

A dark teal background featuring a stylized world map in a lighter shade of teal. The map shows the outlines of continents and major landmasses.

# Investor R&D Briefing

December 10, 2015

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- Welcome
- Introduction & Highlights
- Research & Early Development
- Immunoglobulins & Specialty Products
  - Clinical Development
  - Commercial Opportunities
- Q&A

## *Break*

- Coagulation/Haemophilia
  - Clinical Development
  - Commercial Opportunities
- Breakthrough Medicines
  - CSL112 Clinical Development
- Influenza Vaccines R&D
- Summary
- Q&A

Mark Dehring  
Andrew Cuthbertson  
Andrew Nash

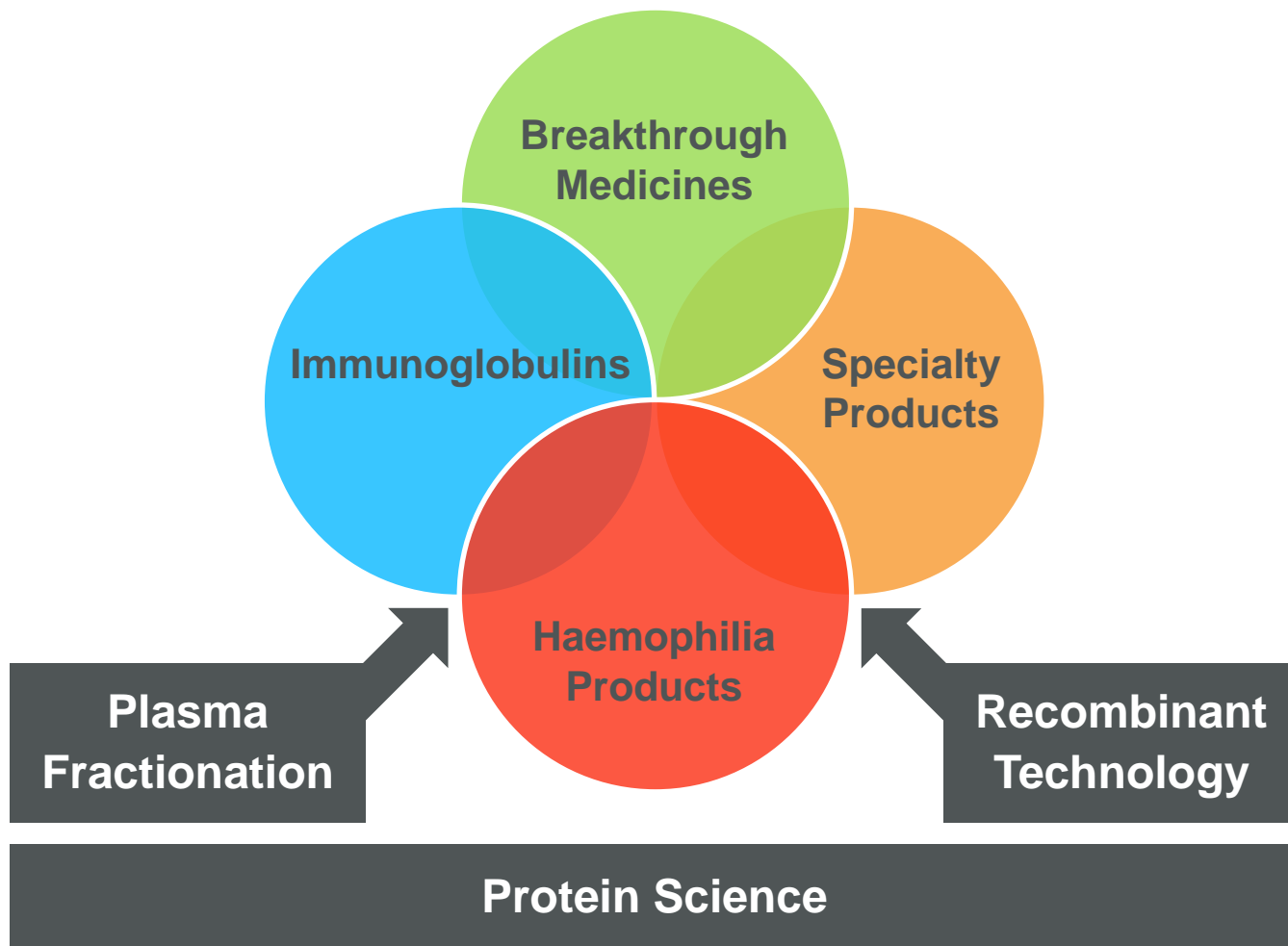
Charmaine Gittleson  
Bob Repella

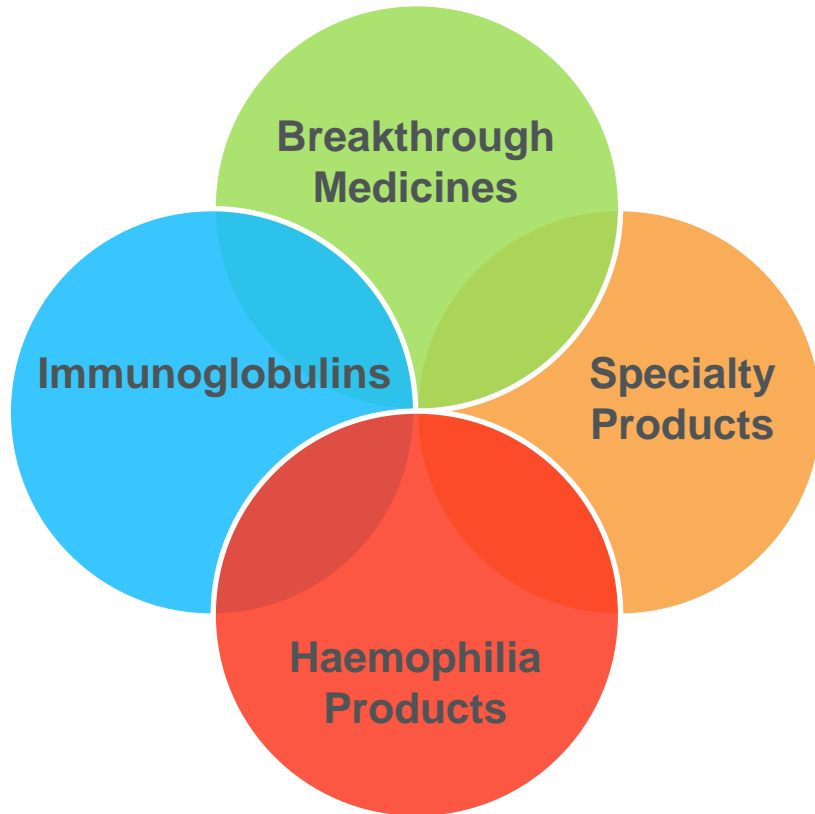
Charmaine Gittleson  
Bob Repella

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Andrew Cuthbertson

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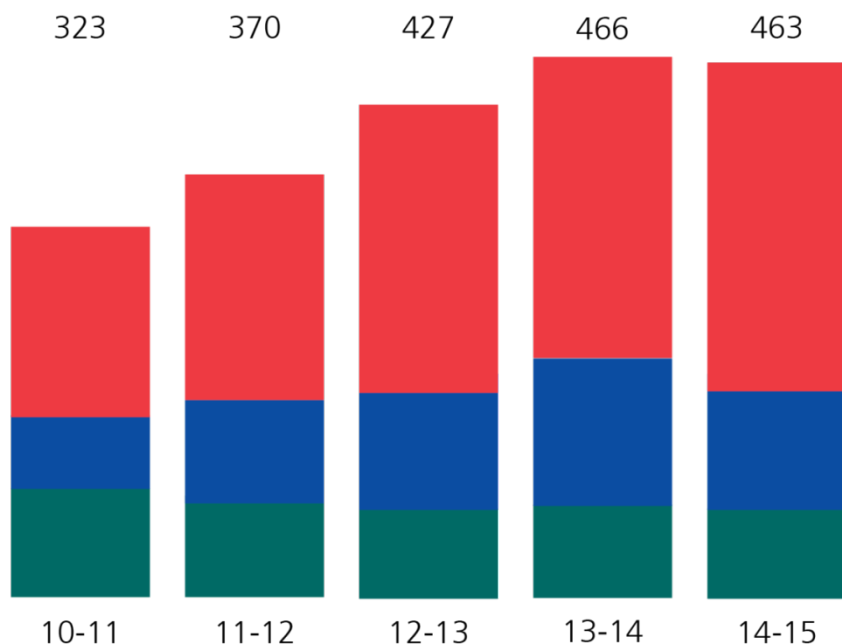
# Introduction and Highlights





- Maintain commitment to extracting maximum value from existing assets and supporting and improving current products
- Develop new protein-based therapies for treating serious illnesses focusing on products that align with our technical and commercial capabilities

## R&amp;D Investment\* (US\$ millions)

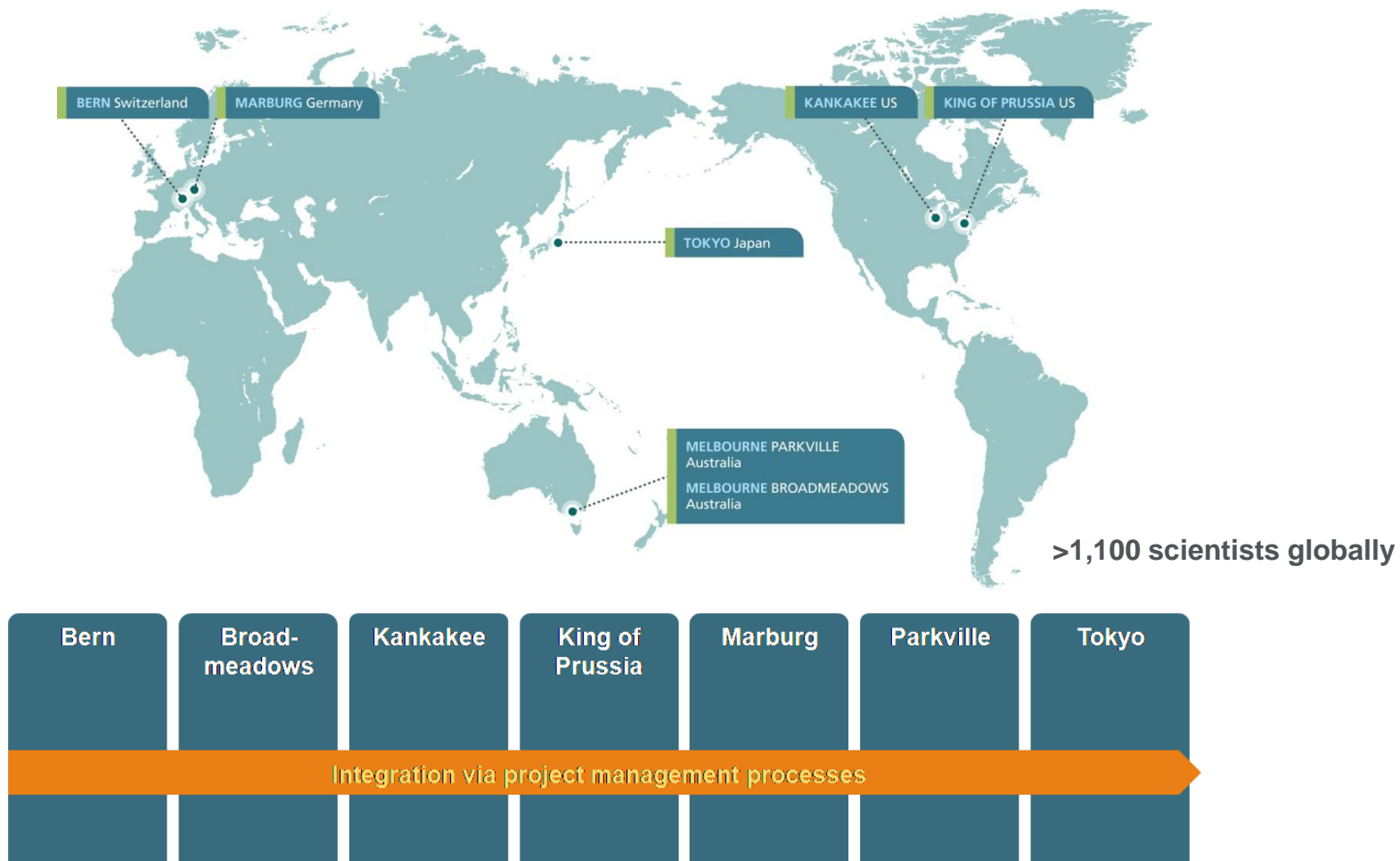


**New Product Development** activities focus on innovative new therapies for life-threatening diseases.

**Market Development** strategies seek to bring therapies to new markets and new indications.

**Life Cycle Development** ensures continuous improvement of existing products.

\*FY14 / FY15 YoY growth 6% at constant currency

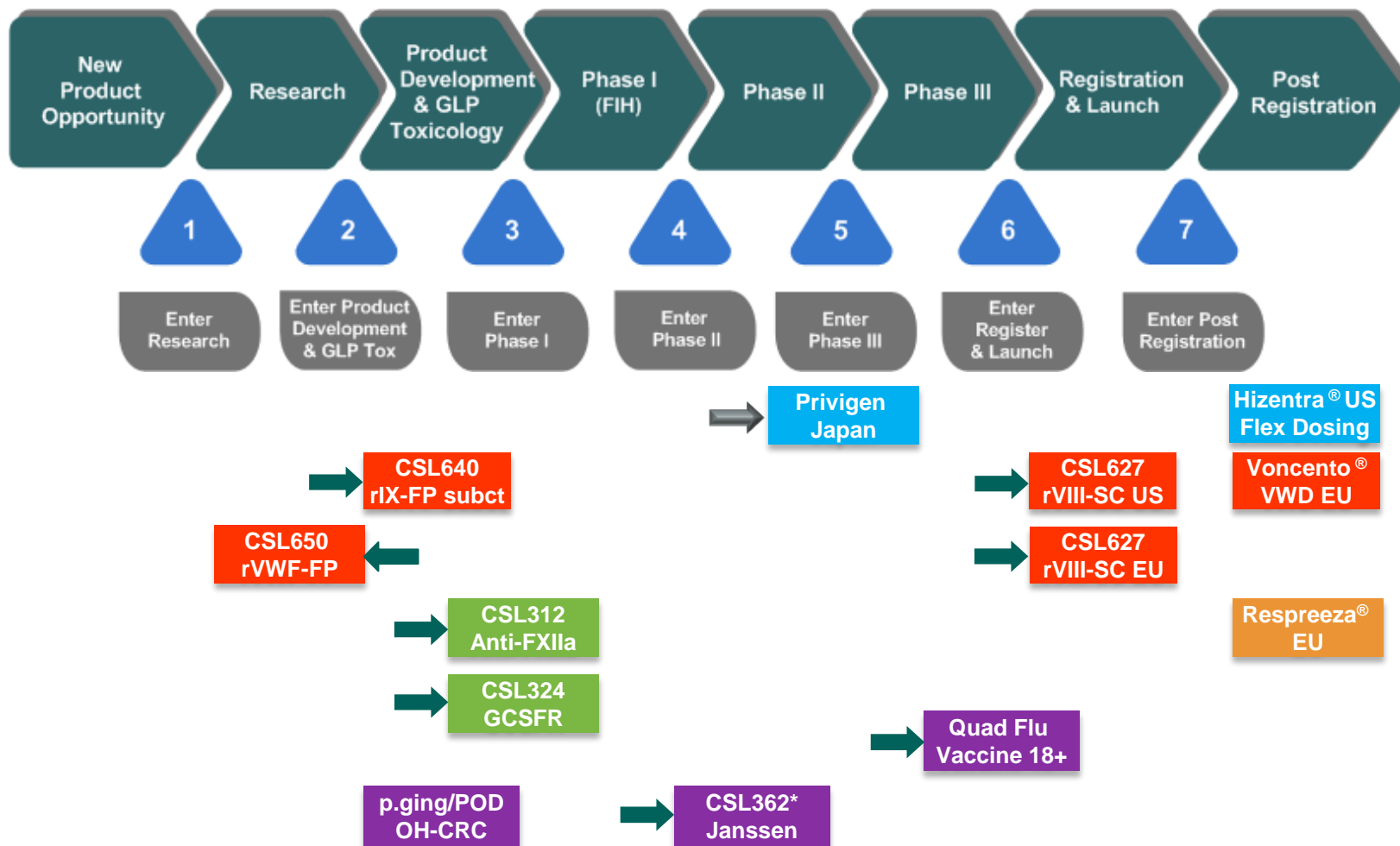


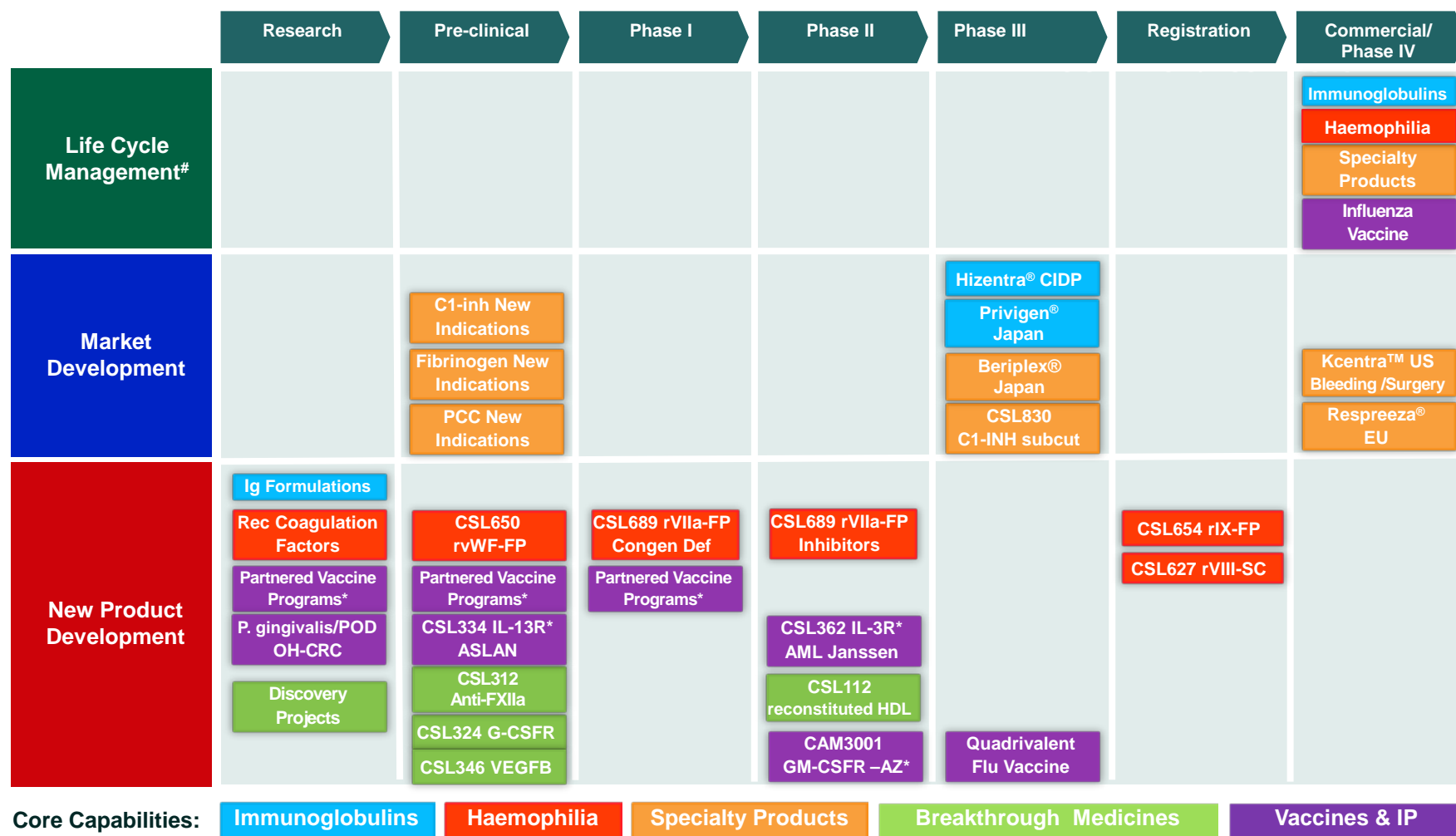


\*Partnered Projects

<sup>#</sup>LCM includes direct post marketing commitments as well as pathogen safety, capacity expansions, yield improvements, new packages and sizes for all registered products

## Progress through Stage Gates in 2015





\*Partnered Projects

<sup>#</sup>LCM includes direct post marketing commitments as well as pathogen safety, capacity expansions, yield improvements, new packages and sizes for all registered products

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## Research & Early Development

- Coordinated global project portfolio

Immunoglobulins

Haemophilia

Specialty  
Products

Breakthrough  
Medicines

- Hub (Bio21, Parkville) & spoke model
- Research excellence in therapeutic proteins
- Plasma and recombinant manufacturing platforms





- Major focus on patient QoL
- Extract maximum value and performance from existing assets
- Develop new protein-based therapies and strategies for treating bleeding disorders
  - Congenital
  - Acquired

