48 hours yielded terminal half-life of 17.04 (15.89, 18.26) for rFIX, consistent with previous studies. Compared to the 82.12 hour half-life for rFIXFc, this represents a 4.8-fold increase with rFIXFc vs rFIX.

rFIXFc, recombinant factor IX Fc fusion protein; rFIX, recombinant factor IX; t½, half-life; Vss, Steady-state volume of distribution; DNAUC, Dose normalised area under the FIX activity time curve; MRT, mean residence time; CI, confidence interval.
### Summary of Adverse Events AE

**Table S4. Summary of Adverse Events AE**

<table>
<thead>
<tr>
<th>Arm 1: Weekly Prophylaxis (Fixed Interval) (N=63)</th>
<th>Arm 2: Individualized Interval Prophylaxis (Fixed Dose) (N=29)</th>
<th>Arm 3: Episodic Treatment (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs, n</td>
<td>158</td>
<td>76</td>
</tr>
<tr>
<td>Patients with ≥1 AE</td>
<td>45 (71.4)</td>
<td>23 (79.3)</td>
</tr>
<tr>
<td>Most common AEs (≥3%), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (20.6)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>5 (7.9)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (9.5)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (6.3)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3.2)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (4.8)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (4.8)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (4.8)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (4.8)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>2 (3.2)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3 (4.8)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Patients with ≥1 SAE†</td>
<td>5 (7.9%)</td>
<td>4 (13.8%)</td>
</tr>
</tbody>
</table>

*For patients with ≥1 AE, percentages are rounded to the nearest whole number. For patients with ≥1 SAE, percentages are rounded to the nearest whole number.*
Dose and dose interval of rFIX-Fc

Average weekly dose during last 3 months on study, Arm 1 (n=58)

Average dosing interval during last 3 months on study, Arm 2 (n=26)
Estimation of Half-life for rFIX vs rFIXFc
Sequential PK Subgroup, N=22

- Terminal $t_{1/2}$ for rFIX (33.8 hours) measured over 96 hours in this study was substantially longer than that reported in the product insert (~18 hours), which is based on 48-hour PK sampling.
- Re-analysis of rFIX PK using data up to only 48 hours resulted in a shorter terminal $t_{1/2}$ (~17 hours), consistent with previous reports.

<table>
<thead>
<tr>
<th>PK Sampling Source</th>
<th>Terminal $t_{1/2}$ (h) Arithmetic Mean (SD)</th>
<th>Terminal $t_{1/2}$ (h) Geometric Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rFIX package insert</td>
<td>18.1 (5.1)</td>
<td>--</td>
</tr>
<tr>
<td>Study rFIX estimate (48 h)</td>
<td><strong>17.2 (2.7)</strong></td>
<td><strong>17.0 (15.9, 18.3)</strong></td>
</tr>
<tr>
<td>Study rFIX estimate (96 h)</td>
<td>35.7 (13.6)</td>
<td>33.8 (29.1, 39.2)</td>
</tr>
<tr>
<td>Study rFIXFc (96 h)</td>
<td>--</td>
<td><strong>82.1 (71.4, 94.5)</strong></td>
</tr>
</tbody>
</table>

Note: Terminal half-life estimates are based on 2-compartmental analysis.

rFIXFc, recombinant factor IX Fc fusion protein; rFIX, recombinant factor IX; $t_{1/2}$, half-life
Factor IX levels after surgery – severe hemophilia B

Day 7
Day 13

Total knee Replacement (second knee)

30 days: Only 20% total factor used
Need to play the “Brackets”

1. Fc fusion technology is based on natural mechanisms
   Has been used in the clinic for over a decade
   with other proteins
2. Has now been used for over a year
   in >360 subjects with hemophilia
3. Every patient experienced an increase in half life,
   All happily continued the extension trial
4. No unexpected safety concerns
5. No inhibitors, none expected

Same vial mixing, same infusion methods,
excellent patient familiarity
topics

1. Progress to date in hemophilia
2. Problems that remain
3. Next generation Factors
4. Developing therapies
5. Gene therapy
Developing therapies

Still in early rounds......
Developing therapies

1. None published Phase 3 yet
2. Two phase 3 clinical trials halted due to formation of neutralizing antibodies
   Factor VIIa with promise and only
   “3 conservative amino acid changes”
3. One phase 1 clinical trial halted due to increased bleeding in normal volunteers
4. Be alert for unexpected safety concerns
   “not all men are mice.....”
Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients

Elena Santagostino, Claude Negrier, Robert Klamroth, Andreas Tiede, Ingrid Pabinger-Fasching, Christine Volgt, Iris Jacobs and Massimo Morfini
Gene therapy

1. last published in December 2011
   Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. Nathwani AC et al
   total of 9 subjects world wide hemophilia B

   update report at ASH in December 2013

   “no safety signals,
   levels of 2-3% continue”
Gene therapy

Therapeutic levels of FVIII following a single peripheral vein administration of rAAV vector encoding a novel human factor VIII variant.


Blood. 2013 Apr 25;121(17):3335-44.

A 5.7-kb rAAV-expression cassette (rAAV-HLP-codop-hFVIII-N6) containing a codon-optimized hFVIII cDNA in which a 226 amino acid (aa) B-domain spacer replaced the entire B domain and a hybrid liver-specific promoter (HLP) mediated 10-fold higher hFVIII levels in mice compared with non-codon-optimized variants.

A further twofold improvement in potency was achieved by replacing the 226-aa N6 spacer with a novel 17-aa peptide (V3) in which 6 glycosylation triplets from the B domain were juxtaposed.
Gene therapy

Therapeutic levels of FVIII following a single peripheral vein administration of rAAV vector encoding a novel human factor VIII variant.


Blood. 2013 Apr 25;121(17):3335-44.

Stable hFVIII expression at 15 ± 4% of normal was observed at this dose in a nonhuman primate. hFVIII expression above 100% was observed in 3 macaques that received a higher dose. These animals developed neutralizing anti-FVIII antibodies that were abrogated with transient immunosuppression.
Not every team gets it right......
...and unforeseen consequences may occur.

Stay tuned......

The USAF and USN announced today that the first ever C-17 carrier landing has been a total success... In other news, the USAF and USN have launched a study to determine the optimal method for getting a C-17 off of an aircraft carrier.
Next steps in Hemophilia? Confused, excited....

On the telephone: patient will be asked if he wants to switch, and we will ship the new factor unless he has a personal reason to continue with the old stuff.

And he will be told:

**Even better products may be coming soon (why wait?),**
**And soon only**
**if all continue to participate and join/support clinical trials enthusiastically working together.**
Any questions?

Future California hemophilia clinic