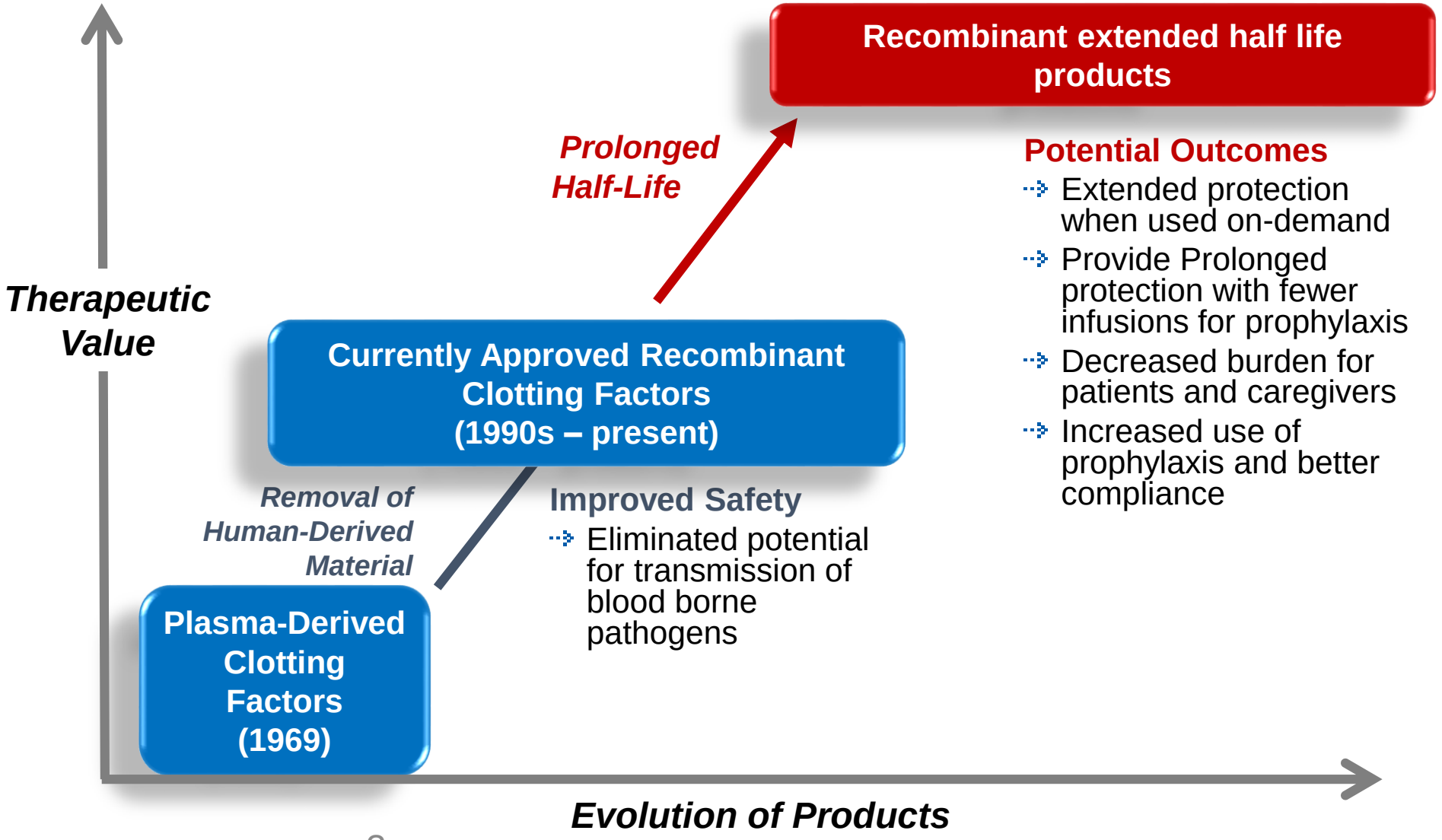
Barry White

Update

- Switch of all factor IX patients to extended half life product
- Gene therapy for factor IX and factor VIII
- Lighthouse project

Evolution of Haemophilia Treatment



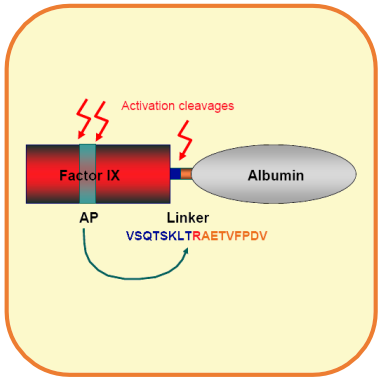
HALF-LIFE IMPROVEMENT

- Products with improved half-life will have the following potential benefits for prophylaxis
  - Less frequent injections
  - Higher trough levels on prophylaxis
  - Avoid need for central lines
  - Improved adherence

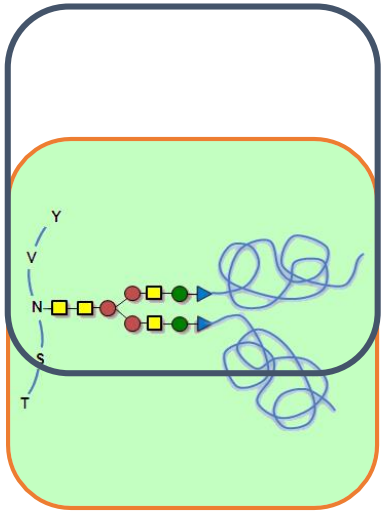
- Products with improved half-life will have the following potential benefits for acute treatment/surgery
  - Higher levels after a bleed
  - Less frequent infusions after surgery
  - Avoid need for central lines

R&D FOR LONGER HALF-LIFE OF FIX

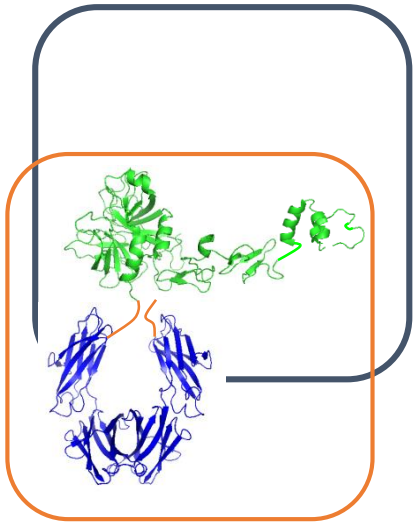
FIX



FIX albumin fusion



Glyco-pegylated FIX



rFIXFc fusion

HALF-LIFE OF DIFFERENT PROTEINS

Proteins	Half-life
Immunoglobulins	3 to 4 weeks
Albumin	19 days
Factor IX	18 hours
Factor VIII	9-13 hours