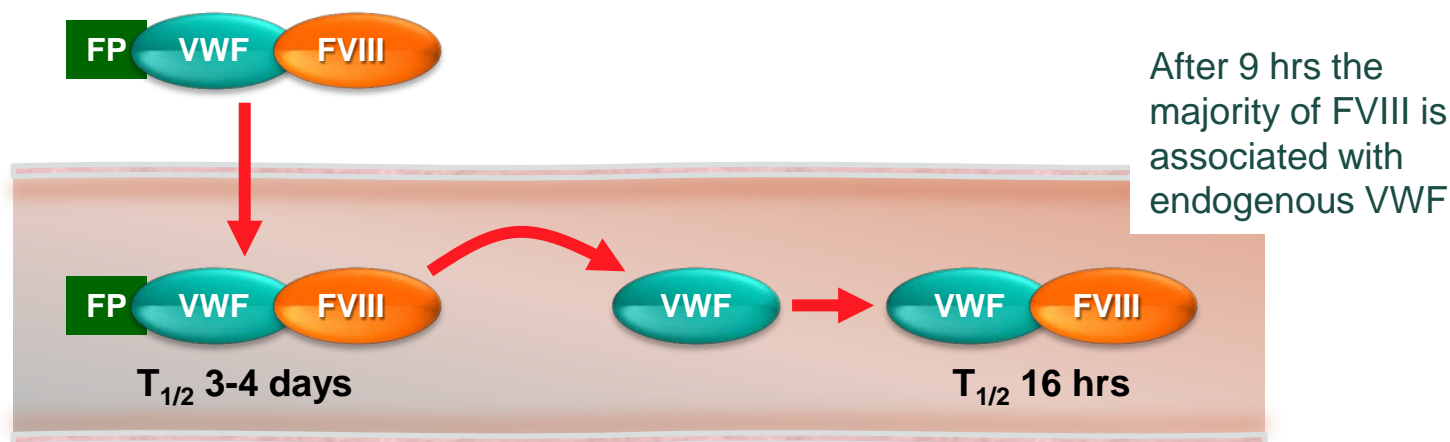
- Improved prophylaxis for haemophilia patients

Product	Features	Phase	Manufacturer	Half-life extension
<b>Eloctate</b>	rFVIII fused to Fc	Market	Biogen Idec	1.1 - 1.5 fold*
<b>N8-GP</b>	BDD FVIII O-linked pegyl <sup>n</sup>	Ph II/III	Novo Nordisk	
<b>BAX 855</b>	FVIII Lys-linked pegyl <sup>n</sup>	Market	Baxter	
<b>BAY 94-9027</b>	BDD FVIII site-specific pegyl <sup>n</sup>	Ph I	Bayer	
<b>CSL627 rVIII-SingleChain</b>	Single chain BDD FVIII	Submitted	CSL Behring	
<b>Alprolix</b>	FIX fused to Fc	Market	Biogen Idec	3 fold
<b>CSL654 rIX-FP</b>	FIX fused to albumin with cleavable linker	Submitted	CSL Behring	5 fold
<b>GlycoPEGylated rFIX</b>	FIX N-linked pegyl <sup>n</sup>	Ph III	Novo Nordisk	5 fold
<b>CSL689 rVIIa-FP</b>	FVIIa fused to albumin	Ph I	CSL Behring	3-4 fold

- FVIII  $T_{1/2}$  extension limited by interaction with VWF

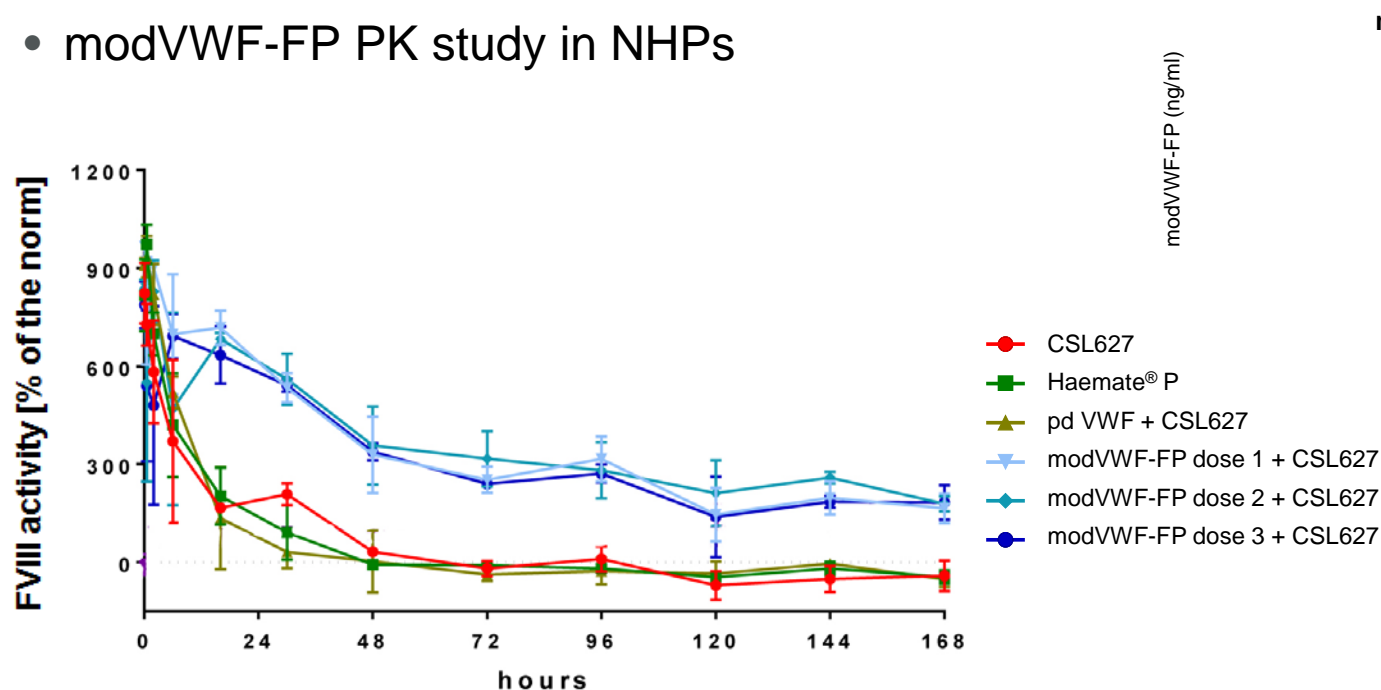
↳ Target VWF  $T_{1/2}$

- VWF – Albumin fusion protein (VWF-FP)
- Haemophilia A patients have normal levels of VWF



- Create novel modified VWF-FP to enable:
  - Administration of higher doses without risk of thrombosis
  - Higher affinity association with FVIII
- Candidate product – modVWF-FP + CSL627

- modVWF-FP PK study in NHPs

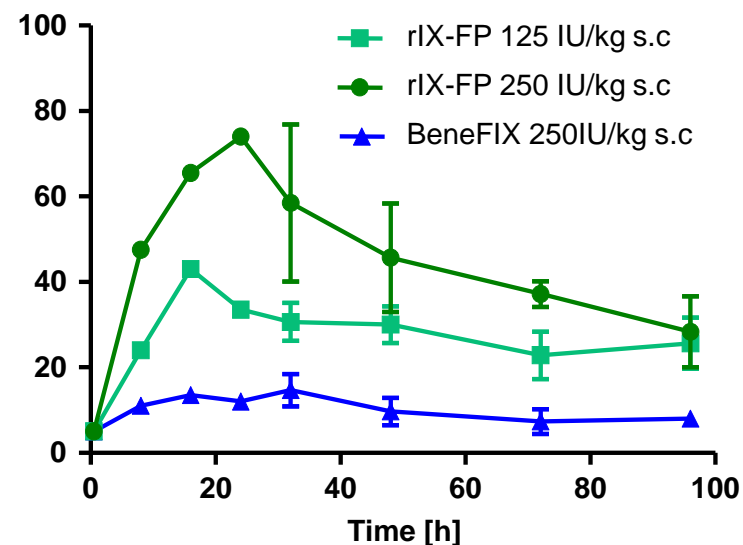
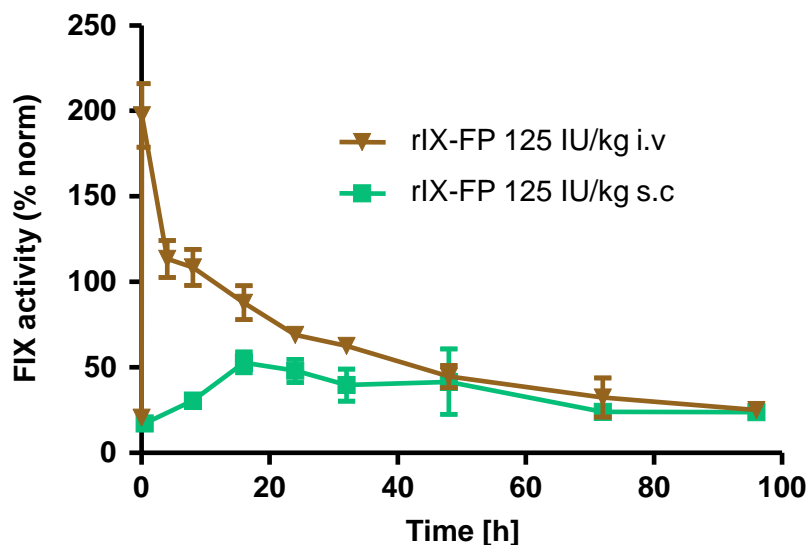


- Prolongation of FVIII exposure by modVWF-FP
- Product development initiated

### **Enabling more flexible and convenient prophylaxis in haemophilia patients**

- New, innovative and unique administration form
- Patients with poor venous access
- Reduction or avoidance of indwelling catheters & associated complications
- Patients with fear for injections / needles
- Maintain consistent trough levels (fewer peaks)

- Subcutaneous delivery of rIX-FP (haemophilia B mice)

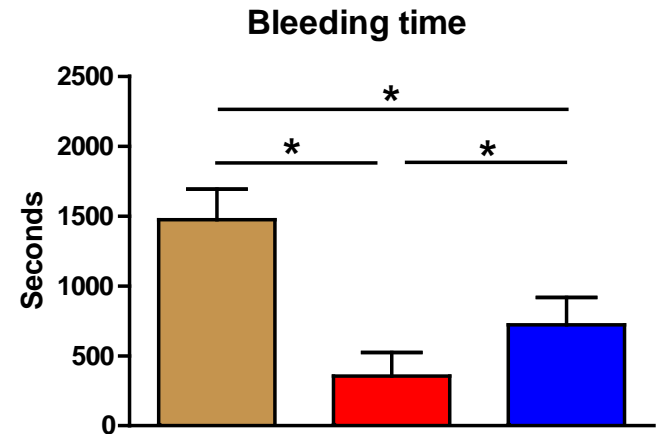
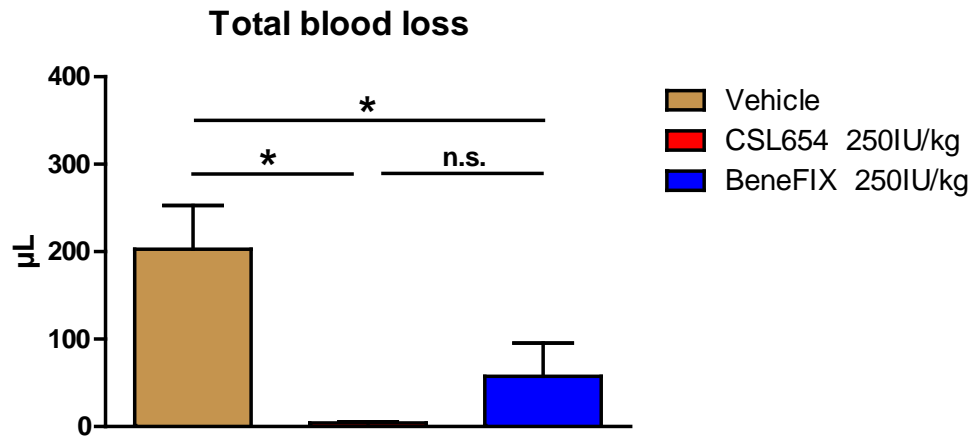


- s.c rIX-FP ~50% bioavailability\* in haemophilia B mice
- s.c.rIX-FP ~8-fold higher AUC than BeneFIX\*\*

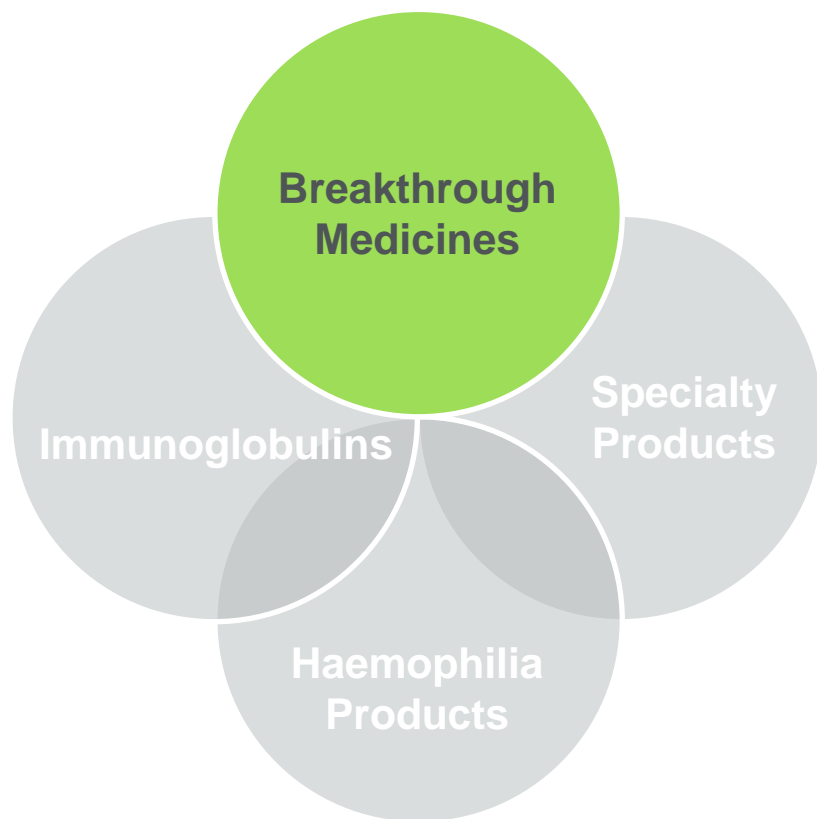
\*Bioavailability 13-50% depending on species

\*\*TM of Pfizer. Inc.

- rIX-FP s.c efficacy in haemophilia B mice



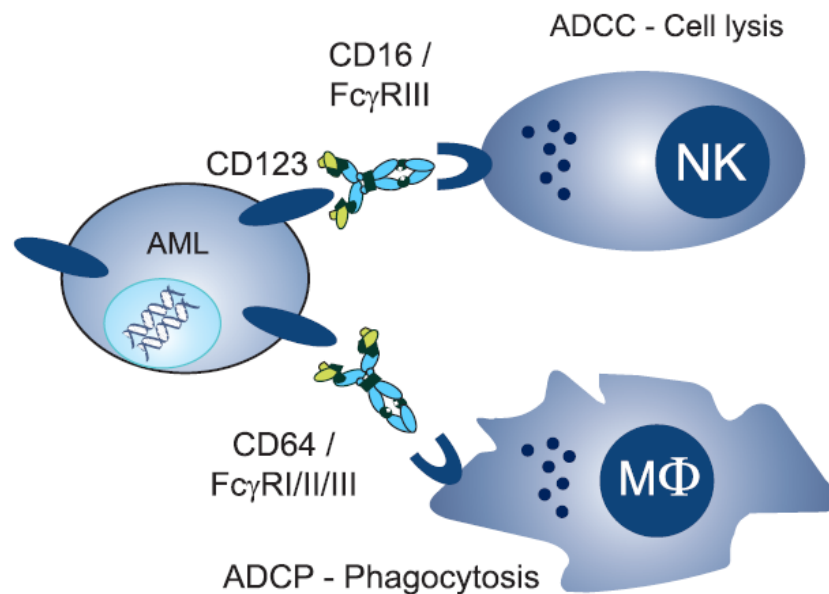
- rIX-FP reduces total blood loss and bleeding time following s.c administration to haemophilia B mice
- Phase 1 to commence mid 2016



- Leveraging clinical and technical insight in developing novel protein-based therapies
  - Significant unmet need
  - Multiple indications
- Key Focus
  - CSL362 (Janssen)
  - CSL324

## CSL362 – Acute Myeloid Leukaemia

- Most common acute leukaemia in adults
- Incidence increases with age
- Untreated AML fatal: 3 – 4 months
- Chemotherapy → 50-75% CR  
~70% will relapse
- CSL362 MOA – targets CD123 overexpressed on leukaemic cells
  - engineered to recruit immune killer cells
  - inhibits IL-3 activity



# CSL362 – Acute Myeloid Leukaemia

- Licence Agreement with Janssen Biotech – June 2013
  - CSL responsible for completing CSL362 AML Phase 1 clinical study

Milestone	Date
Phase 1 Last Patient Last Visit	July 2015

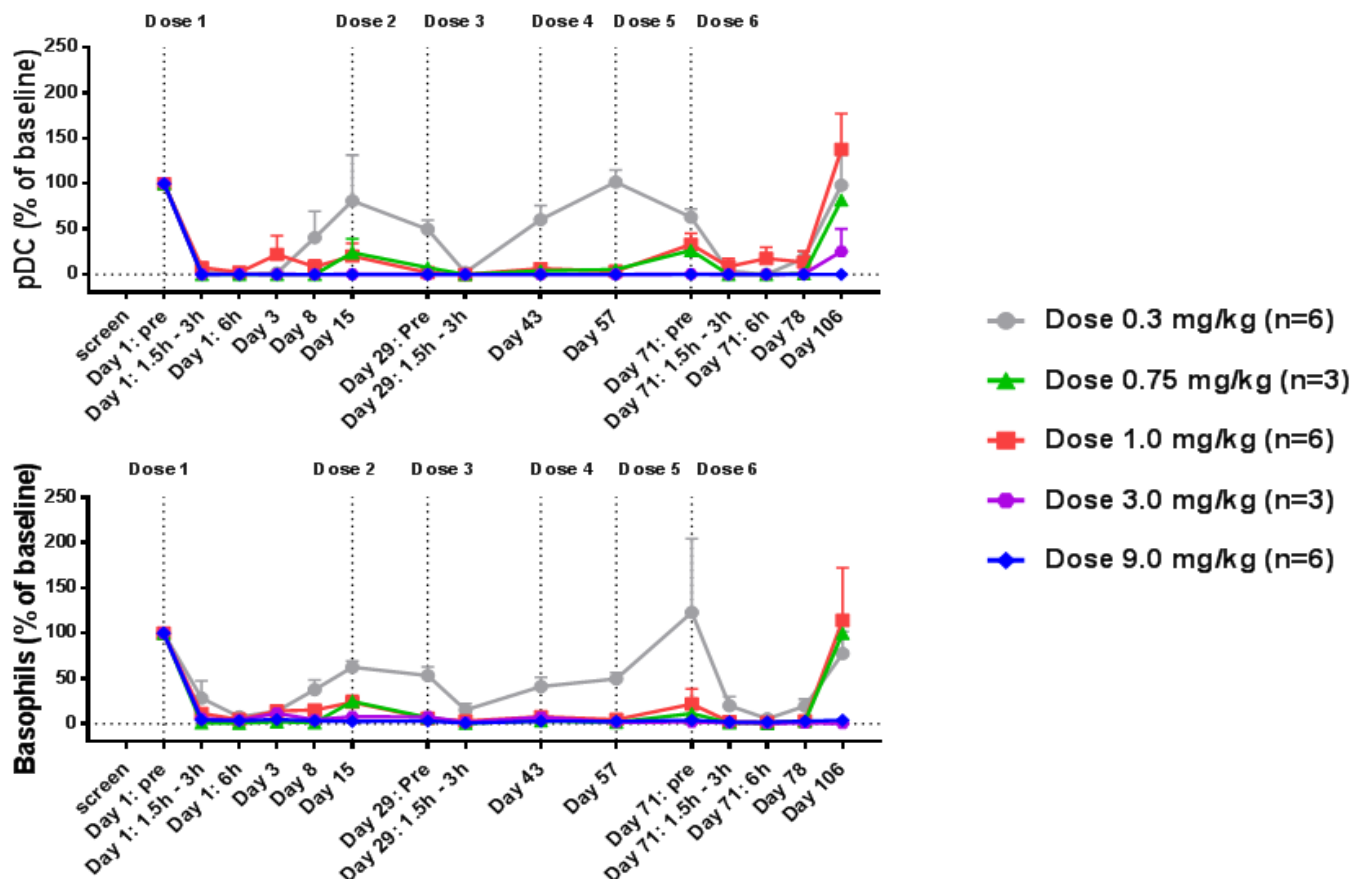
- Janssen responsible for all further oncology development

Milestone	Date
AML Phase 2 First Patient In*	August 2015

\*JNJ-56022473

## CSL362 – Acute Myeloid Leukaemia

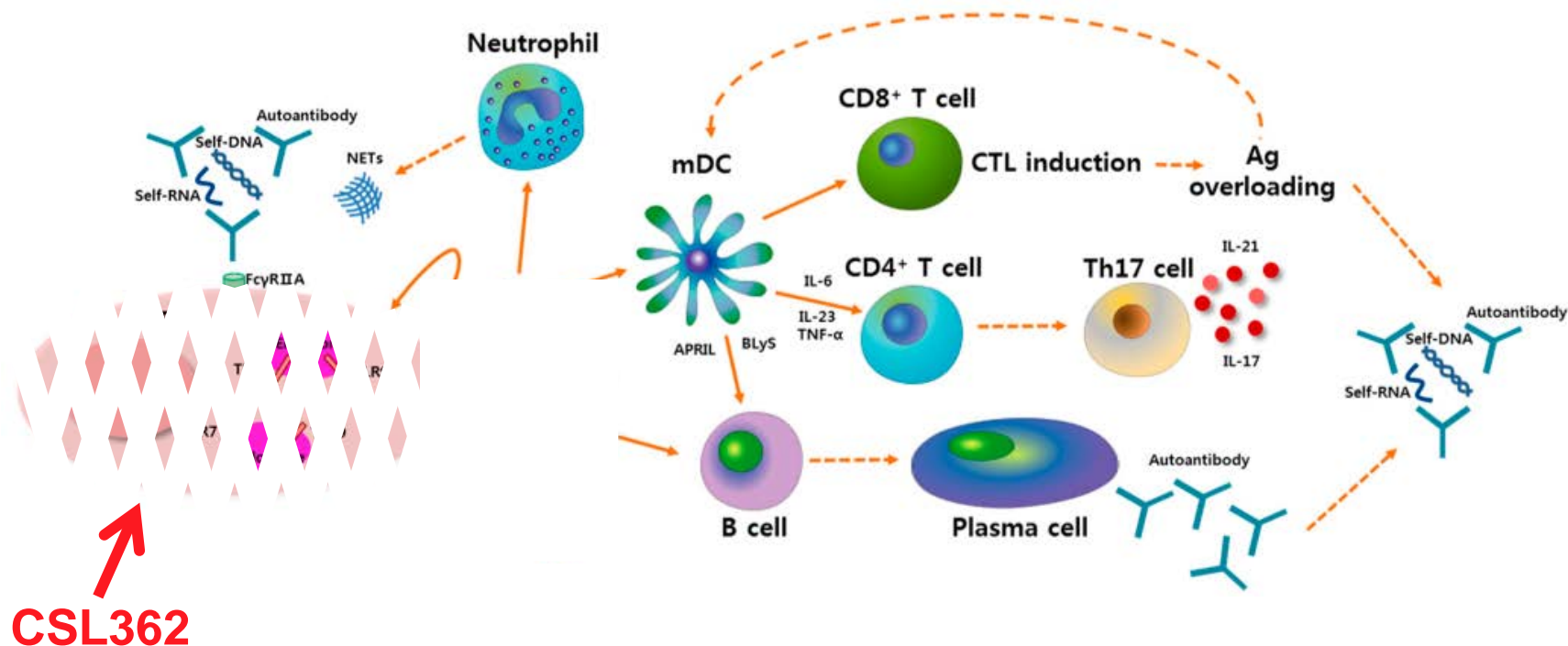
- CSL362 depletes biomarker pDC's and basophils in patients



## Conclusions

- Manageable safety profile:
- Pre-medication with steroids required to prevent infusion reactions
- PD effects confirming CD123-targeted ADCC
- Rapid and full depletion of basophils and pDCs
  - Sustained depletion at CSL362 dose levels  $\geq 3$  mg/kg
- Saturation of CD123 receptor on monocytes at CSL362 dose levels  $\geq 3$  mg/kg (trough concentration  $> 3\mu\text{g/ml}$ )
- Conversion of MRD seen in a subset of pts treated with CSL362
- AML Phase 2 study commenced July 15 (Janssen partnership)

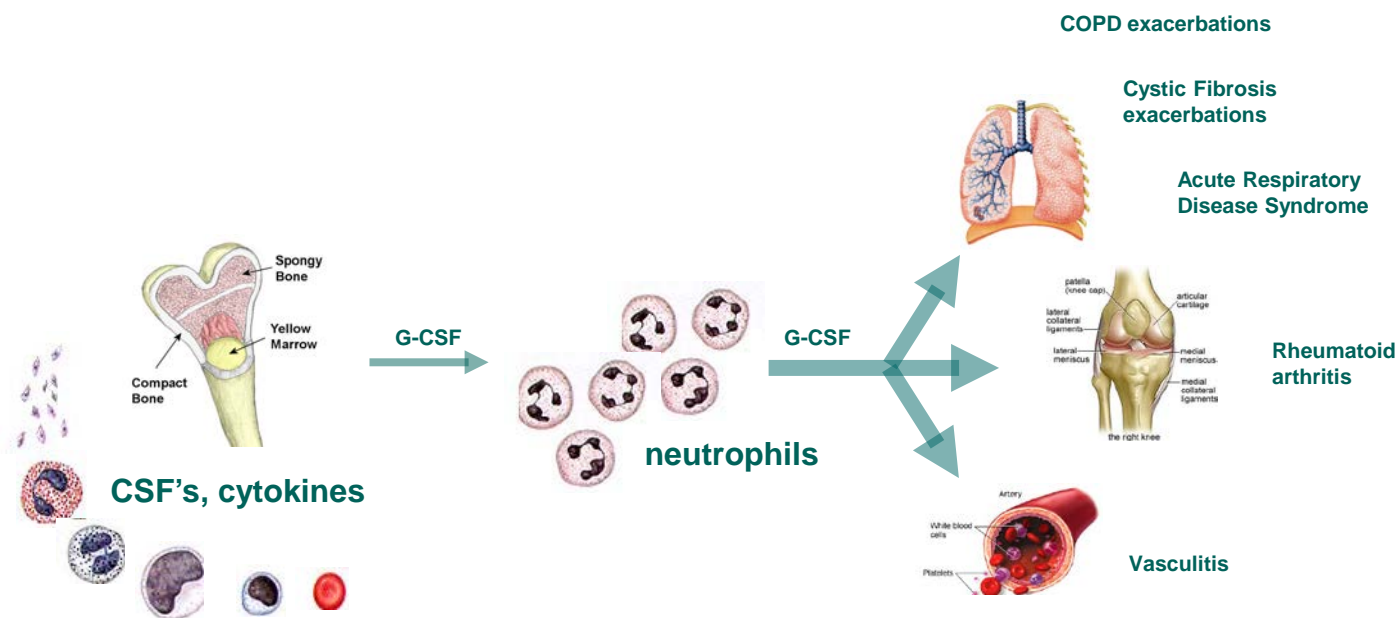
- pDCs contribute to a disease amplification loop in SLE



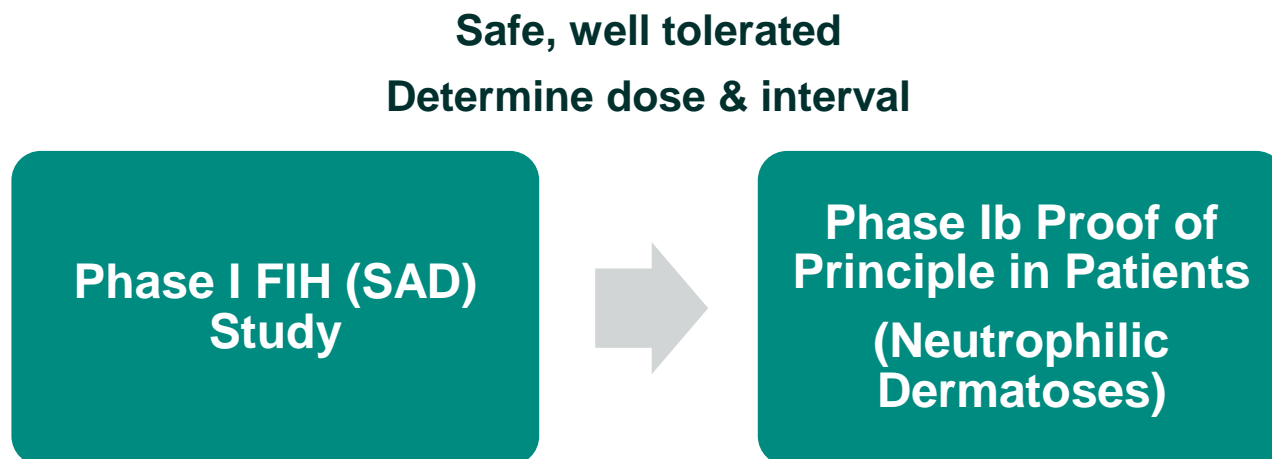
Janssen to commence exploratory study in SLE patients 2H 2016

## CSL324 – anti-G-CSFR mAb

- Targeting the **G-CSF receptor** represents a novel approach to the treatment of neutrophil mediated pathologies
- Efficacy in multiple animal models of inflammatory disease



- Early clinical development strategy



- GLP toxicology completed, CSL324 safe and well tolerated
- Phase 1 to commence mid-late 2016

- Portfolio of early stage opportunities consistent with CSL commercial objectives

Immunoglobulins

Haemophilia

Specialty  
Products

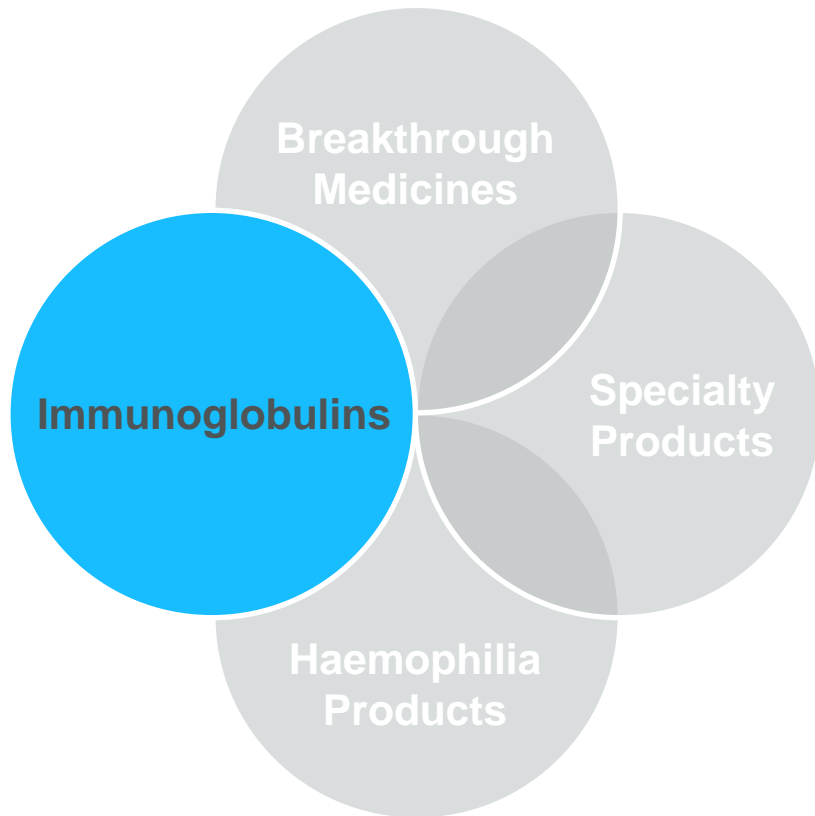
Breakthrough  
Medicines

- Delivery of high quality candidates for clinical development
  - CSL362 (anti-IL-3R, partnered with Janssen Biotech)
  - CSL324 (anti-G-CSFR)
  - CSL312 (anti-FXIIa)

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# Immunoglobulins

# Immunoglobulins



- Maintaining leadership position through focus on:
  - New Indications
  - Geographic expansion
  - Delivery options
- Key Focus
  - Hizentra<sup>®</sup>
  - Privigen<sup>®</sup>

# Immunoglobulins

## *Privigen*<sup>®</sup>

- The first and only 10% liquid intravenous immunoglobulin (IVIG) therapy that is proline stabilized with room temperature storage up to 36 months

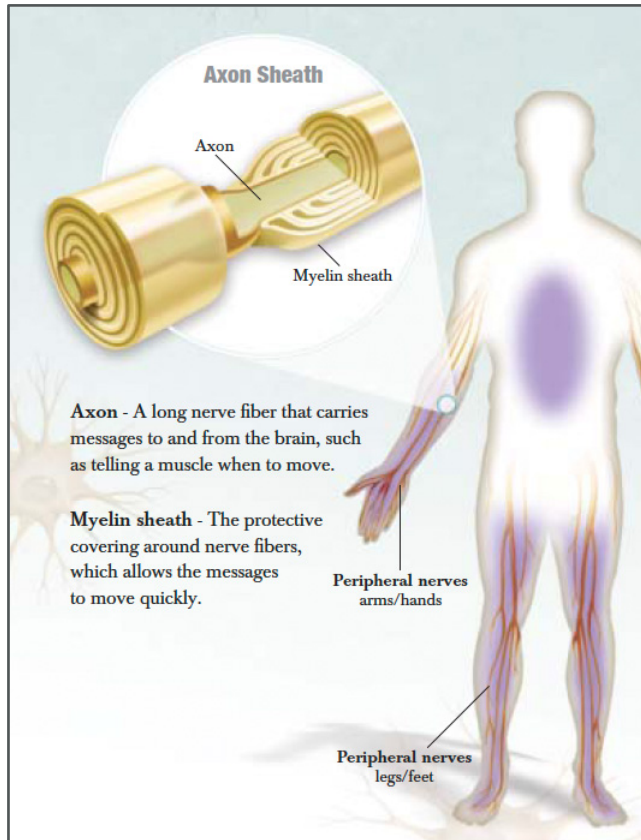


## *Hizentra*<sup>®</sup>

- The first 20% high concentration low volume SCIG for convenient self administration providing steady-state Ig levels and an established long-term safety record with chronic administration



### Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)



- Build on Privigen® experience in CIDP
- Introduce SC infusion method
  - Ease of administration
  - Steady state levels, manages wear off effect

Hizentra®

- Pivotal study
  - Largest randomised placebo controlled study in CIDP (16 countries/69 sites)
  - Study screening completed (n=289)
  - 71 patients have completed the primary study
  - Last patient completing Q4 2016
- FDA and EMA submissions 2H 2017
- PMDA submission 2018



- 83% (n=100) patients said medication in its current form was easy to use (120 subject responses at week 9)



- Clinical trial highest dose/volume required – 160mL in avg 80kg patient
  - 4 infusions sites/session/~120 minute infusion time
  - 2 infusion sites/session x 2 days ~60 minute infusion time
- Infusion volume of 50mL/site well tolerated
- Infusion rate of 35 mL/hr tolerated

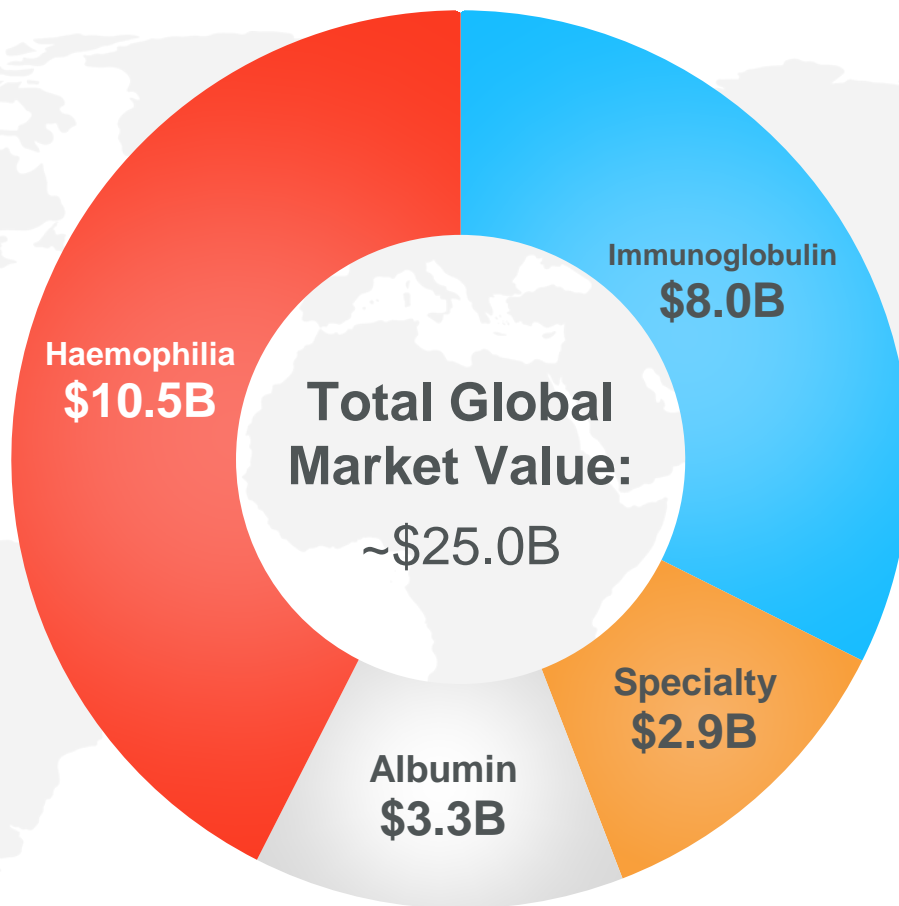


- ~3,500 Primary Immunodeficiency patients in Japan PID network (2014)
- Currently Hizentra® and 5% IVIG available to patients
- CSL will bring first high purity room temperature 10% IVIG product to Japan
- Commence Privigen® PID study Q3/4 2016
  - Agreement on study design reached with PMDA

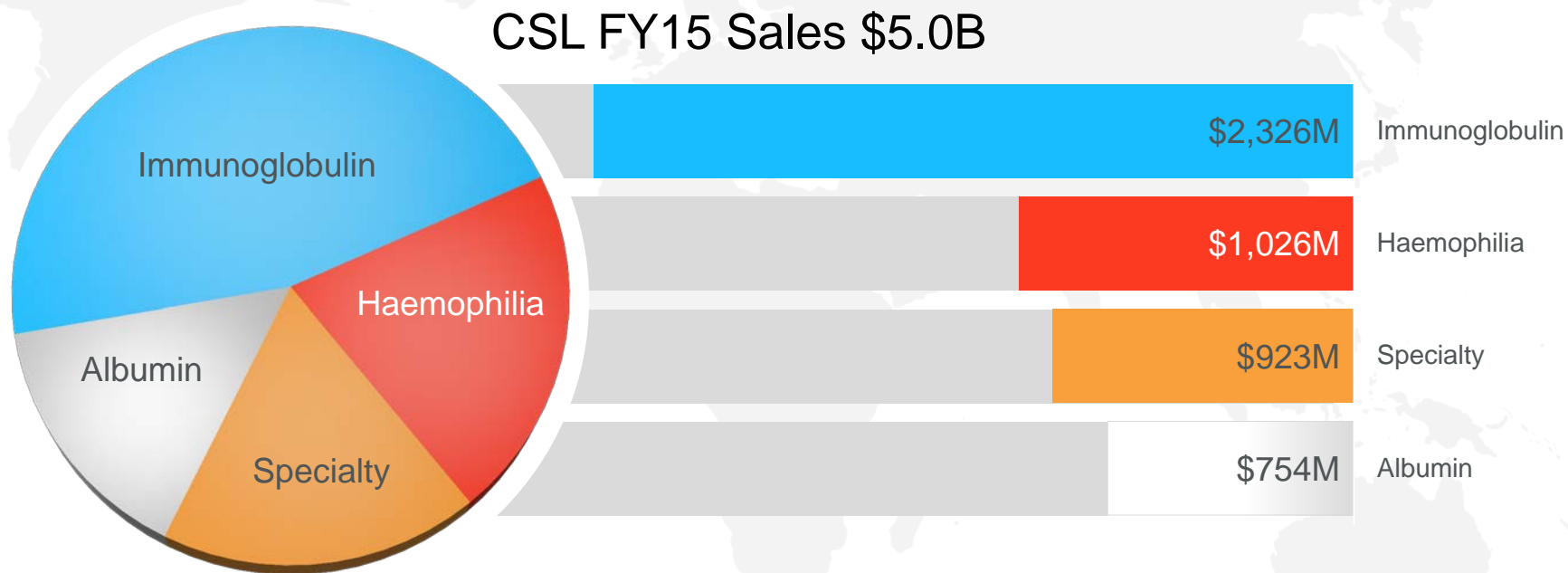


A dark teal background featuring a stylized world map. The map is centered, showing the continents of North America, South America, Europe, Africa, Asia, and Australia. The text is overlaid on the map.