IgG Fc Fusion Technology: Currently Approved Products

Drug	Fusion Partner	Circulation Half-Life	Indication	First FDA Approval (EMA approval)	Company
Etanercept (Enbrel®)[1]	TNFα receptor-1	4 days	Rheumatoid arthritis	1998 (2000)	Amgen
Abatacept (Orencia®)[2]	CTLA-4	13 days	Rheumatoid arthritis	2005 (2007)	BMS
Belatacept (Nulojix®)[3]	CTLA-4 (mutant)	8–10 days	Transplant rejection	2011 (2011)	BMS
Alefacept (Amevive®)[4]	LFA-3	11 days	Psoriasis	2003 (NA)	Astellas Pharma
Rilonacept (Arcalyst®)[5]	IL-1R-I , IL-1RAcP (cytokine trap)	9 days	Autoinflammation	2008 (2009)	Regeneron
Romiplostim (Nplate®)[6]	TPO-R agonist peptide	3.5 days	Idiopathic thrombocytopenic purpura	2008 (2009)	Amgen
Aflibercept (Eylea®)[7] (Zaltrap)[8]	VEGFR1/VEGFR2 (cytokine trap)	5–6 days	Macular degeneration Metastatic Colorectal Cancer	2011 (2012)	Regeneron

FDA=Food and Drug Administration; TNFα=tumor necrosis factor alpha; CTLA-4=cytotoxic T-lymphocyte antigen; LFA-3=lymphocyte function-associated antigen 3; IL-1R-I=interleukin 1 receptor type 1; IL-1R-AcP=interleukin 1 receptor accessory protein; TPO-R=thrombopoietin receptor; VEGFR=vascular endothelial growth factor receptor.

1. Enbrel (etanercept) [package insert]. Thousand Oaks, CA: Amgen; 2011; 2. Orencia (abatacept) [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011; 3. Nulojix (belatacept) [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011; 4. Amevive (alefacept) [package insert]. Deerfield, IL: Astellas Pharma; 2011; 5. Kapur S, Bonk ME. *P T.* 2009;34:138-141; 6. Nplate (romiplostim) [package insert]. Thousand Oaks, CA: Amgen; 2012; 7. Eylea (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals; 2011.8. Zaltrap (ziv-aflibercept) [package insert]. Regeneron Pharmaceuticals /sanofi-aventis USLLC.2012.

What is Alprolix® (rFIXFc)?

Date of Preparation: February 2017. NP-2043

What is rFIXFc?

- rFIXFc is a recombinant fusion protein, composed of **recombinant factor IX covalently fused to the Fc domain of human immunoglobulin G1** (IgG1).[1,2]
- **rFIXFc was developed to** extend the half-life of factor IX, in order to **achieve prolonged haemostatic protection** in patients with haemophilia B and to raise current standards of care.[2,3]
- **Alprolix® is the trade name for rFIXFc.**[4]

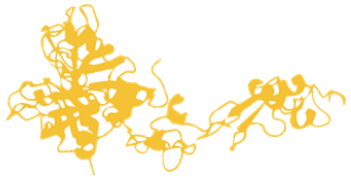
rFIXFc: Recombinant factor IX Fc fusion protein

1. Dumont et al. *Blood* 2012 **2.** Peters et al. *Blood* 2010 **3.** Powell et al. *Blood* 2012 **4.** Sobi Press Release. May 2016

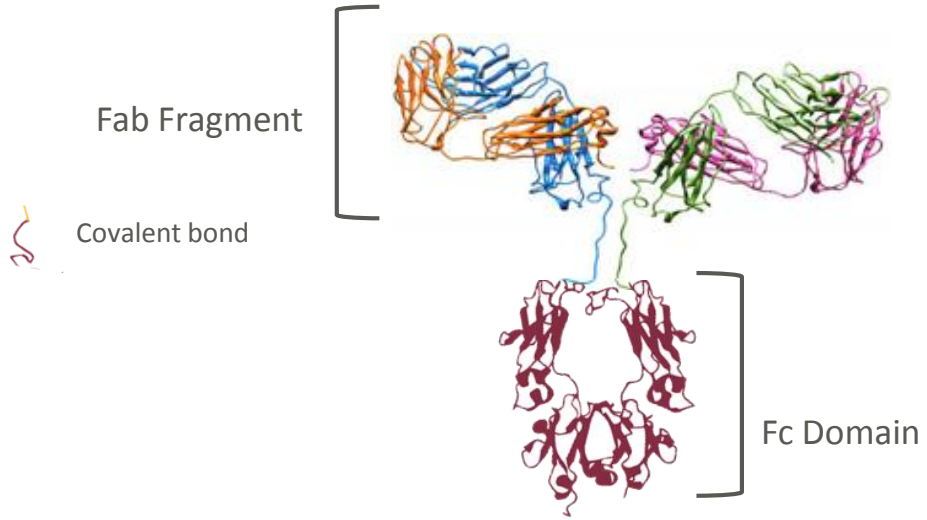
Date of Preparation: February 2017. NP-2043

rFIXFc (Alprolix®)

rFIX



Human IgG

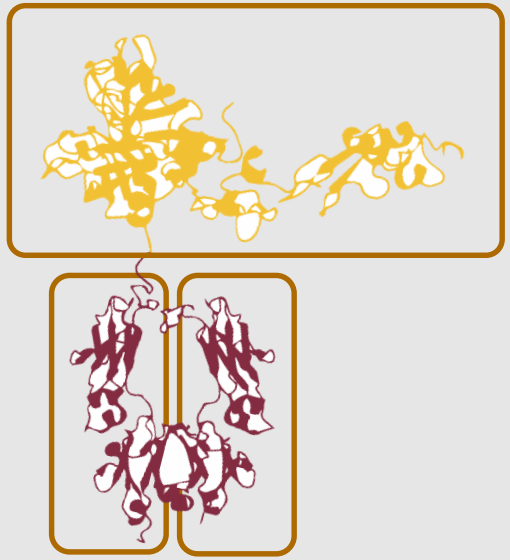


Alprolix®: A recombinant Fc fusion protein

Features of rFIXFc and Fc fusion

rFIXFc fusion protein[1,2]