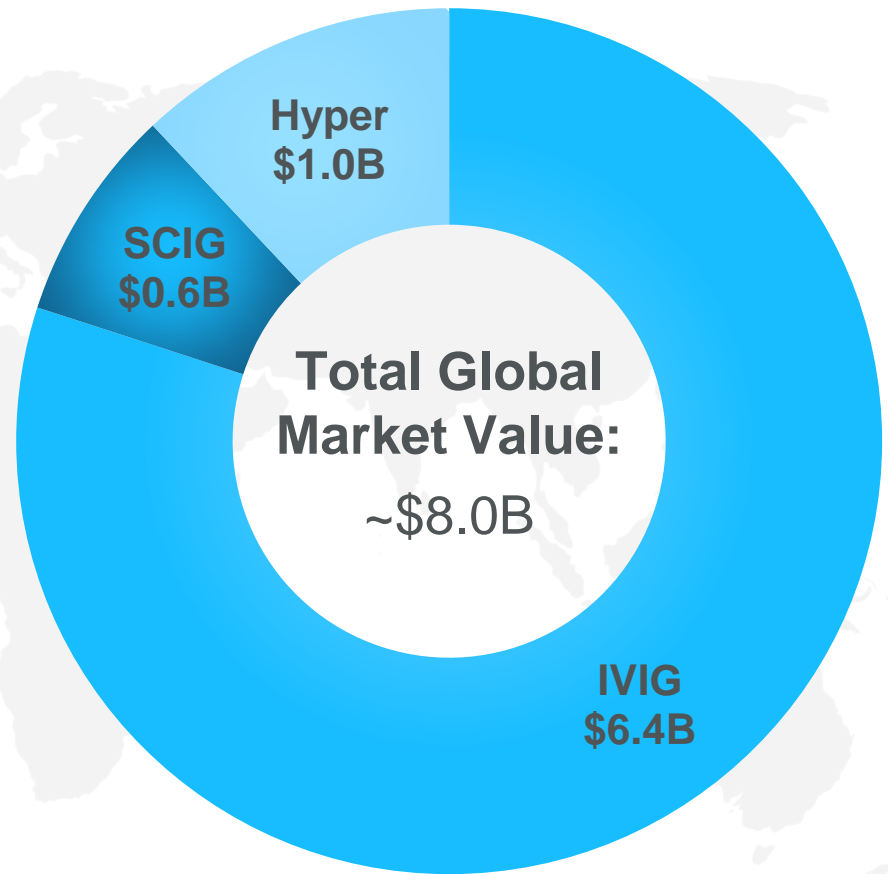
# **Commercial Opportunities and Activities**



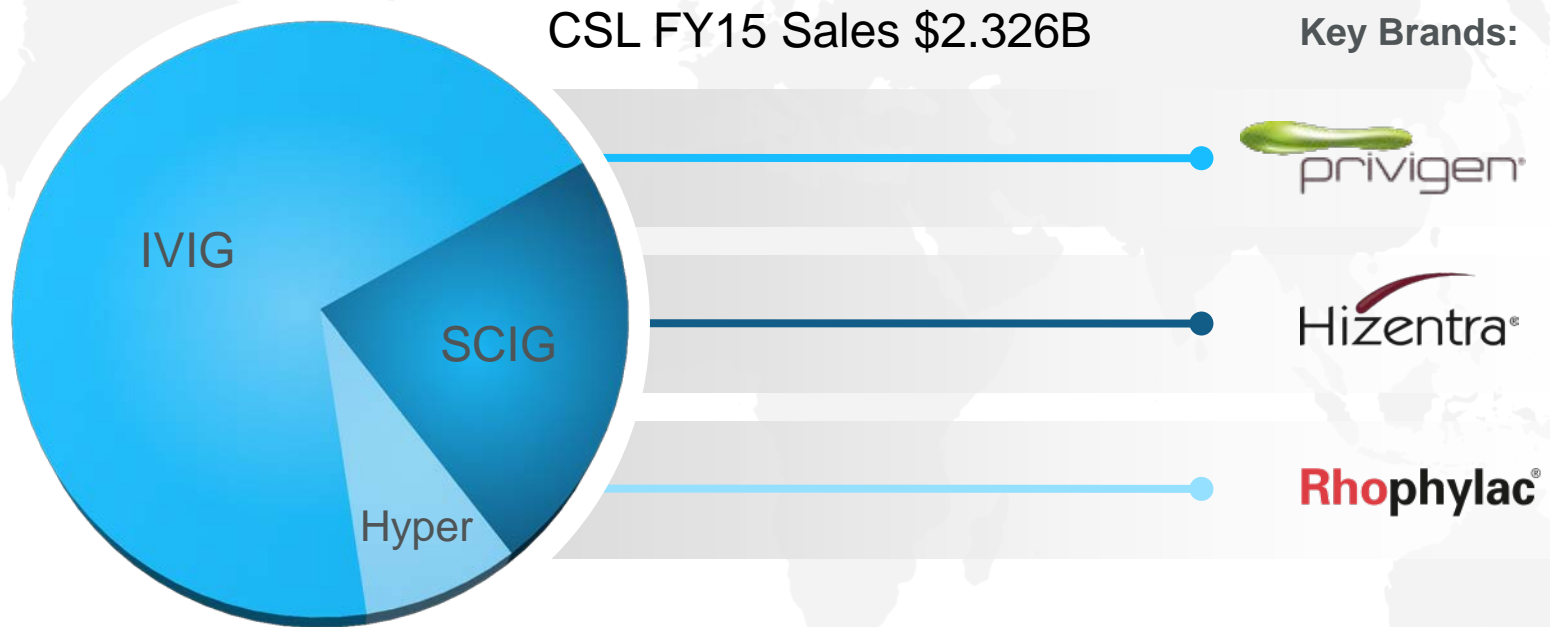
**Sources:** Company annual reports/financial schedules, MRB global Coagulation Factors Concentrate Market 2014 & 2015, MRB WW Plasma Fractionation Market 2014 interim report, CSL Actuals FY15



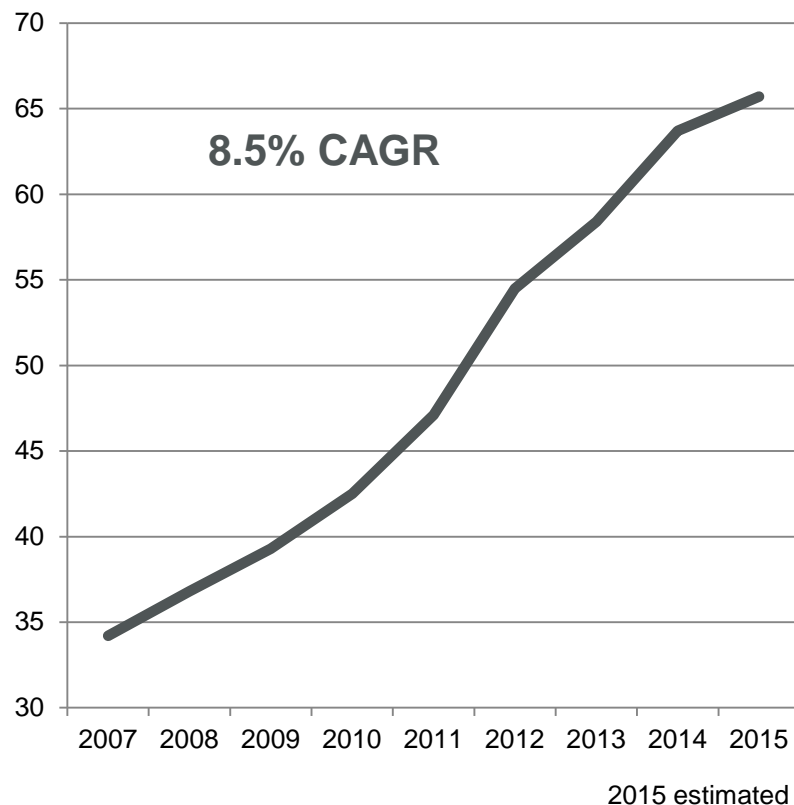
- IVIG continues to hold largest share of market
- Increasing acceptance and growth of SCIG



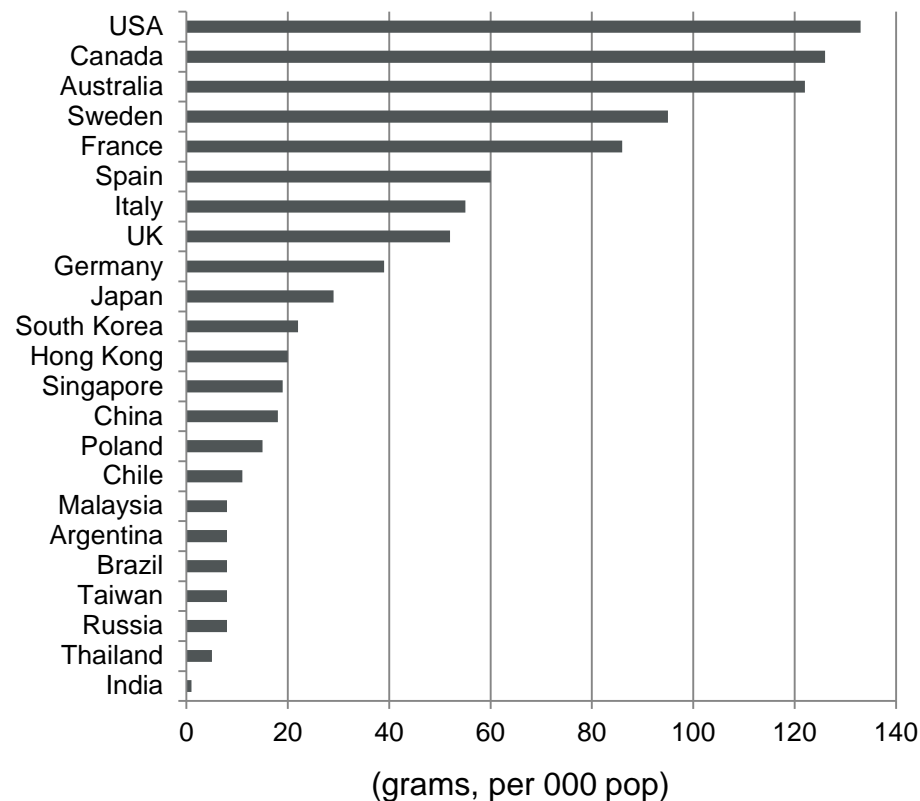
**Sources:** Company annual reports, Markets and Markets Plasma Fractionation Report 2015, based on 2014 data, CSL Actuals FY15



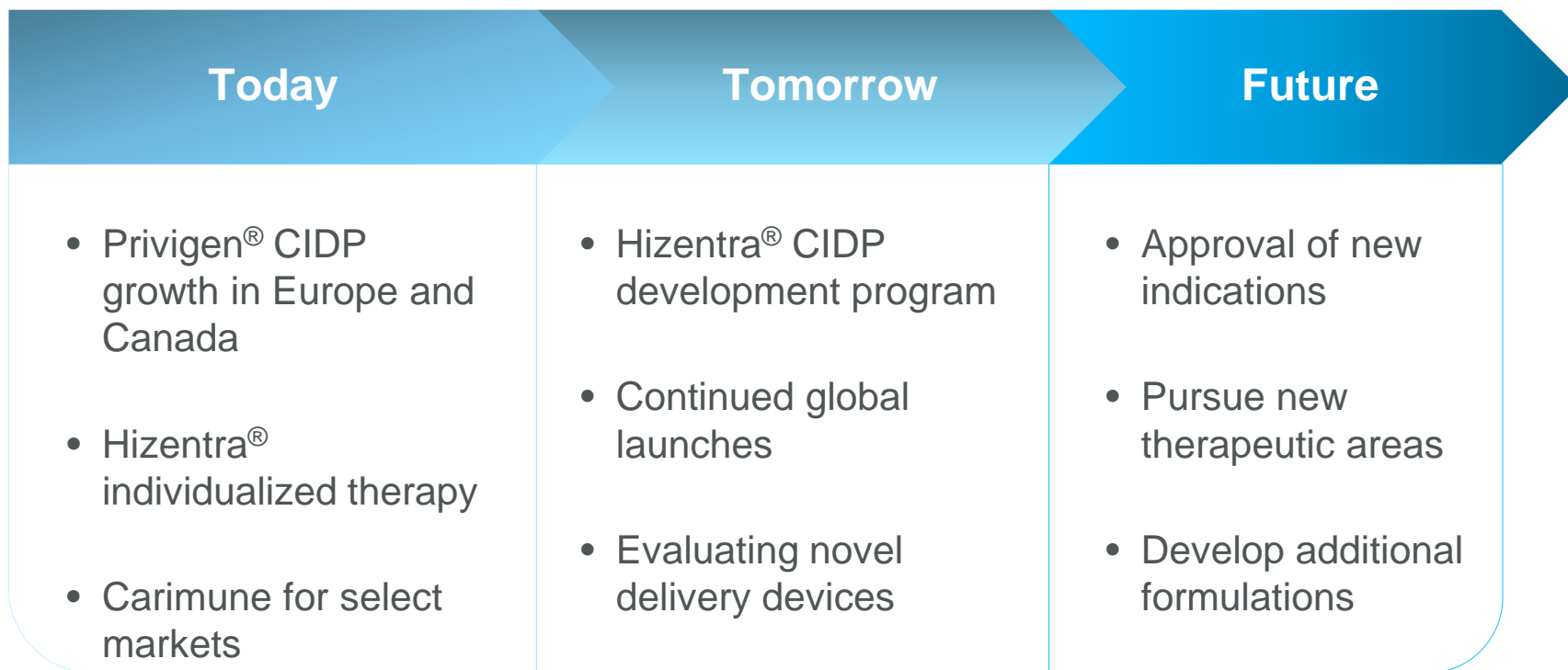
### US-PPTA Data (Kg, 000)



### Per-Capita IG Use

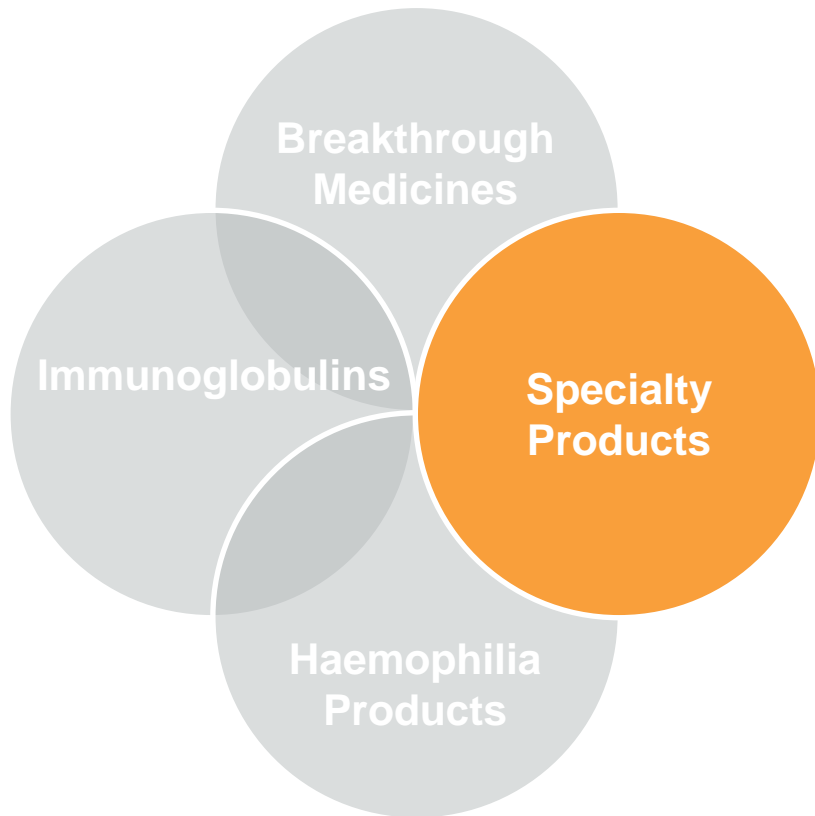


Sources: PPTA. Note: PPTA reported incomplete data for 2011. MRB 2011



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## Specialty Products



- Leveraging high quality broad product portfolio through:
  - New markets
  - Novel indications
  - Novel modes of administration
- Key Focus
  - Beriplex<sup>®</sup>/Kcentra<sup>®</sup>
  - Berinert<sup>®</sup>, CSL830
  - Zemaira<sup>®</sup>/Respreeza<sup>®</sup>

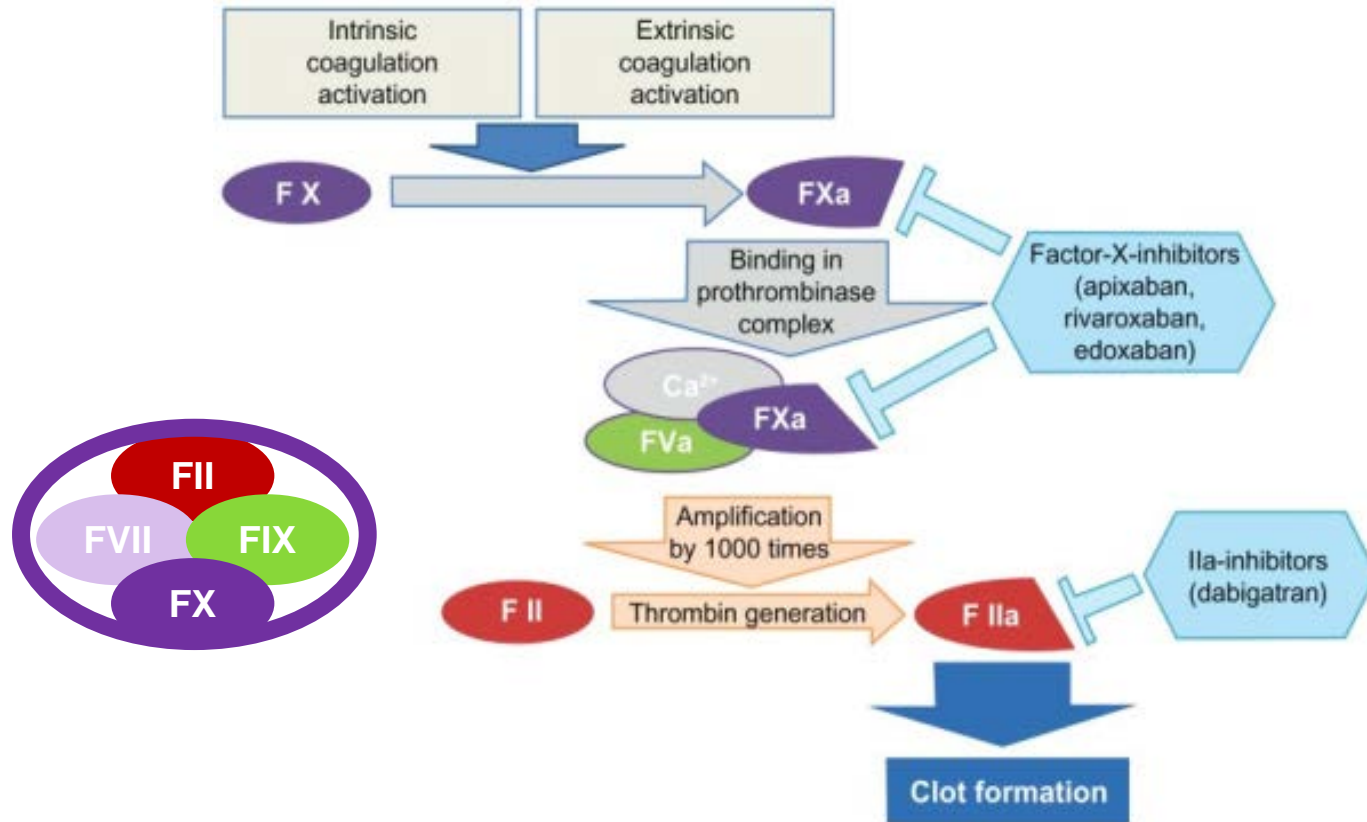
- Prothrombin Complex Concentrate = PCC (4FPCC)
    - Vitamin K-dependent coagulation factors (FII, FVII, FIX, FX)
  - Indicated as an agent to reverse the effects of vitamin K antagonists (e.g. Warfarin) for:
    - Bleeding related to over-anticoagulation
    - Patients needing urgent surgery
- 
- Expanding into new geographies
  - Explore utility in treating patients bleeding with receiving Novel Oral Anticoagulants (NOACs) – Factor Xa and Factor IIa inhibitors

**Kcentra®**  
**Beriplex®** P/N

- Clinical study evaluating vitamin K antagonist reversal in acute bleeding and for surgery
  - Open label study almost completed
  - Demonstrated effective INR reversal at 30 minutes
  - No safety concerns
  - PMDA submission Q2 2016
- Availability of Beriplex<sup>®</sup> will address a high unmet medical need specifically highlighted by Japan Ministry of Health and Welfare

Beriplex<sup>®</sup> P/N

## Coagulation Cascade and Mechanisms of Anti-coagulation



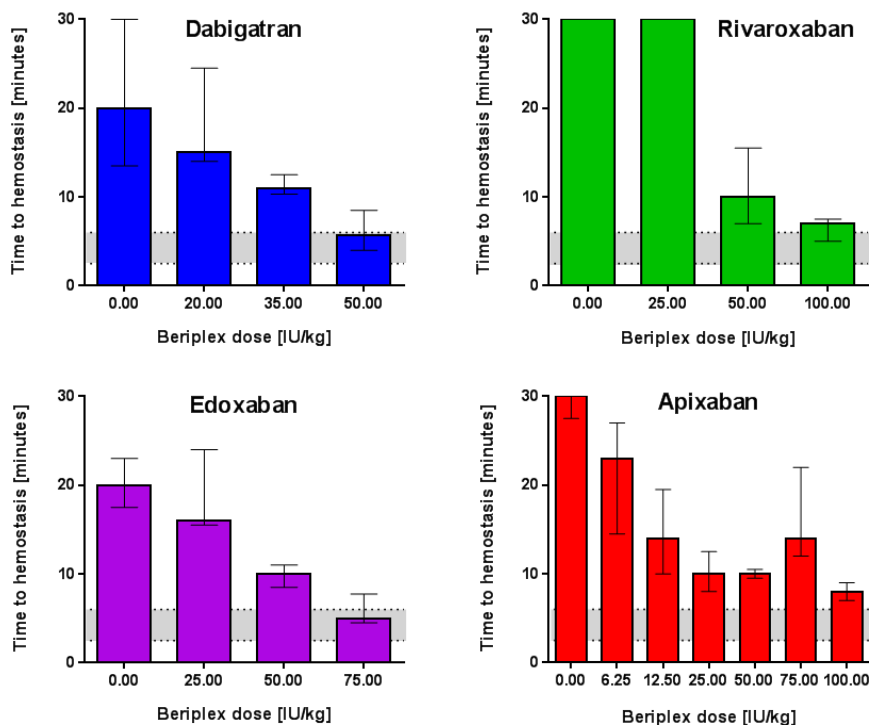
### Reversal of Anti-coagulation Effect in a Bleeding Patient

- Antidotes being developed to reverse the anti-coagulation activity of Factor Xa or IIa inhibitors
  - Studies demonstrate normalisation of clotting tests
  - Bleeding studies not yet available
- 4FPCCs in healthy volunteers also reverse prothrombin time prolongation
  - 50IU/kg Beriplex® dose reversed the anticoagulant effect of edoxaban<sup>1</sup>

**Can bleeding be stopped or controlled to allow for urgent medical or surgical care?**

**References:** 1. Circulation. 2014;CIRCULATIONAHA.114.013445 published online before print November 17 2014

## 4FPCC in the Control of Bleeding – Animal Data



Data represent medial plus interquartile range. Shaded area represents sham treated control range.

**References:** Pragst et al. JTH 2012; 10(9): 1841-48. Herzog et al. Thromb Res 2014; 134(3):729-36. Dickneite and Hoffman 2014; 111(2):189-98. Herzog et al. Anaesthesiology 2015; 122(2):387-98. Herzog et al. Thromb Res 135 (2015) 554–560. Herzog et al. Critical Care 205; 19(1):P348.

### **Kcentra® / Beriplex® in Treatment of Acute Major Bleeding Related to FIIa or FXa Inhibitor Use**

- USA and international expert groups recommend inclusion of PCC in guidelines as agent to reverse anticoagulant effect of NOACs<sup>1,2,3</sup>
- Hospital treatment algorithms increasingly including PCC
- Clinical program under consideration to assess control of severe bleeding

**References:** 1. Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults. *American Society of Hematology* 2011. 2. EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *European Society of Cardiology* 2013. 3. Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: Proposals of the Working Group on Perioperative Haemostasis (GIHP) 2013

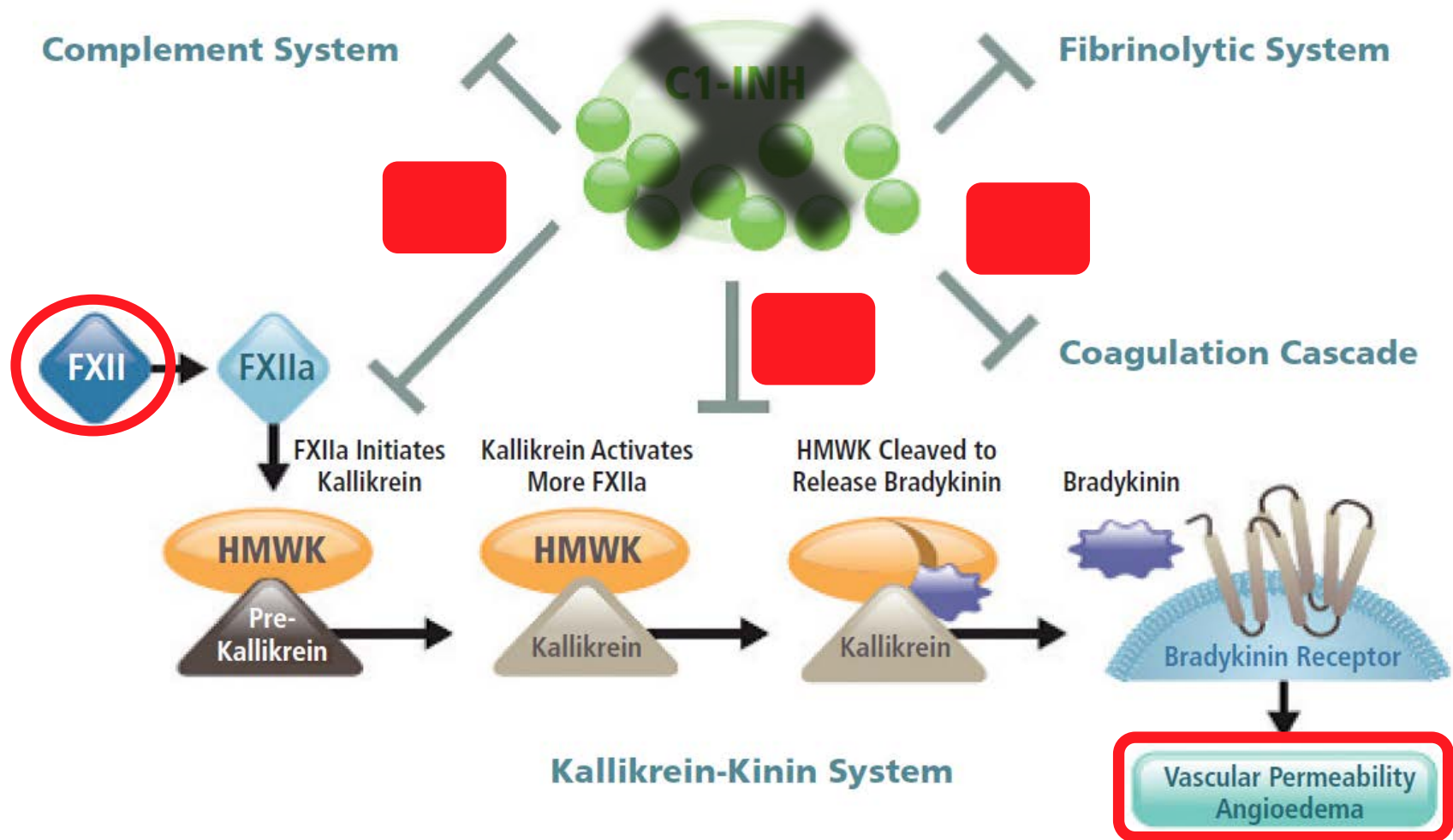
### *Berinert*<sup>®</sup>

- Plasma derived, pasteurised and nanofiltered concentrate of C1 Esterase Inhibitor indicated for the intravenous treatment of acute abdominal laryngeal or facial attacks of Hereditary Angioedema (HAE) in adults and adolescents



### *CSL830*

- Plasma derived, pasteurised and nanofiltered higher concentrated C1 Esterase Inhibitor indicated for the routine prevention of Hereditary Angioedema (HAE) attacks in adult and adolescent patients



HMWK=High molecular weight kininogen.



- HAE is unpredictable
- All body sites are associated with impairment; not just laryngeal attacks
- It impacts people not just during attacks, but also in between attacks
- Attacks are associated with significant anxiety: this anxiety is proportionate to the severity and pain of individual attacks
- Results in missed opportunities in terms of school and career, as well as significant absences from work for both patients and carers

The HAE-Burden of Illness Study in Europe (HAE-BOIS) 2012-4

**References:** Caballero T. *et al. Allergy Asthma Proc.* 2013; Aygören-Pürsün E *et al. ISPOR* 2012; Bygum *et al. Acta Derm Venereol* 2015.

## HAE attack frequency does not link with severity

1-24  
attacks/year



25-52  
attacks/year



53-104  
attacks/year



>104  
attacks/year



~78%



~13%



~6%

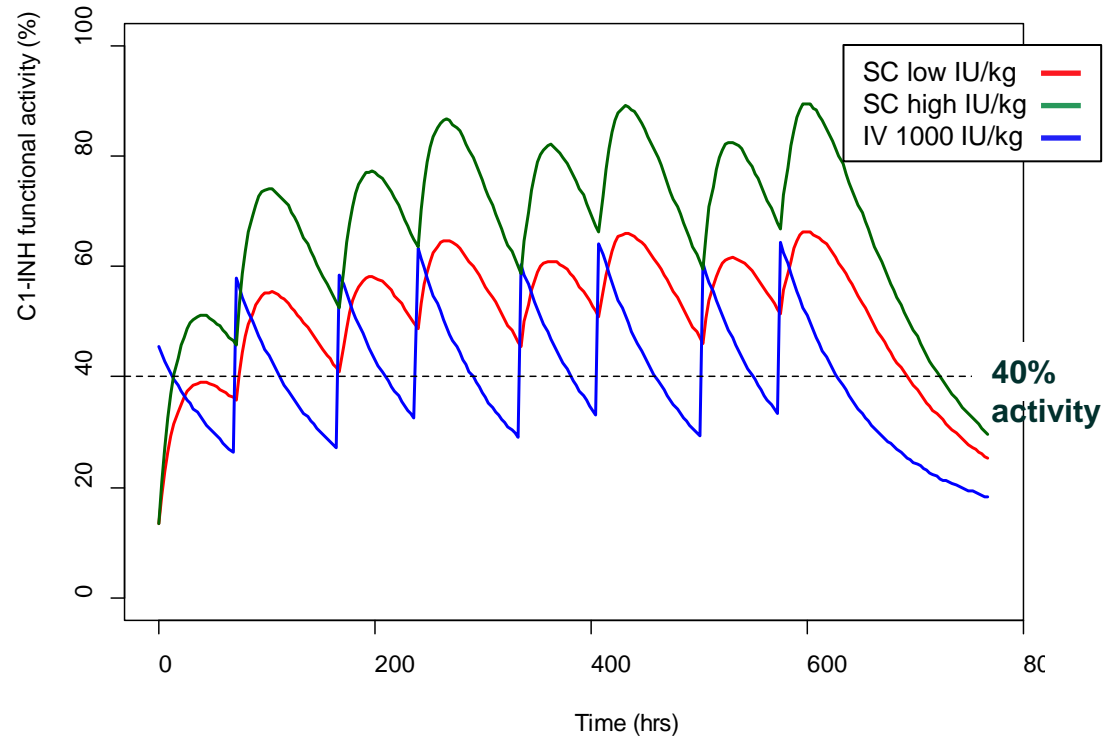


~3%

Still has significant  
disease burden

## Subcutaneous Dosing Maintains Trough above Protective C1-INH Level

- SC trough remains above predictive 40% threshold
- Potential for reduced attack rate

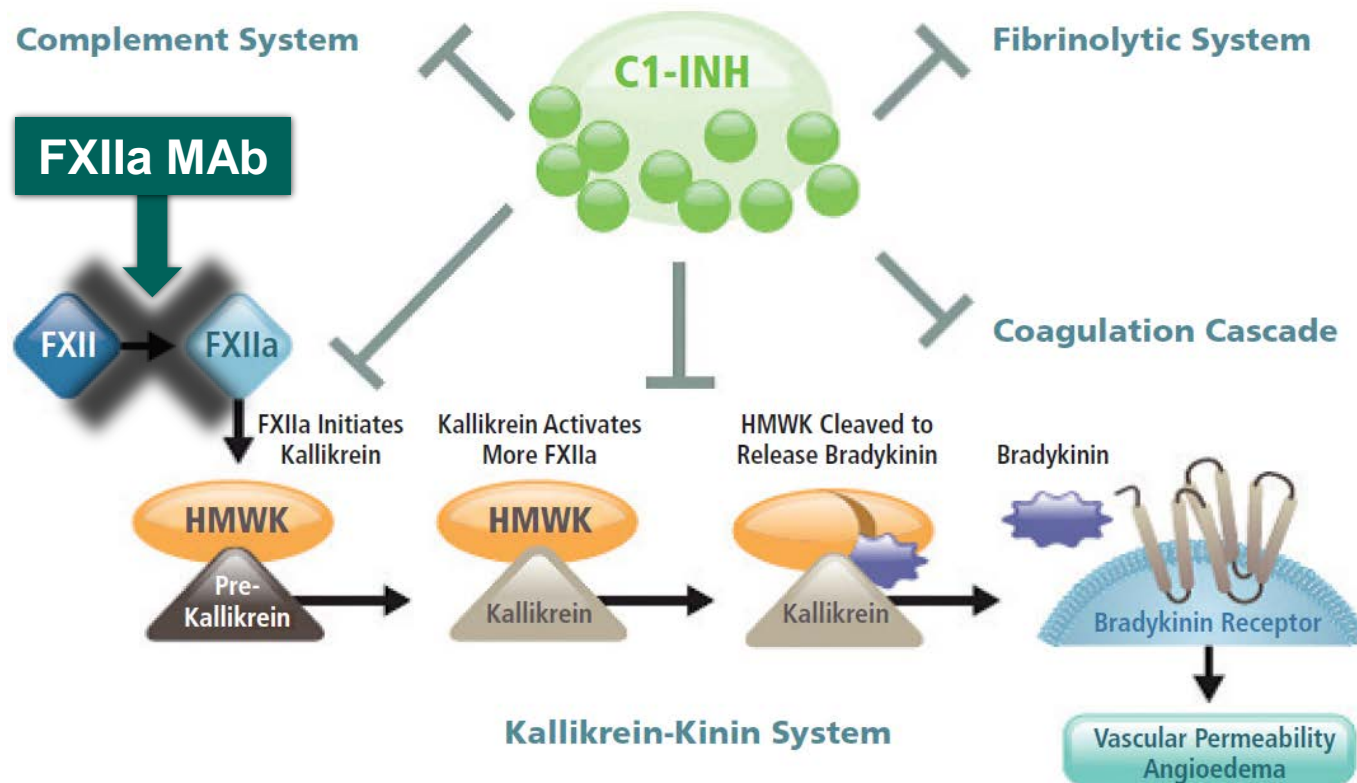


References: Zuraw et al. Allergy 2015; 70: 1319-1328

- Phase III study rapidly completed enrollment (n=90)
- Patients moving into extension study
  - Allowed for individualised dosing
  - Well tolerated
  - No withdrawals for lack of efficacy
- Submission to FDA and EU anticipated 2H 2016

**compact**  
Clinical Studies for Optimal Management in  
Preventing Angioedema with low-volume  
subcutaneous C1-inhibitor Replacement Therapy

## Bringing new technologies to the HAE space CSL312 – Anti XIIa monoclonal antibody

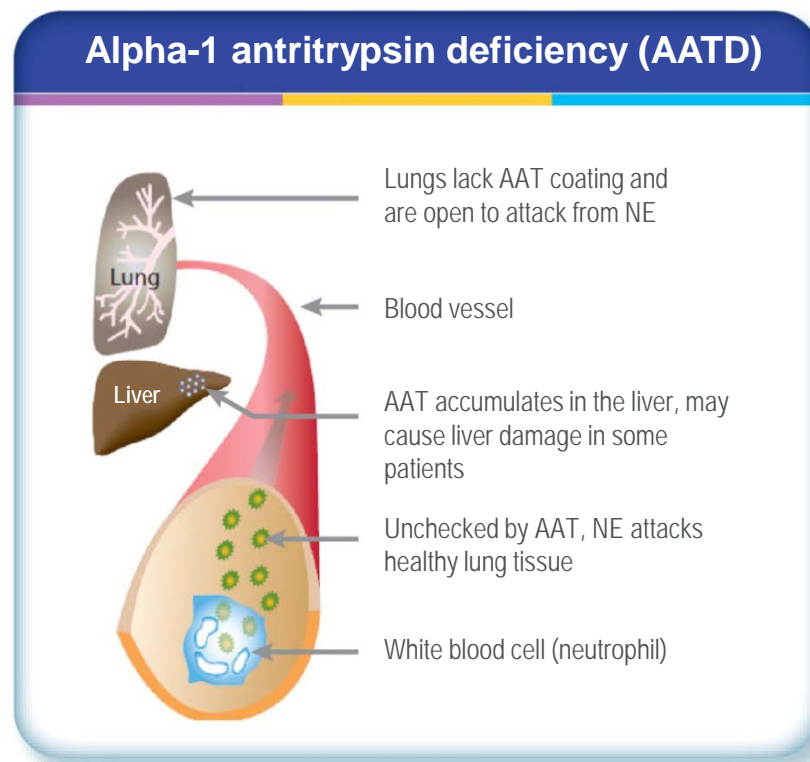
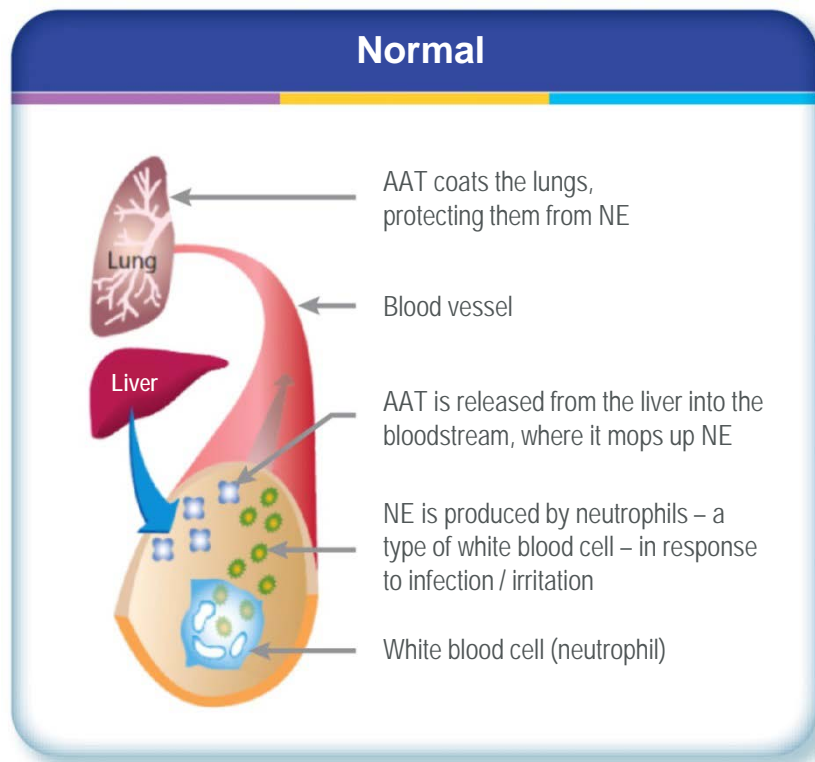


HMWK=High molecular weight kininogen.

- New molecule and target – potential benefit:
  - In refractive patients
  - For HAE types I, II and III as well as ACE inhibitor induced oedema
  - For subcutaneous delivery every 2 to 4 weeks
  - Other indications
- Commence first in man studies 2H 2016

- Respreeza® is a highly purified alpha-1 therapy approved by EMA for maintenance treatment to slow the progression of emphysema in adults with severe alpha-1 antitrypsin deficiency (AATD)
- RAPID trial is largest placebo controlled study in patients with AATD (Chapman KR *et al. Lancet* 2015; 386: 360-368)
- Respreeza® approved by EMA in August 2015

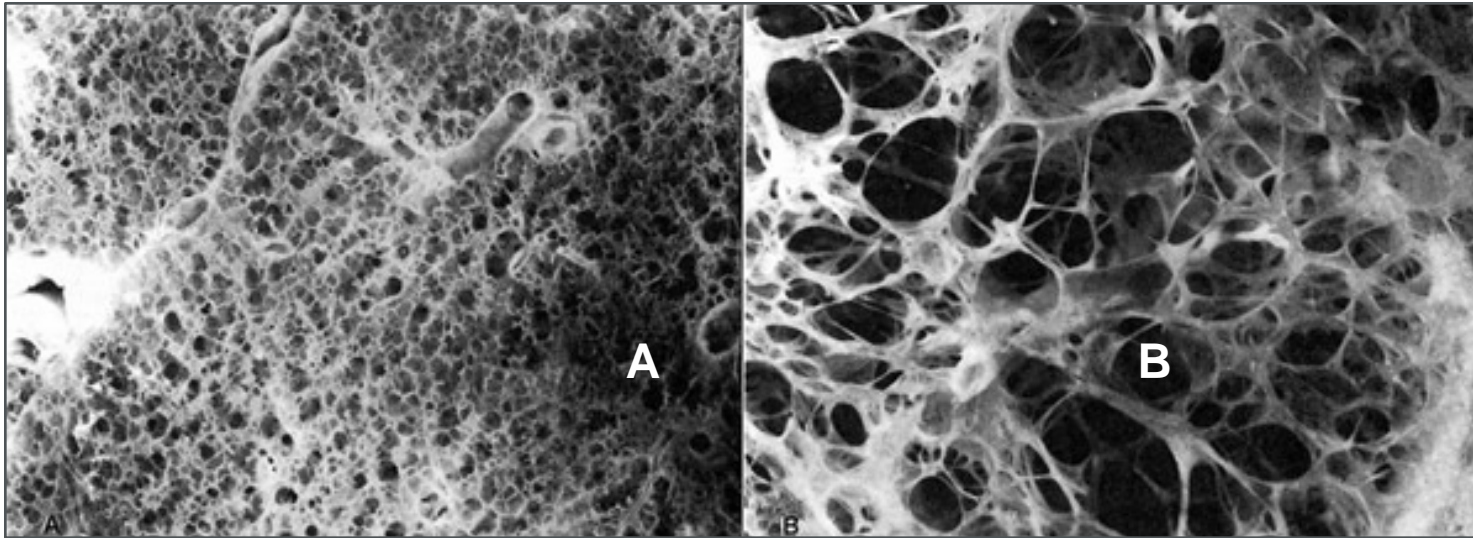




**References:** CSL Behring Data on File. Alpha-1 Antitrypsin Deficiency Counseling Tool 2008

## AATD Leads to Lung Tissue Deterioration

Images from high-resolution computerised tomography scanning



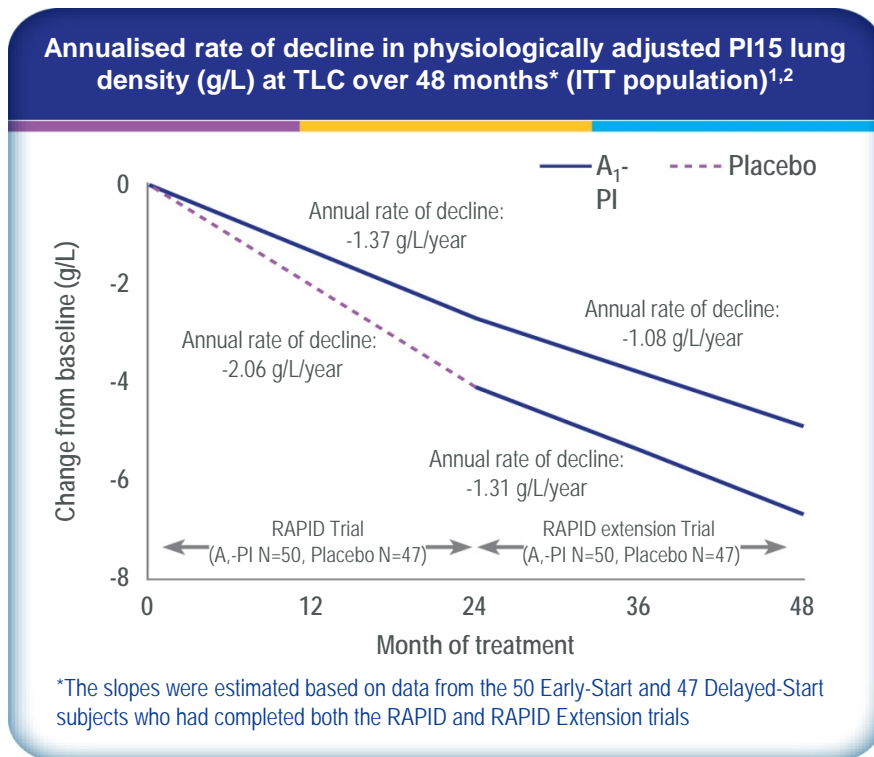
normal lung (left; A)

severe emphysema (right; B)