Effector molecule



Fc domain

rFIXFc and Fc fusion

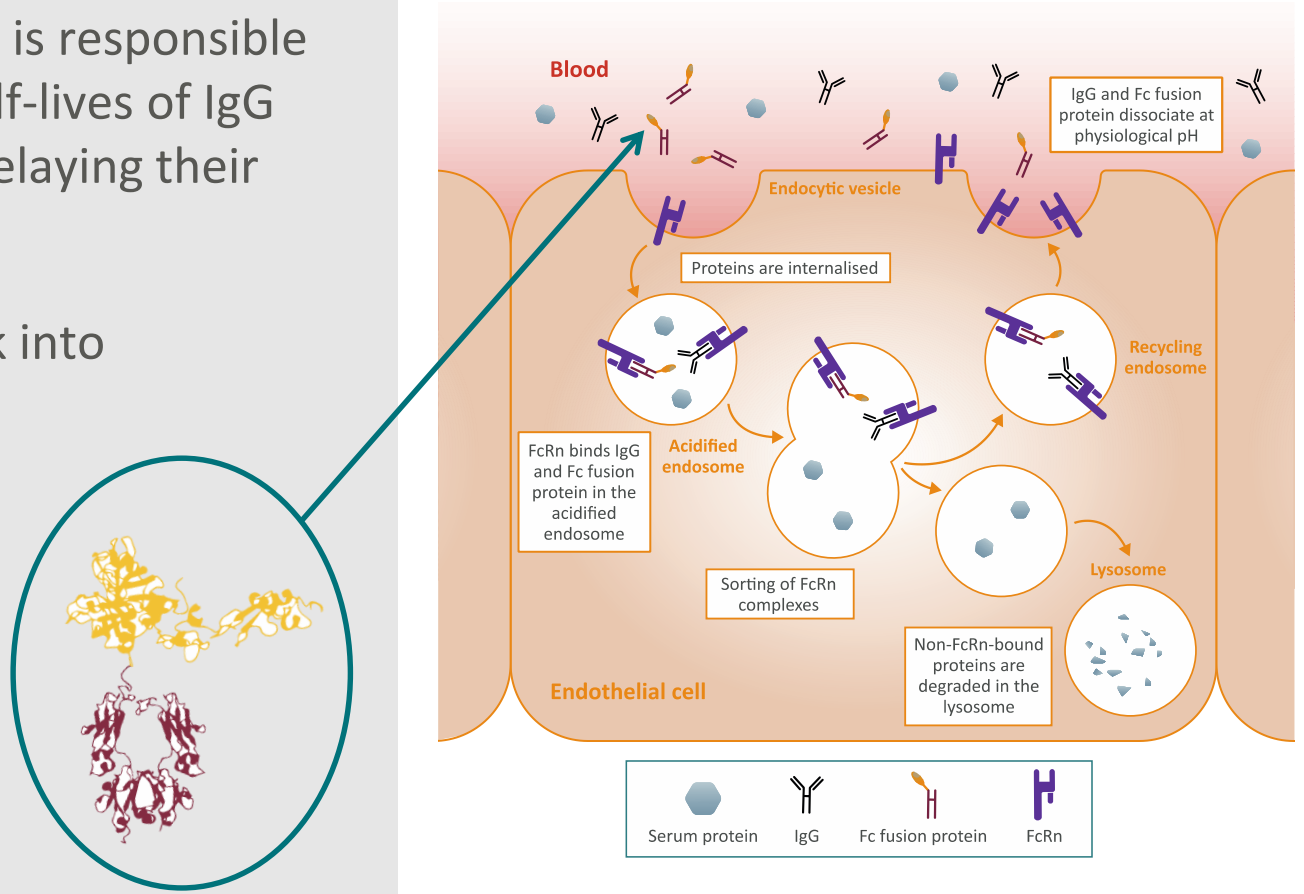
- **Fc fusion has been applied in other biotherapeutics for more than a decade**, including therapeutics used for chronic diseases, such as Enbrel™ (approved by the EMA in 2000 and the FDA in 1998) in rheumatoid arthritis[3-5]
- **Consists of natural components** and is thus fully metabolised[1-3]
- **Produced in a human cell line**, potentially minimising immunogenicity risks[1,6]

1. Peters et al. *Blood* 2010 **2.** Adapted from McCue et al. EAHAD 2014 Poster PO098 **3.** Shapiro et al. *Blood* 2012 **4.** EMA. Enbrel Summary of Product Characteristics
5. FDA. Enbrel Prescribing Information **6.** McCue et al. *Haemophilia* 2014

Date of Preparation: February 2017. NP-2043

A naturally occurring pathway is used to extend the half-life of rFIX

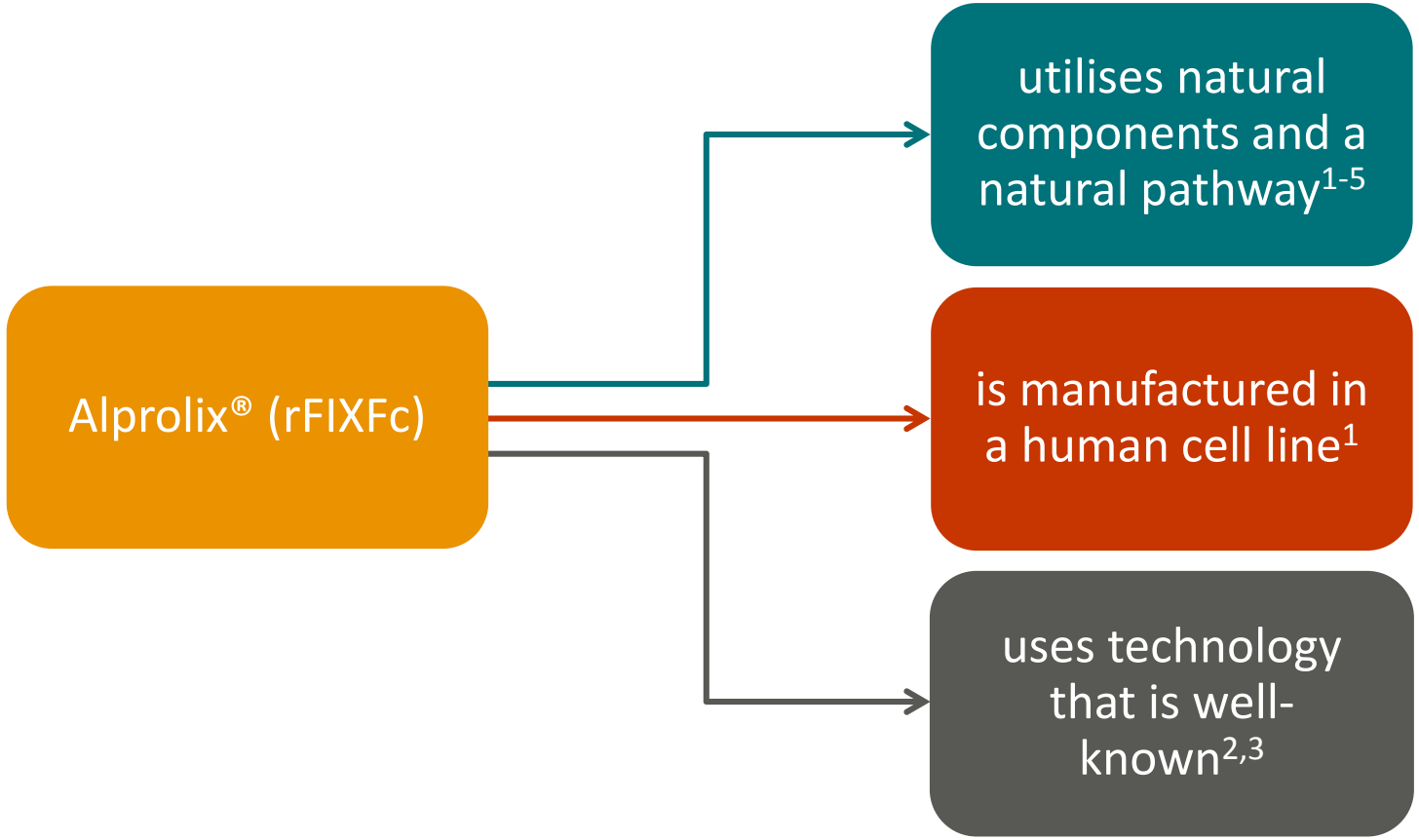
- The neonatal Fc receptor (FcRn) is responsible for the prolonged circulating half-lives of IgG and Fc-containing proteins by delaying their lysosomal degradation[1,2]
- FcRn recycles bound rFIXFc back into circulation[3,4]



1. Roopenian & Akilesh. *Nat Rev Immunol* 2007 **2.** Shapiro. *Expert Opin Biol Ther* 2013 **3.** Peters et al. *Blood* 2010 **4.** Shapiro et al. *Blood* 2012

Date of Preparation: February 2017. NP-2043

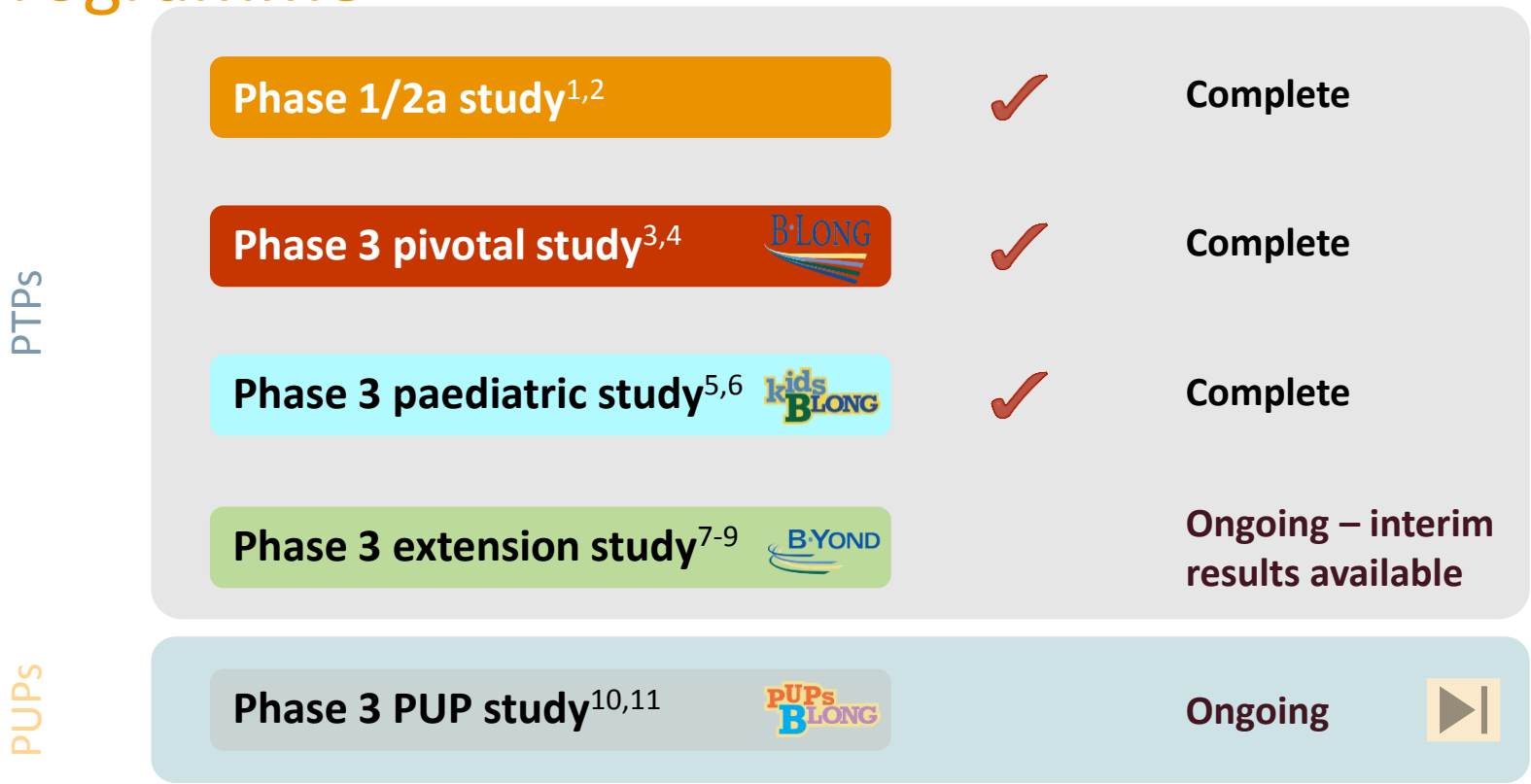
Summary – Fc technology



1. McCue et al. *Haemophilia* 2014 **2.** Shapiro et al. *Blood* 2012 **3.** Shapiro. *Expert Opin Biol Ther* 2013 **4.** Peters et al. *Blood* 2010 **5.** Roopenian & Akilesh. *Nat Rev Immunol* 2007