**References:** <http://www.ctsnet.org/portals/thoracic/newtechnology/article-4>

## RAPID Program – Respreeza® Slowed Rate of Lung Density Decline from Baseline

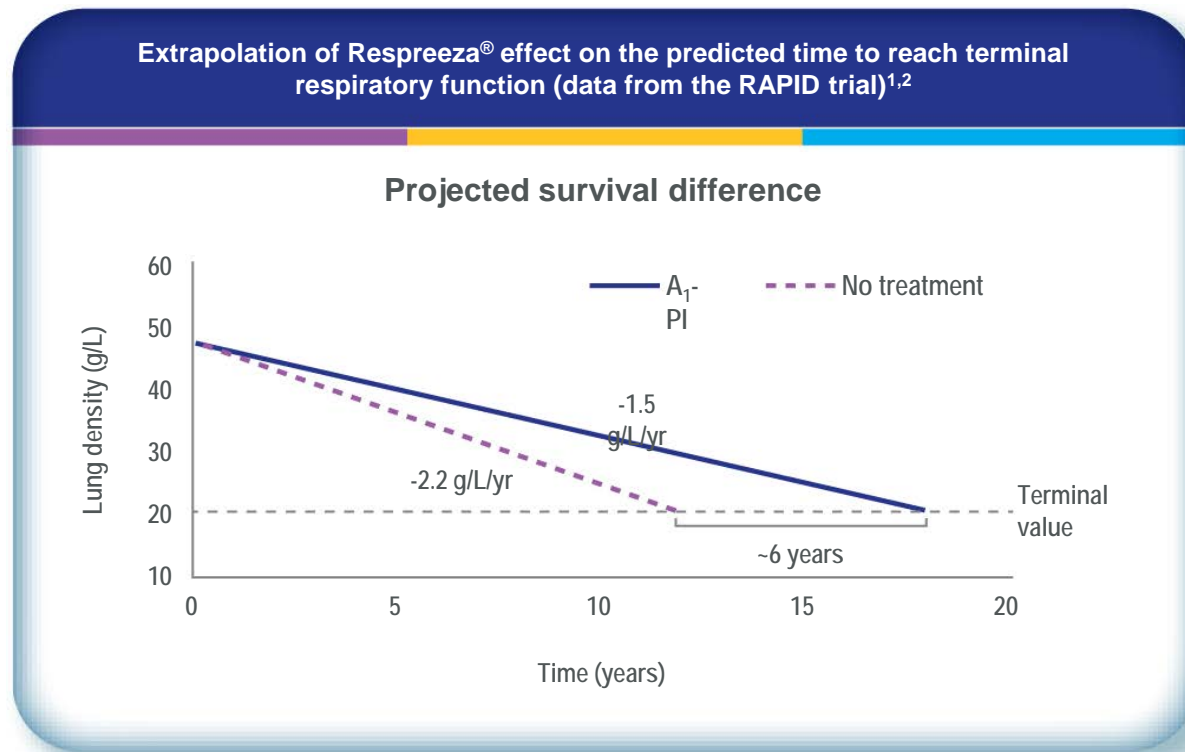
- Difference in annual decline from baseline to Month 24 favours Early-Start
- Lost lung density in the Delayed-Start group could not be regained
- Early-Start group maintained a therapeutic benefit for 4 years



References: 1. Chapman, KR *et al. Lancet* 2015; 386: 360-368. 2. CSL Behring. Data on File. Dec 2013 Interim Analysis of Extension Trial

## Estimate of Long-Term Clinical Benefit<sup>1,2</sup>

- RAPID program demonstrates a specific treatment has been shown to delay the progression of and modify disease in patients with severe AATD

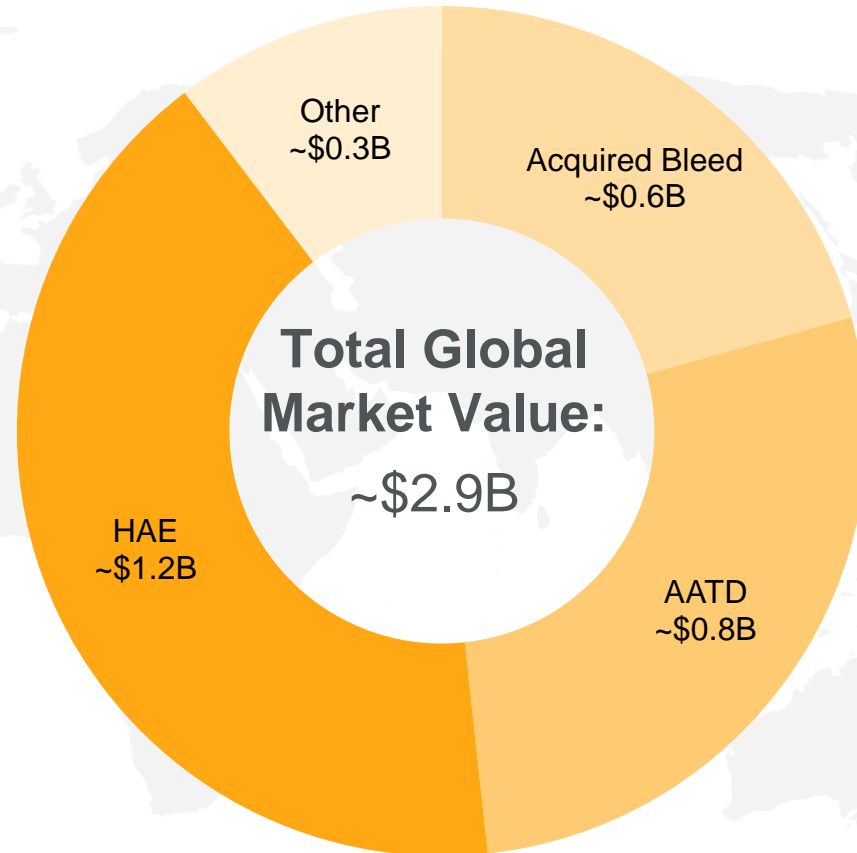


Extrapolation based on: 1. Chapman, KR *et al. Lancet* 2015; 386: 360-368. 2. CSL Behring. Data on File. RAPID Trial Clinical Study Report. November 2013

A dark teal world map is centered in the background of the slide. The map shows the outlines of the continents in a slightly lighter shade of teal.

## **Commercial Opportunities and Activities**

- Orphan/rare diseases
- Unmet medical need
- Often under or misdiagnosed
- Awareness and education
- Significant patient value

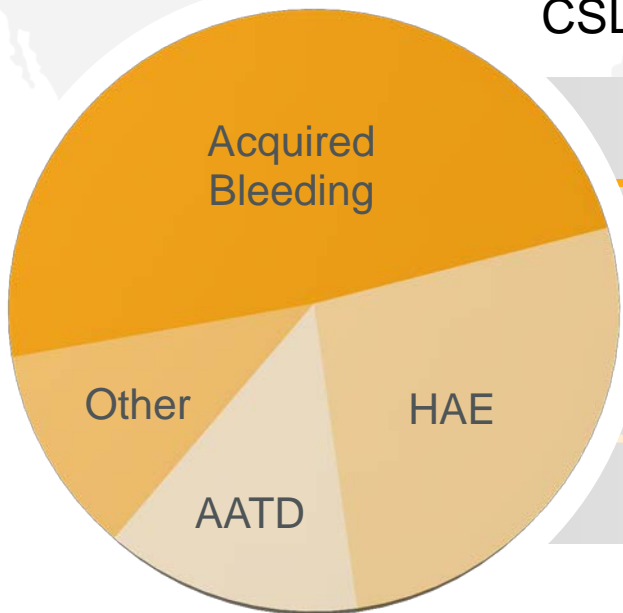


**Sources:** Company annual reports/financial schedules, based on 2014 data, MRB WW Plasma Fractionation Market 2014 interim report, CSL Actuals FY15

- Increase demand
- Geographical expansion
- Appropriate diagnosis

CSL FY15 Sales \$923M

Key Brands:



**Kcentra®**  
**Beriplex® P/N**  
**RiaSTAP®**

**BERINERT®**

**Zemaira®**  
**Respreeza®**

### *Warfarin Reversal*

- Indicated for patients with acute major bleeds, requiring urgent surgery or invasive procedure
- Data published in Lancet
- Utilised by over 2,000 hospitals in the US
- Broad EU experience and expansion in emerging markets
- Japan clinical development program ongoing

### *NOAC Reversal*

- Evaluating clinical development options
- Potential benefit in patients with significant bleeds
- Institutional guidelines, expert groups and scientific societies
- Animal and human data published in peer-review journals
- Prospective registry data

<i>Berinert</i> <sup>®</sup>	<i>CSL830</i>	<i>CSL312</i>
<ul style="list-style-type: none"> <li>• C1-INH for acute treatment</li> <li>• Fast relief of pain and swelling</li> <li>• Short-term prophylaxis in EU</li> <li>• Geographic expansion (Asia, LATAM)</li> </ul>	<ul style="list-style-type: none"> <li>• C1-INH for prophylaxis</li> <li>• Phase III pivotal study fully enrolled</li> <li>• Subcutaneous delivery</li> <li>• Steady-state blood levels could reduce breakthrough attacks</li> <li>• Eliminates need for patient IV ports</li> <li>• US and EU filing targeted for 2016</li> </ul>	<ul style="list-style-type: none"> <li>• Fully human, high affinity mAb targeting FXIIa</li> <li>• Activation of FXIIa is key step in complement pathway</li> <li>• Effective in animal models for HAE I, II and III and ACE inhibitor induced oedema</li> <li>• Subcutaneous delivery every 2 to 4 weeks</li> <li>• Phase I 2H 2016</li> </ul>

### *Zemaira*<sup>®</sup>

- Indicated in the US for chronic augmentation and maintenance therapy
- Ongoing education programs to support appropriate diagnosis
- DNA1 test kit to confirm known/unknown variants
- Geographic expansion in Latin America

### *Respreeza*<sup>®</sup>

- Approved in the EU for hereditary emphysema 3Q2015
- EU API market is ~\$200M USD
- Demonstrated to slow the progression of emphysema
- Rapid data published in the Lancet
- Only highly purified formulation available in EU

A stylized world map in a light teal color, centered on the Atlantic Ocean, serving as a background for the slide.

**Q&A**

A dark teal world map is centered in the background of the slide. The word "Break" is written in white, bold, sans-serif font, centered over the map.

**Break**

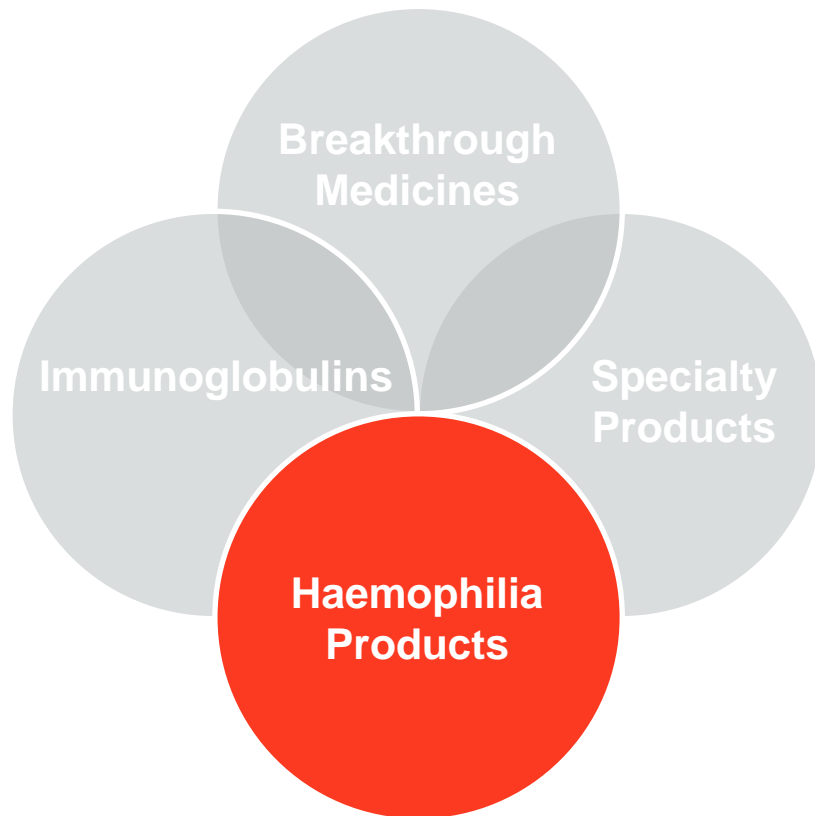
A dark teal background featuring a stylized world map in a lighter shade of teal. The map shows the outlines of continents and major landmasses.

# Investor R&D Briefing

December 10, 2015

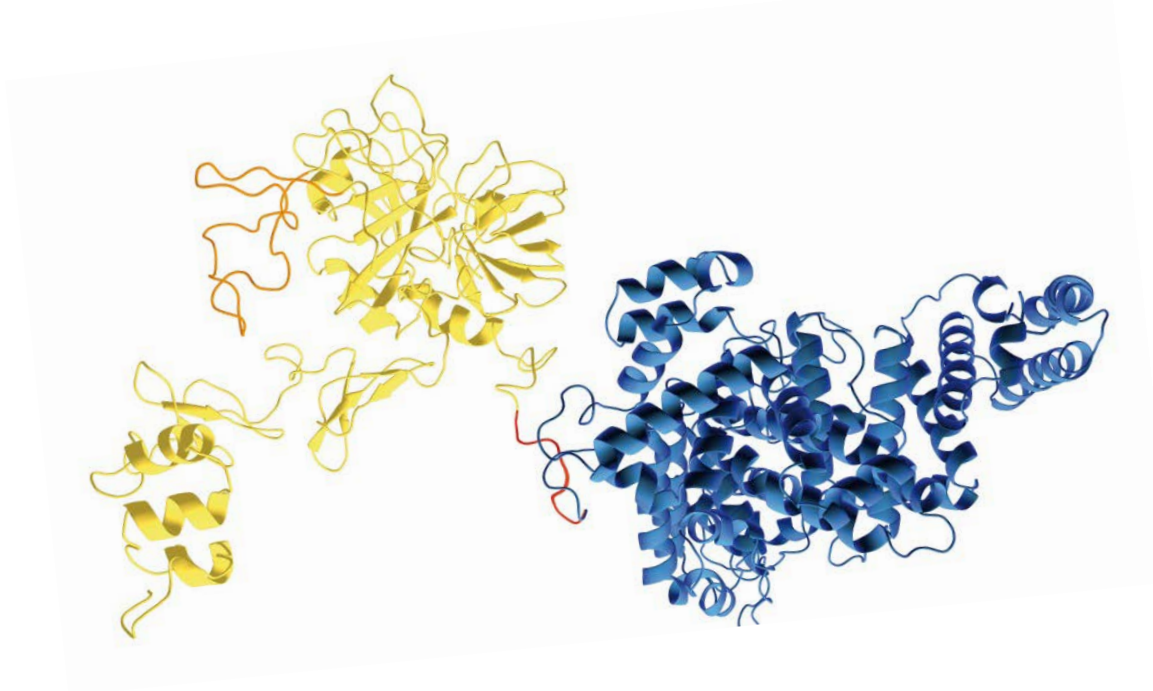
A dark teal world map is centered in the background of the slide. The continents are visible in a slightly lighter shade of teal.

# Haemophilia Products



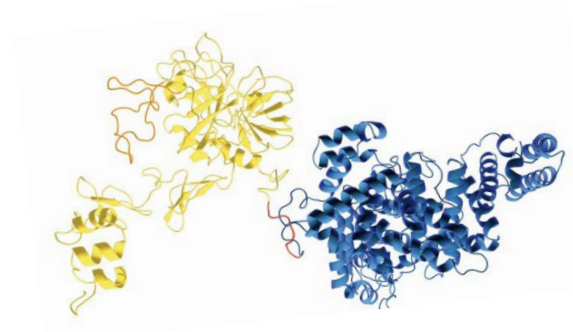
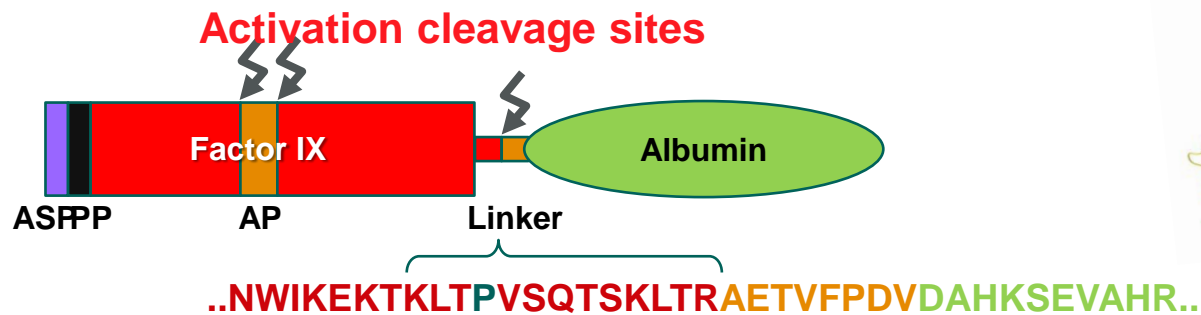
- Supporting and enhancing plasma products and developing novel recombinant portfolio with focus on:
  - Scientific and product innovation
  - Patient benefit
- Key Focus
  - IDELVION™ (rIX-FP)
  - AFSTYLA™ (rVIII-Single Chain)
  - Long acting rVIIa-FP

## PROLONG-9FP Clinical Development Program IDELVION™ (rIX-FP)



References: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

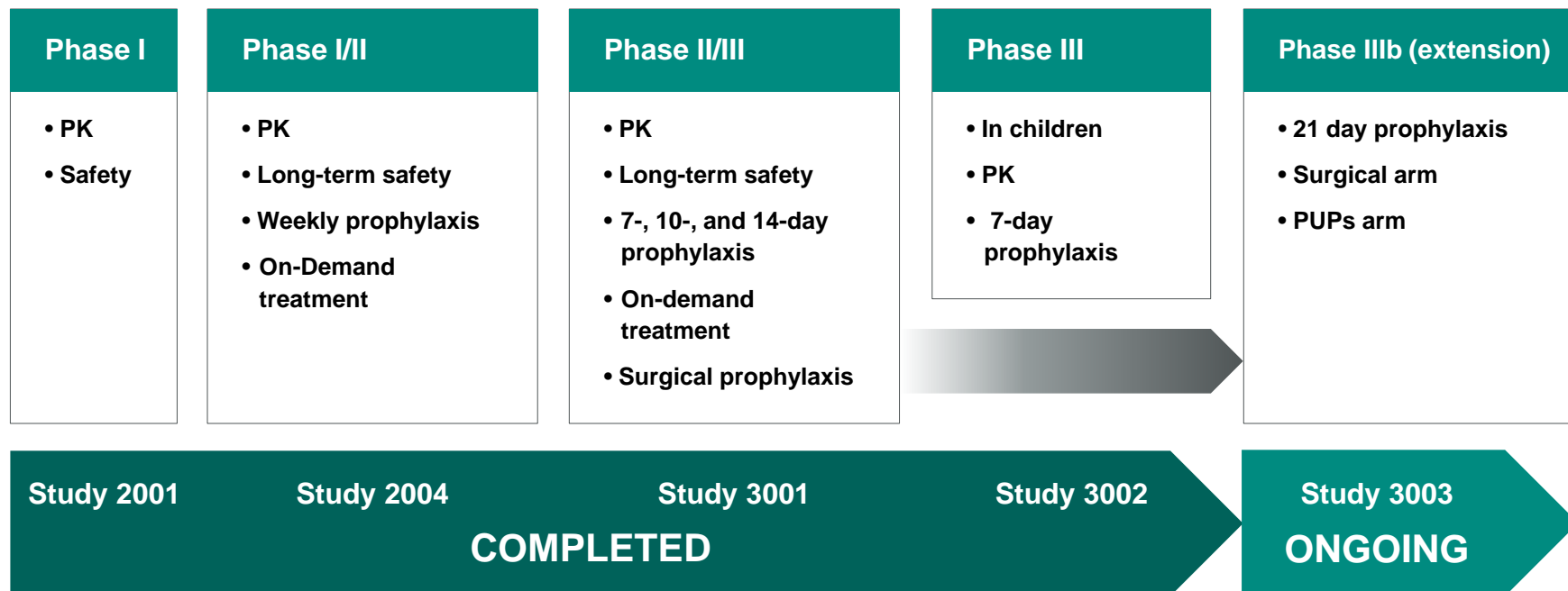
PROLONG **9** FP



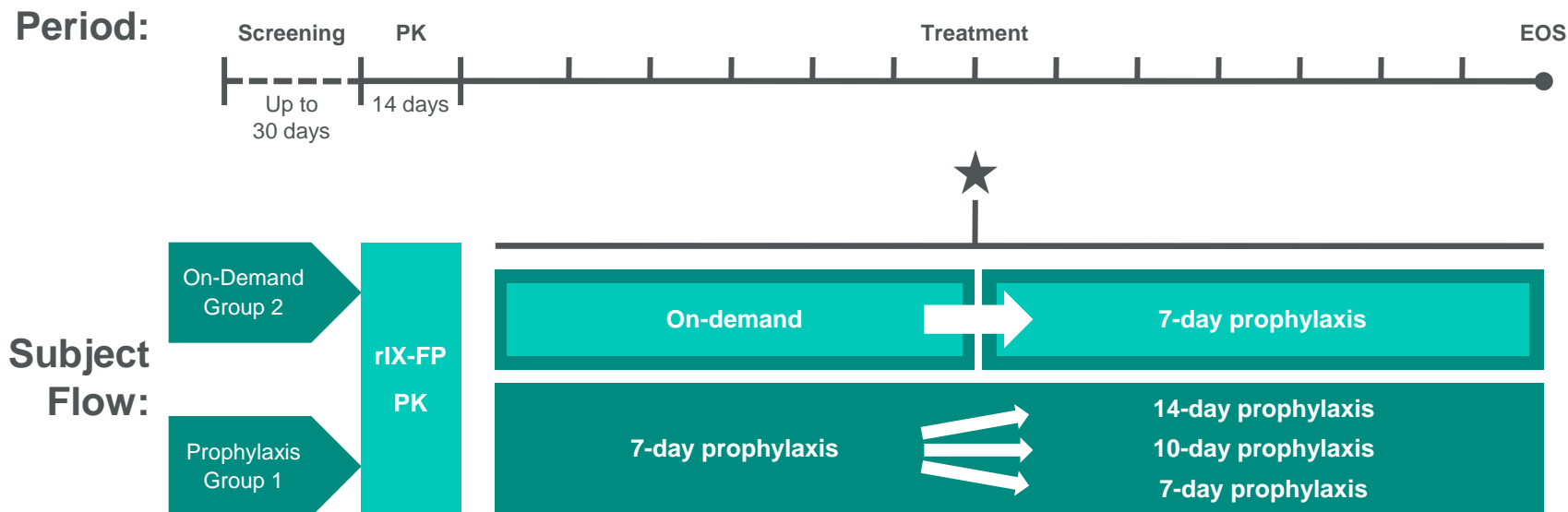
- rIX-FP is
  - A recombinant protein purified from CHO cells
  - Generated by the genetic fusion of recombinant albumin to rFIX