Date of Preparation: February 2017. NP-2043

Clinical programme

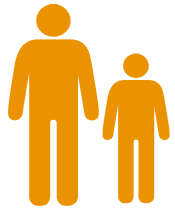


1. ClinicalTrials.gov NCT00716716 **2.** Shapiro et al. *Blood* 2012 **3.** ClinicalTrials.gov NCT01027364 **4.** Powell et al. *NEJM* 2013 **5.** ClinicalTrials.gov NCT01440946 **6.** Kulkarni et al. NHF 2015 Poster CRCT07 **7.** ClinicalTrials.gov NCT01425723 **8.** Mahlangu et al. EAHAD 2016 Poster P044 **9.** Bennett et al. NHF 2015 Poster CRCT01 **10.** ClinicalTrials.gov NCT02234310 **11.** Nolan et al. NHF 2014 Poster ACS05

Date of Preparation: February 2017. NP-2043

Patient experience with Alprolix® (rFIXFc)

153 patients treated in pivotal clinical studies



123 in B-LONG (≥12 yrs)[1]

30 in Kids B-LONG (<12 yrs)[2]

116 patients continued into the extension study, B-YOND.[3,4] Median clinical treatment duration from the start of B-LONG until the B-YOND interim data cut (Oct 2014):

~3.3 years[3]

~1000 patients treated in the real-world setting*[5]

~1100 patient-years of exposure as of March 2016*[5]

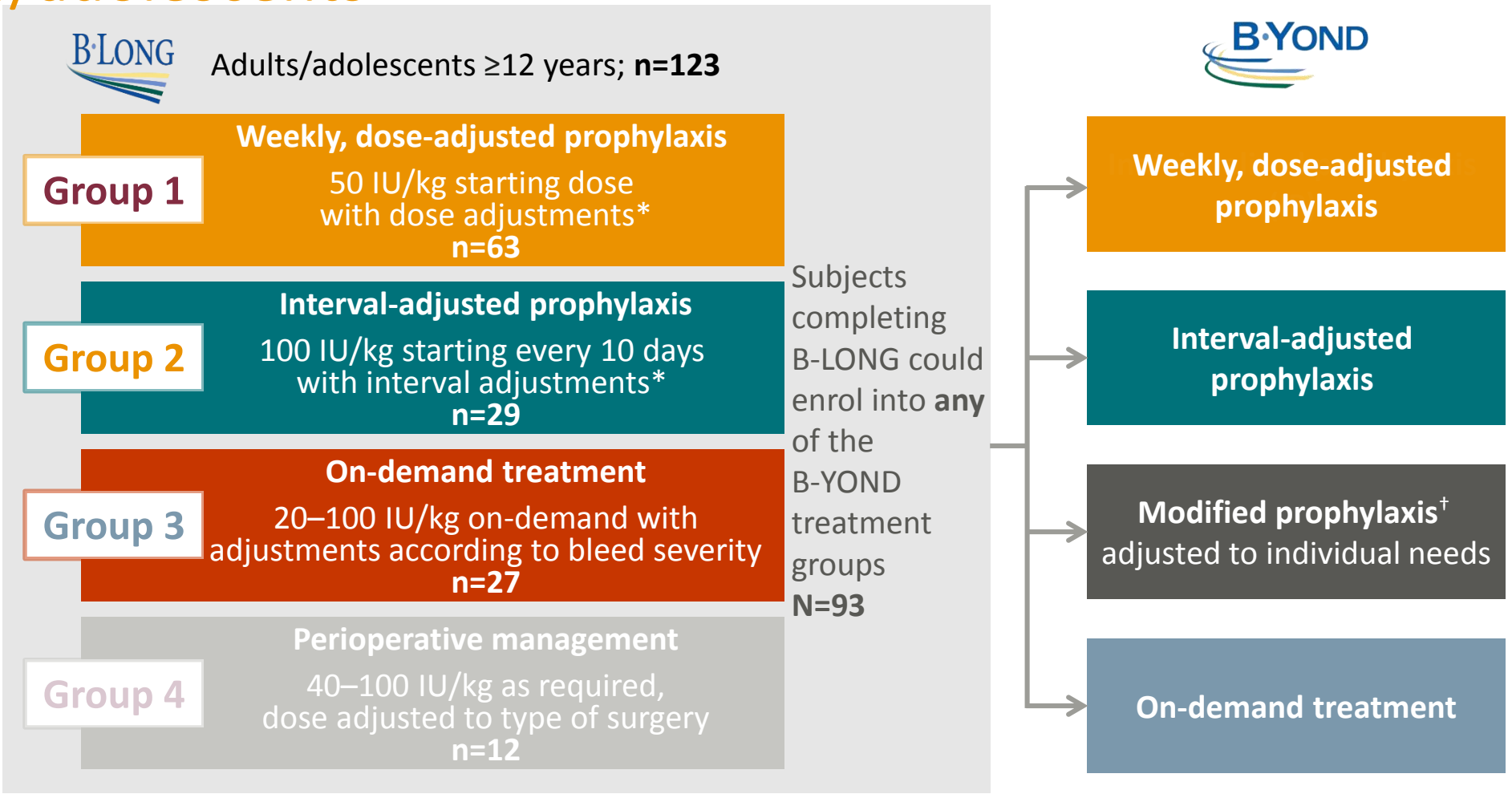
>2 years of real-world experience[6,7]

*Data were estimated based on a combination of sales data, prescription data, wholesale shipping units and/or units shipped to blood banks and clinics. These numbers do not include the people with haemophilia treated in the World Federation of Hemophilia (WFH) humanitarian aid programme

1. Powell et al. *NEJM* 2013 **2.** Kulkarni et al. NHF 2015 Poster CRCT07 **3.** Shapiro et al. NHF 2015 Poster CRCT12 **4.** Bennett et al. NHF 2015 Poster CRCT01
5. rFIXFc PSUR (up to March 2016) **6.** Sobi™ Press Release. 31 March 2014 **7.** Biogen™ Press Release. 13 May 2016

Date of Preparation: February 2017. NP-2043

Phase 3 study designs – adults/adolescents[1,2]

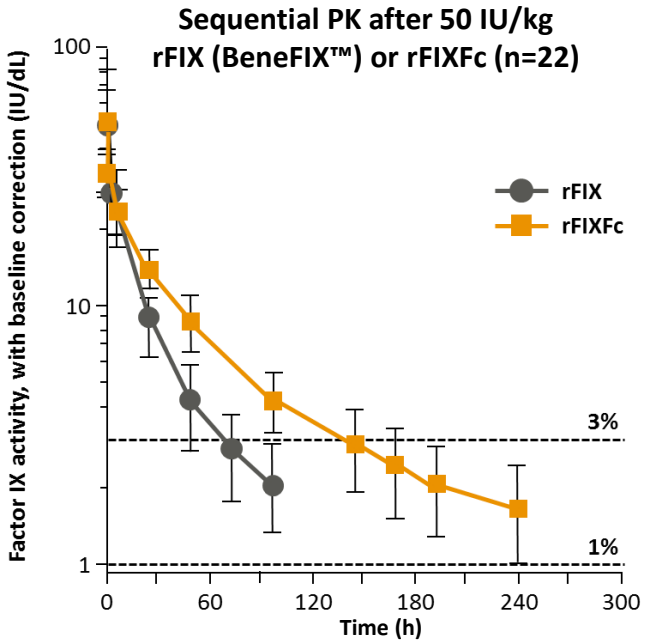


*The dose (in Group 1) or the interval (in Group 2) were adjusted during the study to maintain a trough level of 1 to 3 IU/dL above baseline, or higher if clinically necessary;
†This included, but was not limited to: more frequent dosing, addition of 'prevention' doses prior to strenuous activity, or targeting a FIX trough level of >5 IU/dL (if required by the bleeding history and/or activity level)

1. Powell et al. *NEJM* 2013 **2.** Mahlangu et al. EAHAD 2016 Poster P044

Date of Preparation: February 2017. NP-2043

Reduced rFIXFc clearance is the basis for prolonged haemostatic protection[1,2]



The geometric mean elimination half-life (CI) in adults/adolescents was:

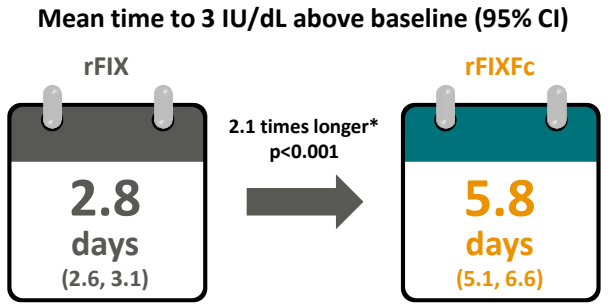
rFIXFc **82.1** (71.4–94.5) hours based on 240-hour sampling†

rFIX **33.8** (29.1–39.2) hours based on 96-hour sampling

rFIX **17.0** (15.9–18.3) hours based on 48-hour sampling

→ Compared to rFIX, rFIXFc showed on average a:

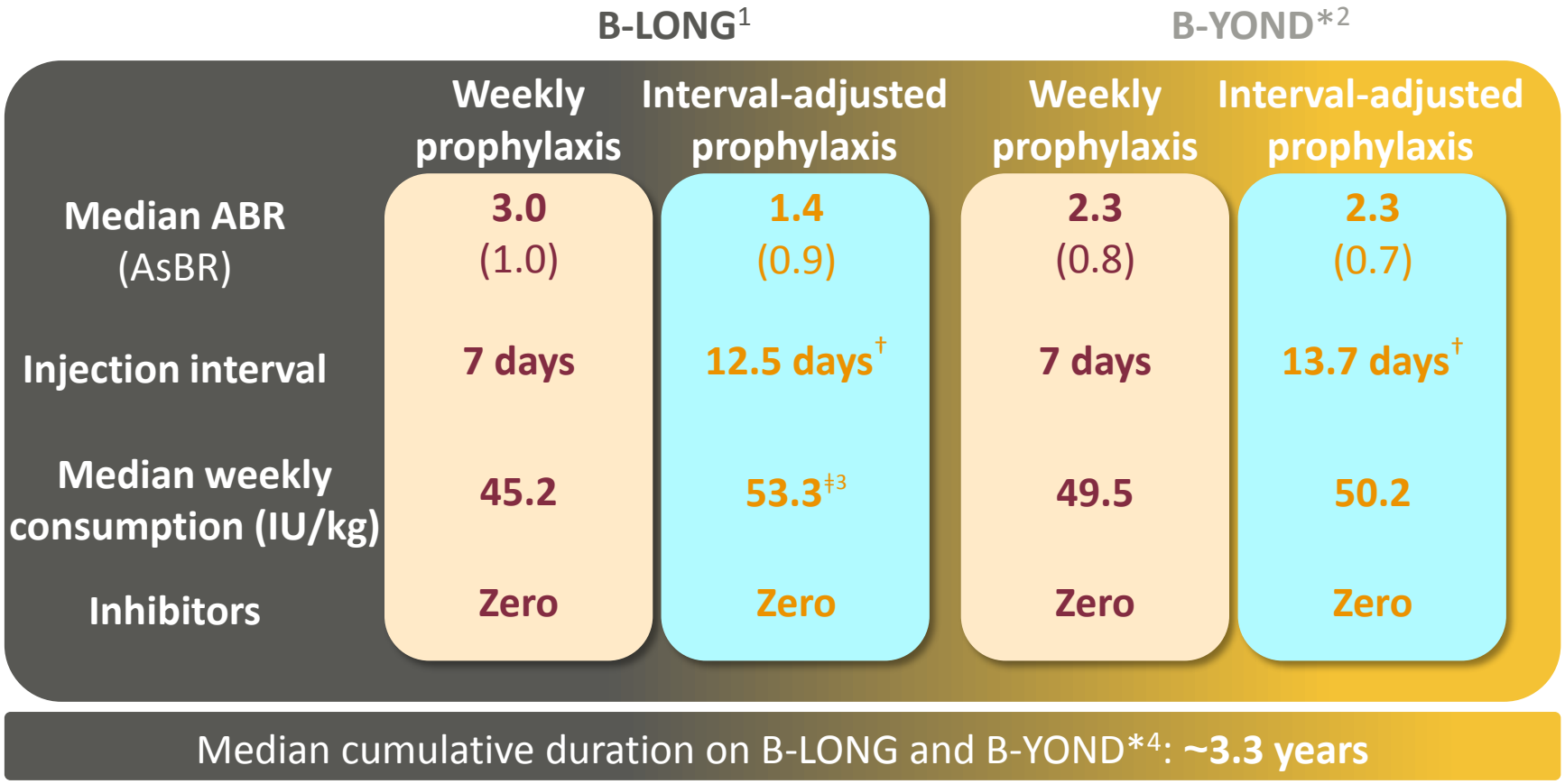
- **4.8-fold longer half-life** (82.1 versus 17.0 hrs*‡)