### PROLONG-9FP PROGRAM

Prove longer duration of action of rIX-FP addresses existing unmet medical needs by providing less frequent dosing

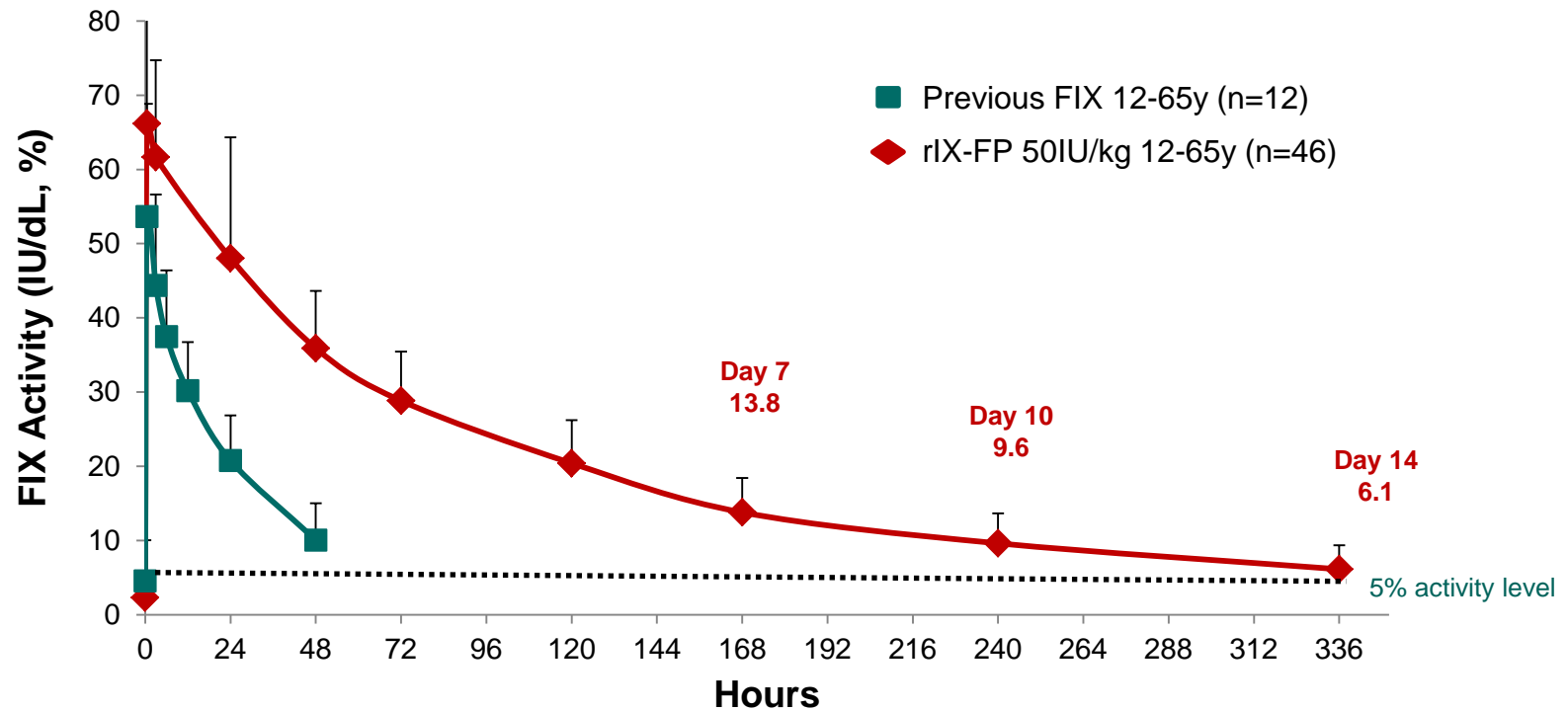


PK – pharmacokinetics; PUP – previously untreated patient



★ PK assessments were repeated in a subset of patients at Week 26; patients who met the switching criteria began a longer treatment interval  
EOS – end of study; PK – pharmacokinetics

## IDELVION™ shows sustained activity above 5% activity out to 14 days



- Shifts patient from severe  $<1\%$  to mild  $\geq 5\%$  FIX activity

\*WFH Guidelines for the Management of Hemophilia. 2<sup>nd</sup> Edition. Hemophilia; Epub 6 July 2012

## rlX-FP prophylaxis reduced spontaneous and overall bleeding rate

Adult On-Demand vs. Prophylaxis	Within-subject comparison (n=19) rlX-FP		AsBR reduction
	On-demand period ~6 months	Prophylaxis period ~12 months	
AsBR, median (IQR)	15.43 (7.98–17.96)	0.0 (0.00–0.96)	100% (p<0.0001)
Target joint(s), n (%)	10 (53)	0	
Estimated total ABR (95% CI)*	18.22 (15.38-21.58)	1.81 (0.97–3.37)	

\*Assuming Poisson distribution

ABR – annualised bleeding rate; AsBR – annualised spontaneous bleeding rate; CI – confidence interval; IQR – interquartile range

## rIX-FP Effective in 7 and 14 days regimens in Adults

	Within-subject comparison	
	7-day n=21	14-day n=21
<b>AsBR, median (IQR)</b>	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)
Median dose (IU/kg)	40 IU/kg	75 IU/kg

AsBR – annualised spontaneous bleeding rate; IQR – interquartile range

## Paediatric Reduction of ABR among previously on-demand patients

Subject	Age	AsBR		Total ABR		Weekly rIX-FP dose (IU/kg)
		Prior to study	In study	Prior to study	In study	
1	8y	31	3.5	39	5.9	65 IU/kg
2	7y	34	2.4	42	4.7	65 IU/kg
3	4y	15	0	19	1.2	50 IU/kg

ABR – annualised bleeding rate; AsBR – annualised spontaneous bleeding rate

## Low Bleeding Rates During Weekly Prophylaxis Treatment in Children

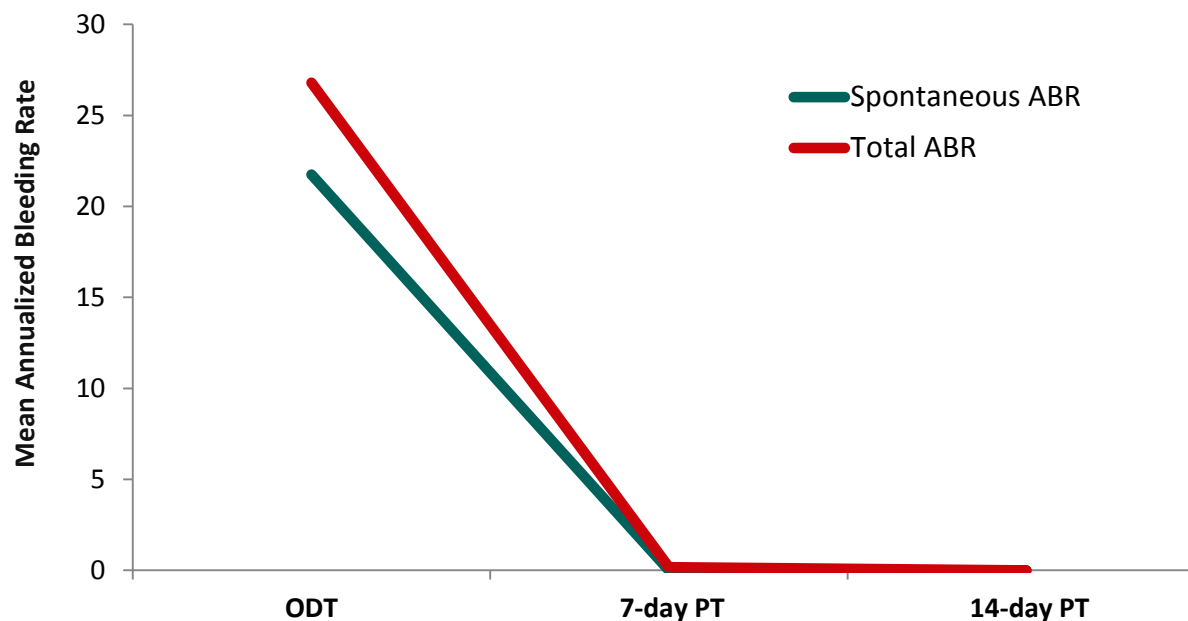


ABR		Age <6 years (n=12)	Age 6-11 years (n=15)
Spontaneous	Median	<b>0.00</b>	<b>0.78</b>
	IQR	0.00, 0.10	0.00, 1.99
Total Joint	Median	<b>0.5</b>	<b>1.13</b>
	IQR	0.00, 1.45	0.00, 2.36
Total	Median	<b>2.6<sup>1</sup></b>	<b>3.4<sup>1</sup></b>
	IQR	2.00, 6.48	0.76, 5.91
Prophylaxis IU/kg	Median	<b>48.7</b>	<b>42.6</b>
	IQR	44.8, 56.2	40.4, 51

**References:** 1. Data include 3 subjects previously receiving only on-demand treatment; 8 treated nasal bleeds

ABR – annualised bleeding rate; IQR – interquartile range

## Patients respond to long-term prophylaxis therapy (4.2 years) in PROLONG-9FP program

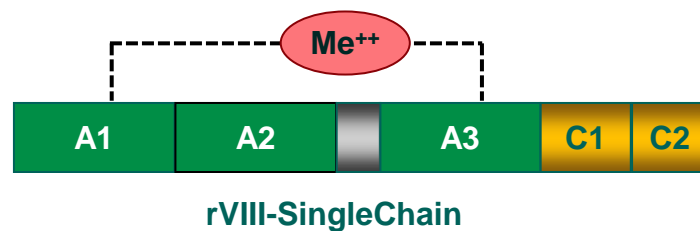
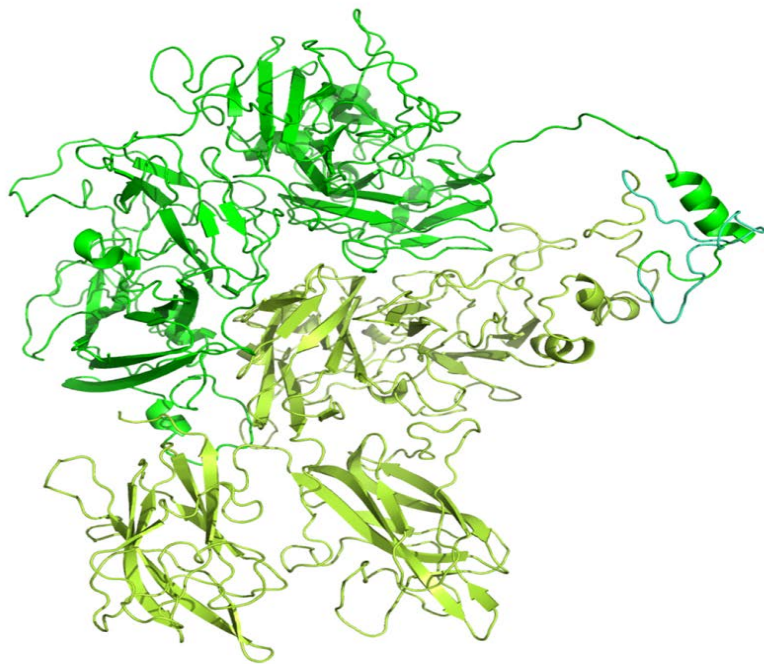


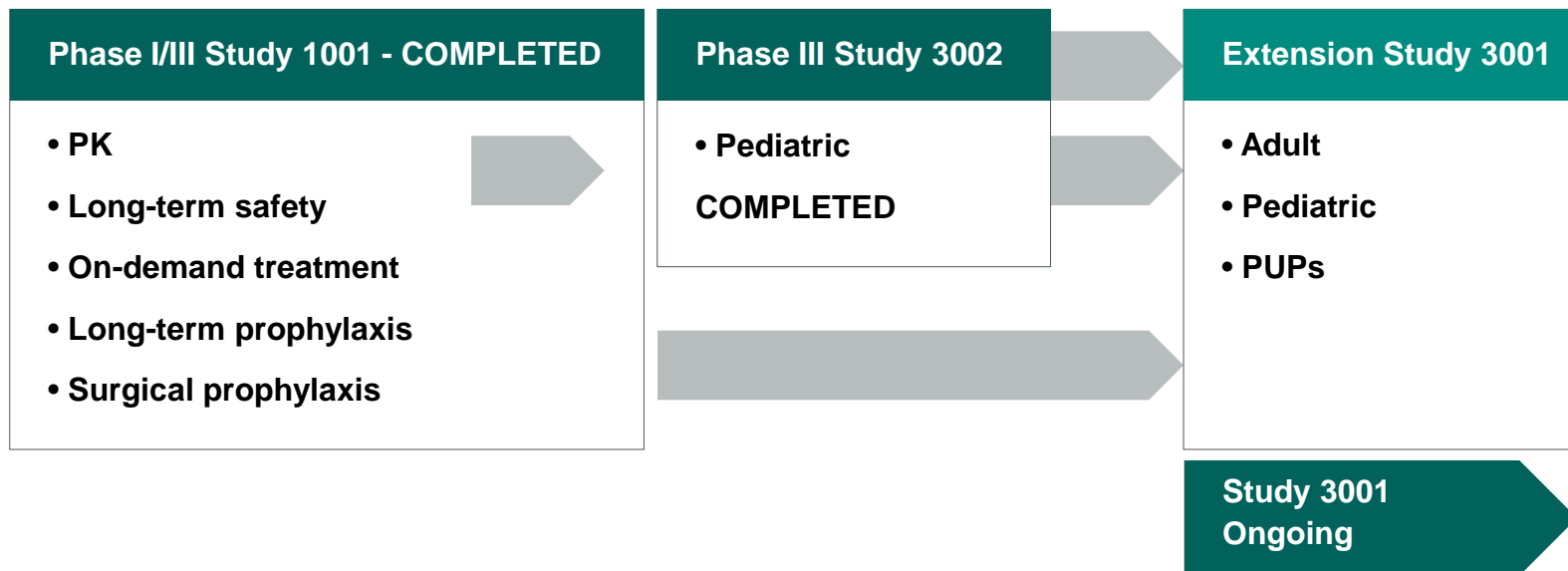
Reduction in ABR and AsBR in patients moving from on-demand to long term prophylaxis

15 males (ages 15-46 years) with hemophilia B (FIX  $\leq 2\%$ ) with a mean of 175 Exposure Days (EDs) (range 121-232) to rIX-FP over 4.2 years on rIX-FP

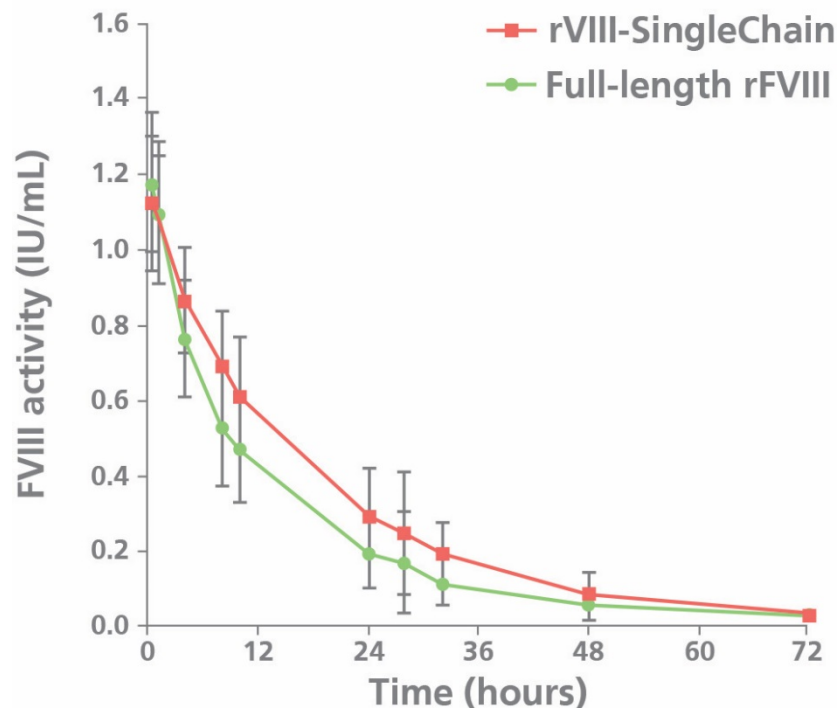
- Extension study ongoing EMA post marketing commitment
  - Previously untreated patients being enrolled
- Adult and pediatric indications under review by EMA and FDA
- FDA and Canadian approval expected Q1 2016
- EMA approval expected Q2 2016







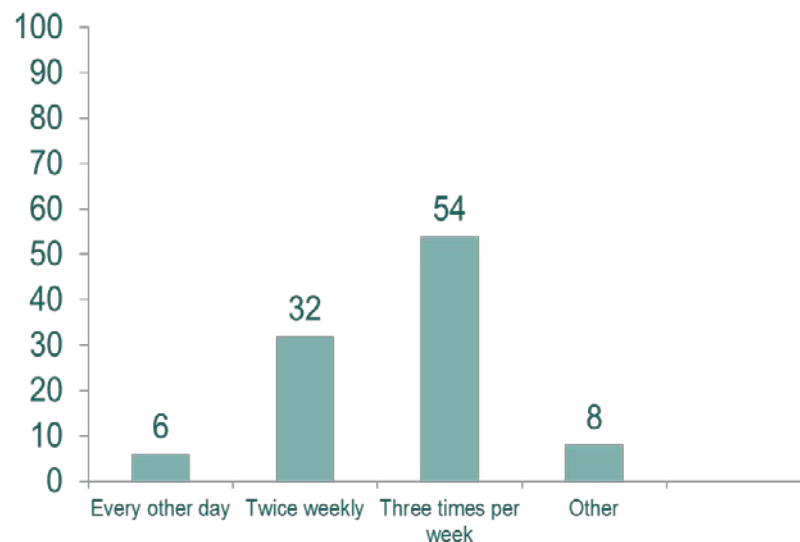
- Improved PK:
  - Lower clearance, greater AUC and longer half-life compared with otcocog alfa
- Well tolerated locally and systemically
- Excellent efficacy controlling bleeds and for surgical procedures



## rVIII-SingleChain effective in 2x and 3x weekly Prophylaxis Regimen

- On demand arm (n=27)
  - median ABR = 19.64
- Prophylaxis arm (n=146)
  - median ABR = 1.14
  - median AsBR = 0.00
- Comparable ABR in the 2x and 3x week regimens

Routine Prophylaxis: Percentage of subjects in each assignment (%)



	Individualized (mean 3.5 days)		3x Weekly		2x Weekly		Weekly	
	ABR	AsBR	ABR	AsBr	ABR	AsBr	ABR	AsBr
rVIII SC			1.14	0	1.14 (20-50IU/kg)	0		
Efmorotocog alfa <sup>1</sup> (rVIII Fc fusion)	1.6 (25-65IU/kg)						3.6 (65IU/kg)	
BAX855 <sup>2</sup> (rVIII pegylated)					1.9 (40-50IU/kg)	0		
Octocog alfa <sup>3</sup> (rVIII 3 <sup>rd</sup> generation)			4					
Turtucog alfa <sup>4</sup> (rVIII 3 <sup>rd</sup> generation)			3.7					