*Calculated from Powell et al. *NEJM* 2013. Supplementary Information; †When based on 336-hour sampling and a dose of 100 IU/kg the $t_{1/2}$ of rFIXFc was 101.0 hours (SD: 36)[3]
‡Based on 240-hour sampling of rFIXFc and traditional 48-hour sampling for BeneFIX

1. Adapted from Powell et al. *NEJM* 2013 **2.** Powell et al. *NEJM* 2013. Supplementary Information **3.** Berntorp et al. EAHAD 2016. Poster P040

Outcomes maintained long-term in adults/adolescents: B-LONG & B-YOND[1,2]



*As of first B-YOND interim data cut (17 October 2014); †Median injection interval; ‡Based on sub-group analysis of subjects receiving pre-study PPx and being on-study PPx ≥6 months; AsBR: Annualised spontaneous bleeding rate

1. Powell et al. *NEJM* 2013 **2.** Mahlangu et al. EAHAD 2016 Poster P044 **3.** Powell et al. *Br J Haematol* 2015 **4.** Shapiro et al. NHF 2015 Poster CRCT12

Date of Preparation: February 2017. NP-2043

Table S3. Summary of Efficacy in Control of Bleeding Episodes

Total no. of new bleeding episodes	636
No. of injections to treat bleeding episodes, n (%)	
1 injection	575 (90.4)
2 injections	44 (6.9)
3 injections	17 (2.7)
Median dose per injection to treat a bleeding episode, IU/kg (IQR)	46.07 (32.86, 57.03)

*n=634
IQR, interquartile range.

Overall safety results[1-5]

Inhibitors*

No subjects developed inhibitors across either study

Safety summary

rFIXFc was well-tolerated

No reports of anaphylaxis or serious vascular thrombotic events

Adverse events (AEs) were consistent with those expected in the general haemophilia population

1 serious AE in each of B-LONG† and B-YOND‡ considered related to rFIXFc

* Inhibitors are defined as anti-FIX neutralising antibodies. A positive inhibitor test result was defined in the study as a neutralising antibody value ≥0.6 BU/mL (by Nijmegen-modified Bethesda assay) and confirmed on retesting within 2–4 weeks; †In this subject, who had a history of painful haematuria, an obstructive clot developed in the urinary collecting system. The clot resolved with medical management, and the subject continued with the study treatment and completed the study; ‡Renal colic in a subject with a history of previous clot colic

1. Powell et al. *NEJM* 2013 **2.** Kulkarni et al. NHF 2015 Poster CRCT07 **3.** Shapiro et al. NHF 2015 Poster CRCT12 **4.** Mahlangu et al. EAHAD 2016 Poster P044
5. Bennett et al. NHF 2015 Poster CRCT01

Date of Preparation: February 2017. NP-2043

Alprolix®– dosing for treatment of bleeding episodes[1]

Degree of haemorrhage/ Type of surgical procedure	Factor IX level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20–40	Repeat injection every 48 hours, until the bleeding episode as indicated by pain is resolved or healing is achieved
More extensive haemarthrosis, muscle bleeding or haematoma	30–60	Repeat injection every 24 to 48 hours until pain and acute disability are resolved*
Life threatening haemorrhages	60–100	Repeat injection every 8 to 24 hours until threat is resolved
***In some patients and circumstances the dosing interval can be prolonged up to 48 hours**		

1. EMA. Alprolix Summary of Product Characteristics

Date of Preparation: February 2017. NP-2043

Available Vial Sizes and Injection Volumes[1]

Vial Size	Volume of Solution for Injection after Reconstitution
250 IU powder and solvent for solution for injection	5 mL
500 IU powder and solvent for solution for injection	5 mL
1000 IU powder and solvent for solution for injection	5 mL
2000 IU powder and solvent for solution for injection	5 mL
3000 IU powder and solvent for solution for injection	5 mL
The rate of administration should be determined by the patient's comfort level and should not exceed 10 mL/min.	

1. EMA. Alprolix Summary of Product Characteristics

Date of Preparation: February 2017. NP-2043

Storage[1]

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light

Shelf Life

4 Years*

Unopened Vial

- Product may be stored at room temperature (up to 30°C) for a single period not exceeding 6 months
- After storage at room temperature, the product may not be returned to the refrigerator

After Reconstitution

- Product should be used immediately after reconstitution
- Product is stable for up to 6 hours after reconstitution
- If the product is not used within 6 hours, it must be discarded

* Unopened Vial stored in a refrigerator (2°C - 8°C)

1. EMA. Alprolix Summary of Product Characteristics

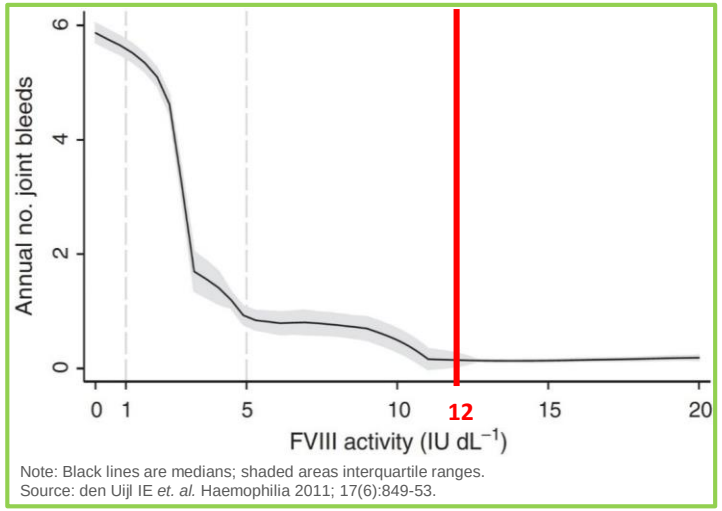
Date of Preparation:

GENE THERAPY

Objectives of a gene therapy for hemophilia

- **Sustained, long-term expression** at optimal therapeutic levels without the troughs that characterize weekly infusions of protein therapeutics
- **Consistent results across treated patients** reliably leading to a more predictable outcome
- **Lowest possible frequency of immune response** minimizes the use of steroids and leads to optimal outcome
- **Lowest possible dose decreases risk of immune response** and lowers manufacturing hurdles / cost

Factor activity levels >12% at all times reduces risk of bleeds and need for chronic infusions



Note: Black lines are medians; shaded areas interquartile ranges.
Source: den Uijl IE *et. al.* Haemophilia 2011; 17(6):849-53.

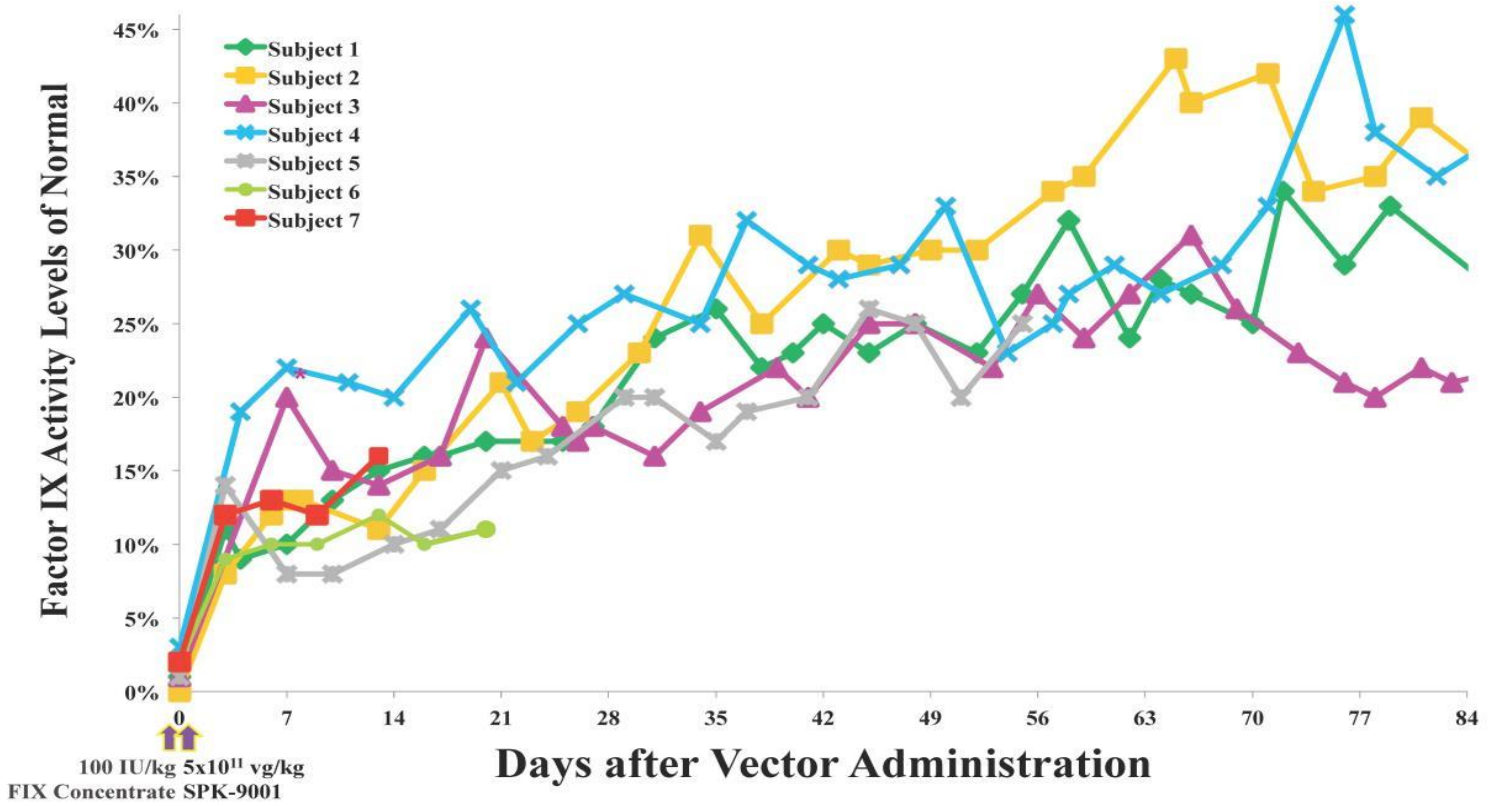
Phase 1/2 open-label study of *SPK-9001* for hemophilia B

- *SPK-9001* is a novel bio-engineered AAV capsid (Spark100) expressing a codon-optimized, high-activity human factor IX (FIX) variant directed by an optimized liver-specific promoter
  - Lead investigational compound in *SPK-FIX* program in collaboration with Pfizer
- Enrollment criteria
  - Adult males with hemophilia B (≤2% FIX activity levels)
  - No prior history of FIX inhibitors and neutralizing antibody titer <1:5 to Spark100 capsid
  - No active HCV infection or evidence of significant underlying liver disease
- Vector infused intravenously over ~1 hour in an outpatient setting
- Subjects enrolled sequentially into one of up to three cohorts of 2-5 subjects each
  - Initial low dose cohort complete (n=4) at 5 x 10^{11} vector genomes (vg) per kilogram (kg) of body weight
  - Initiated an expanded cohort at the initial low dose which has began to infuse subjects

SPK
He
wit

>30%

Figure 1: Factor IX:C in the first 12 weeks of the first 7 subjects



Current status at NCC

- Seroprevalance study for Freeline gene therapy study due to complete in March 2017
- Seroprevalance study for SPK-9001 – possible start date in Q3
- Gene therapy study start date – unclear

INFORMATION TECHNOLOGY

Key deliverables from new IT system

- Patient portal
  - Medical record with translate function and including summary, results, letters and appointments
  - Ability to choose and book appointments and cancel visits. Incudes dental and multiple appointments
  - Registration and pre clinic questionnaires
  - E clinics and communications
  - Patient information
    - Haemophilia and non haemophilia
    - Videos, leaflets etc
    - Rated
  - Care plans and links to health apps
  - Outcome measures

New IT system – lighthouse project

- Medical record
  - Cloud based in Ireland
  - Data protection
  - Patient access
  - Summary and all details available
  - Break-glass function
  - Option to limit patient access – time based
  - Translate function
  - Digital dictation
  - Patient recorded information including

New IT system – lighthouse project contd

- Choose and book
  - On line booking system
  - Multiple appointment option
  - Online cancel and reschedule
  - Automatic link to your phone calendar
  - Self registration
  - Notification of estimated time to be seen if clinic running late

New IT system – lighthouse project contd

- E-communication
  - E-mails
  - Messaging and reminders
  - Skype clinics
- Self care function
  - Education content e.g. videos, leaflets
  - Rating of content
  - Link to fitness Apps
  - Self management tools e.g. medication management, meditation
- Joint care plans
- Outcome measures including PREMS and PROMS

Current status

- Awaiting approval

THANK YOU FOR YOUR ATTENTION

Lighthouse project

- Enhancement cement of existing system
- Medical record