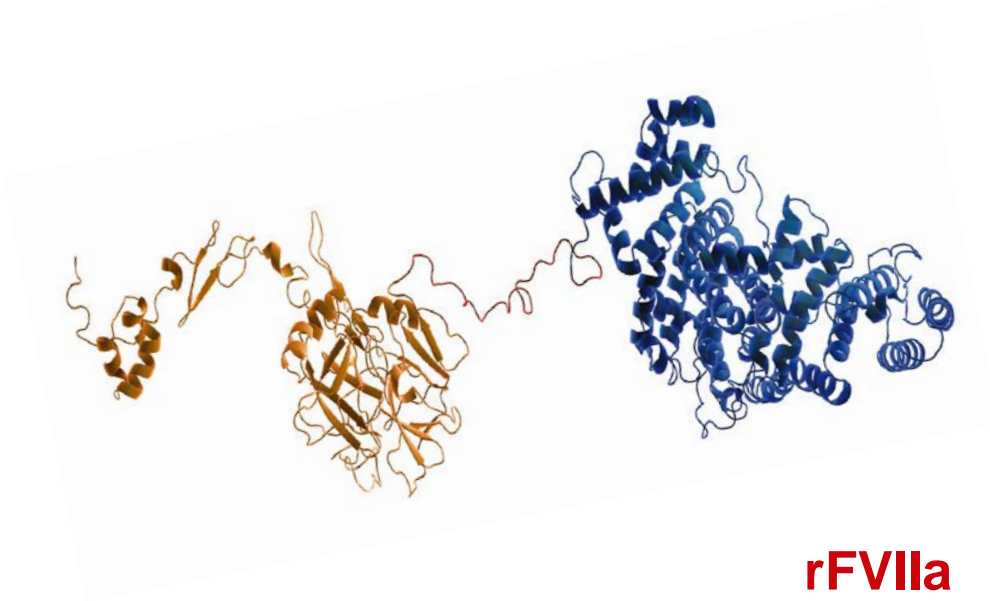
\*Not direct head to head clinical comparison

**References:** 1. Mahlangu, J et al. *Blood* 2014;123(3):317-25. 2. Adynovate full prescribing information Baxalta Nov 2015. 3. Kavakli K et al. *J Thromb Haemost* 2015;13:360-9. 4. Lentz SR et al. *Haemophilia* 2013;19(5):691-7

ABR – annualised bleeding rate; AsBR – annualised spontaneous bleeding rate

- Extension study ongoing fulfilling EMA post marketing commitment
  - Previously untreated patients being enrolled
- Accepted by FDA June 2015, approval expected mid 2016
- Filed to EMA December 2015





**rFVIIa**

**Linker**

**rAlbumin**

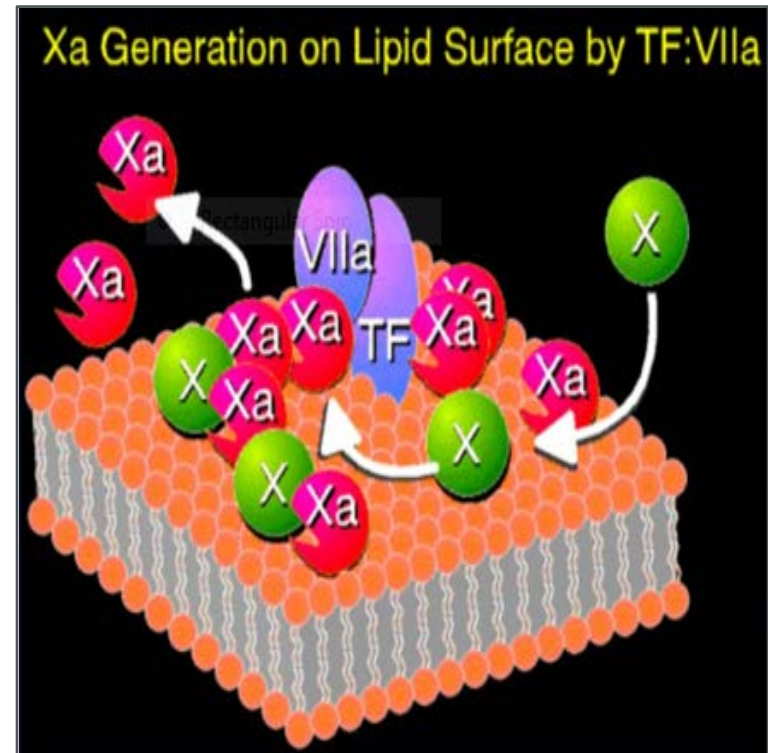


**PROLONG 7 FP**

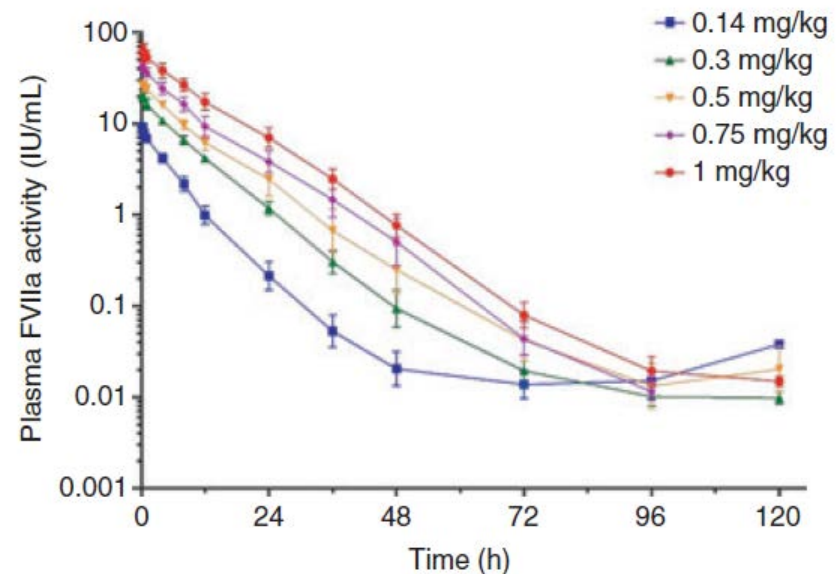
- Occurs when patient develops inhibitory antibodies to the coagulation factor (FVIII or FIX)
- Genetic predisposition / mutations
- Occurs early, highest risk in previously untreated patients
  - 34% inhibitor incidence, develop within 20 exposures

**References:** Peyvandi et al. <https://ash.confex.com/ash/2015/webprogram/Paper82866.html>

- rVlla-FP can lead to the formation of a stable hemostatic plug to control bleeding
  - works locally by binding to tissue factor exposed at the site of vascular injury
  - Also binds to factor X on activated platelets

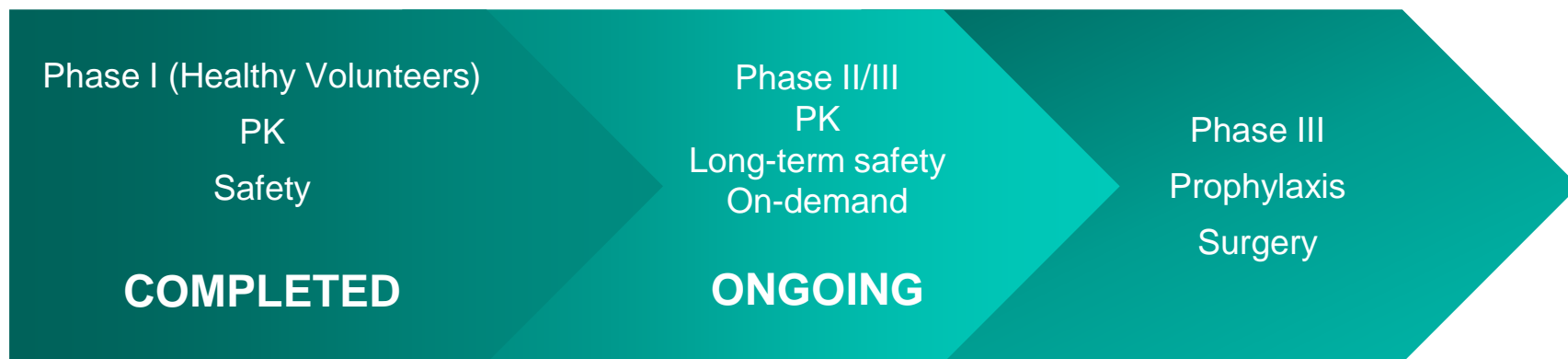


- CSL689 half-life = 8.5 hrs<sup>1</sup>
  - Potential to dose 2-3 x weekly
  - Possibility of on demand and manageable prophylaxis regimen
- rFVIIa (Novoseven) half life ~2-3hrs
  - Indicated for treatment of bleeding episodes- requires dosing every 2-3 hours<sup>2</sup>



**References:** 1. Golor G et al. *J Thromb Haemosr* 2013 Nov;11(1):1977-85. 2. NovoSeven Full Prescribing Information USA

### Congenital Haemophilia with Inhibitors



- Pivotal Phase II/III trial in haemophilia A & B patients with inhibitors
  - Dose finding, safety & efficacy on-demand therapy
  - Commenced first half 2015
  - Bleeding episode successfully treated

PROLONG **7** FP

### Congenital Factor VII Deficiency



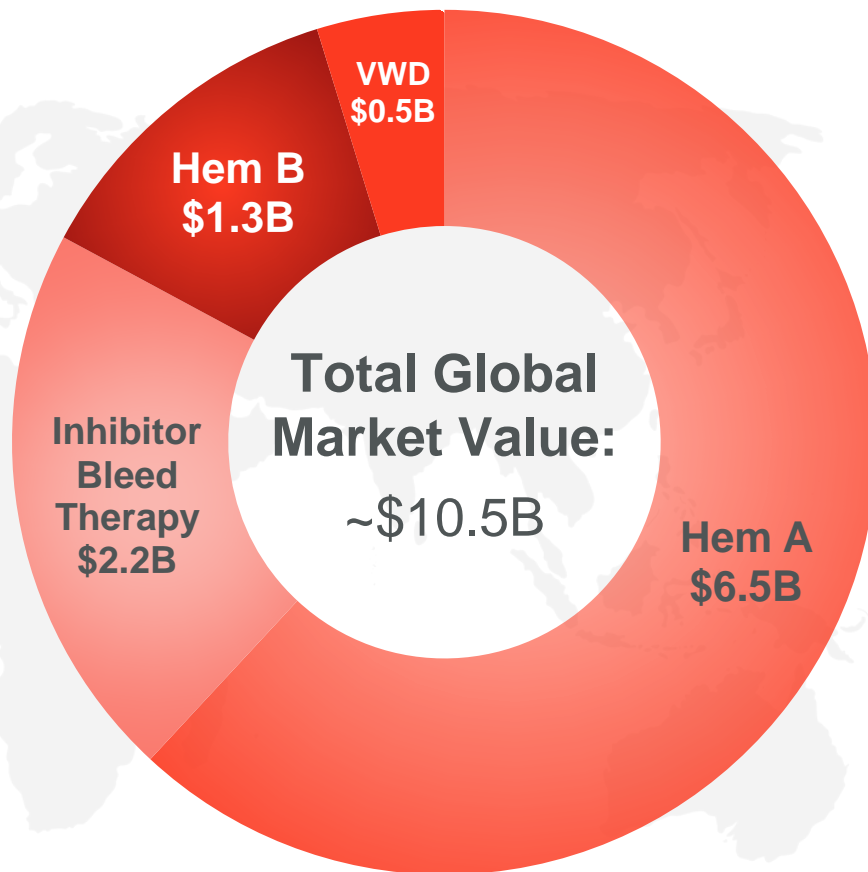
- Phase I PK/PD study in congenital FVII deficiency patients
  - PK and safety in patients
  - Commenced December 2014

PROLONG **7** FP

A dark teal background featuring a stylized world map. The map is centered, showing the continents of North America, South America, Europe, Africa, Asia, and Australia. The text is overlaid on the map.

# **Commercial Opportunities and Activities**

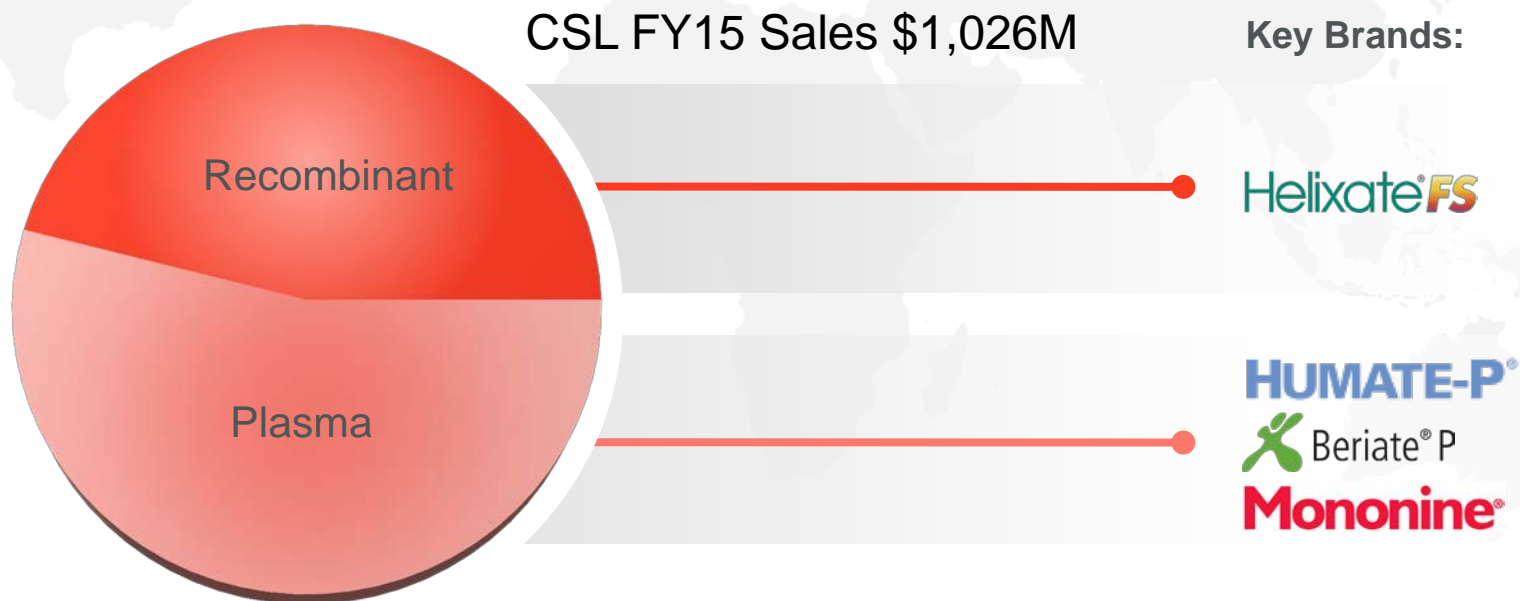
- Trend toward recombinants in developed markets
- New longer-acting product launches
- 75% of patients with bleeding disorders are under/un-treated

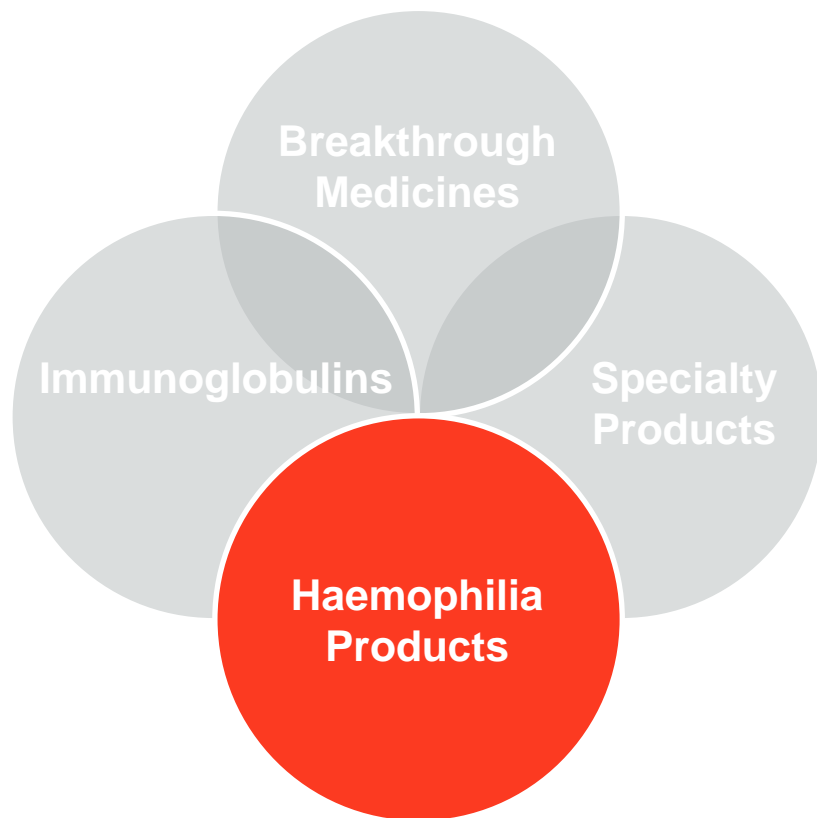


**Sources:** Company annual reports/financial schedules, based on 2014 data, MRB global Coagulation Factors Concentrate Market 2014 & 2015, Hemophilia World, December 2013, Vol 20. No 3, CSL Actuals FY15

### Grow range of differentiated pd and recombinant therapies

- Broad portfolio presence
- Growth in developed and emerging markets
- Continued balance between recombinant and plasma derived portfolio





- Successfully launch the new recombinant products globally
- Position Idelvion™ (rIX-FP) as the new SOC for haemophilia B
- Afstylia™ (rVIII-SingleChain) product profile highly competitive

- Unique recombinant albumin fusion protein molecule
- Pharmacokinetic profile includes extended half-life and greater area under the curve (AUC) resulting in increased activity levels

### **Attributes of Albumin**

- Naturally occurring protein
- Binds endogenous components
- Not associated with immune response
- Long serum half-life

### **Potential Differentiated Profile**

- Dosing interval up to 14 days
- Trough level  $\geq 5\%$
- Zero median AsBR
- Well tolerated
- No inhibitors in pivotal program

- Single chain design with most of B-domain deleted
- Covalent link between heavy and light chains

### **Single Chain Design**

- Strong affinity to vWF
- Greater molecular integrity and stability
- Improved pharmacokinetic profile

### **Potential Differentiated Profile**

- Twice-weekly dosing
- Effective bleeding control
- Well tolerated
- No inhibitors in pivotal program

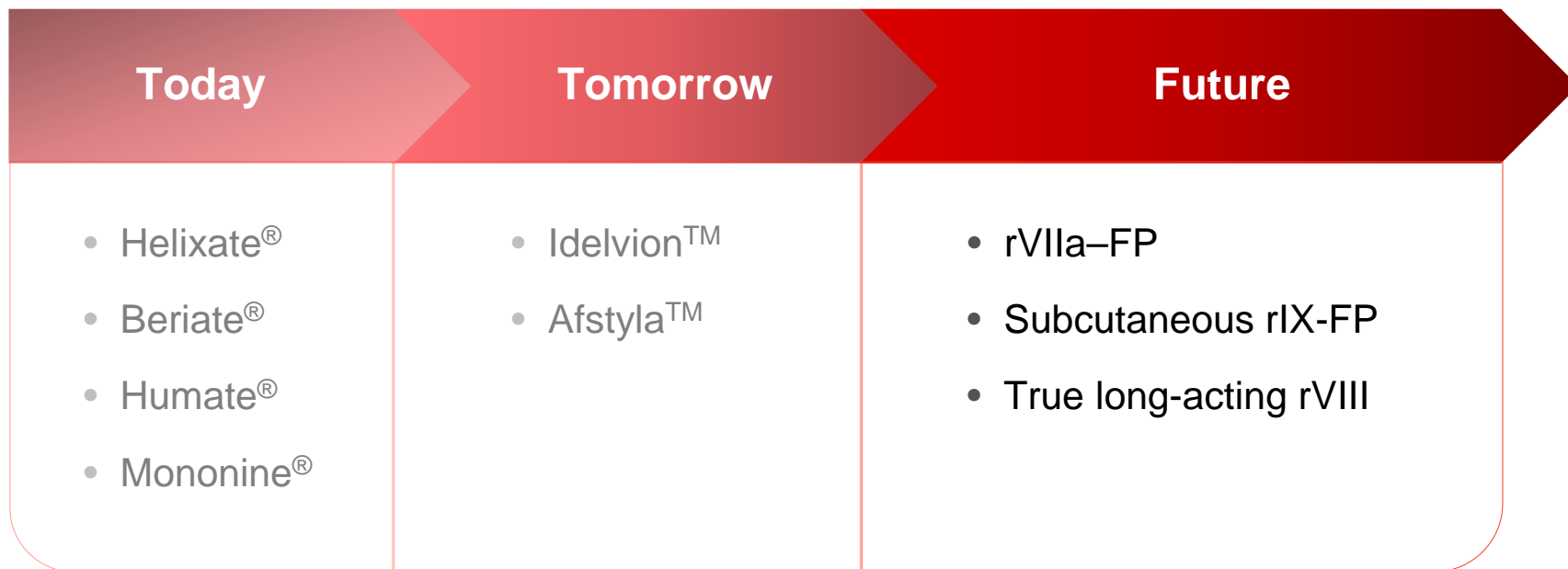
- Prophylaxis and treatment of adult, adolescent and pediatric patients with congenital haemophilia A or B with inhibitors and congenital FVIIa deficiency

### **Attributes of rVIIa-FP**

- Unique recombinant albumin fusion protein molecule
- Significantly longer half-life
- Extended dosing interval ~3 x per week

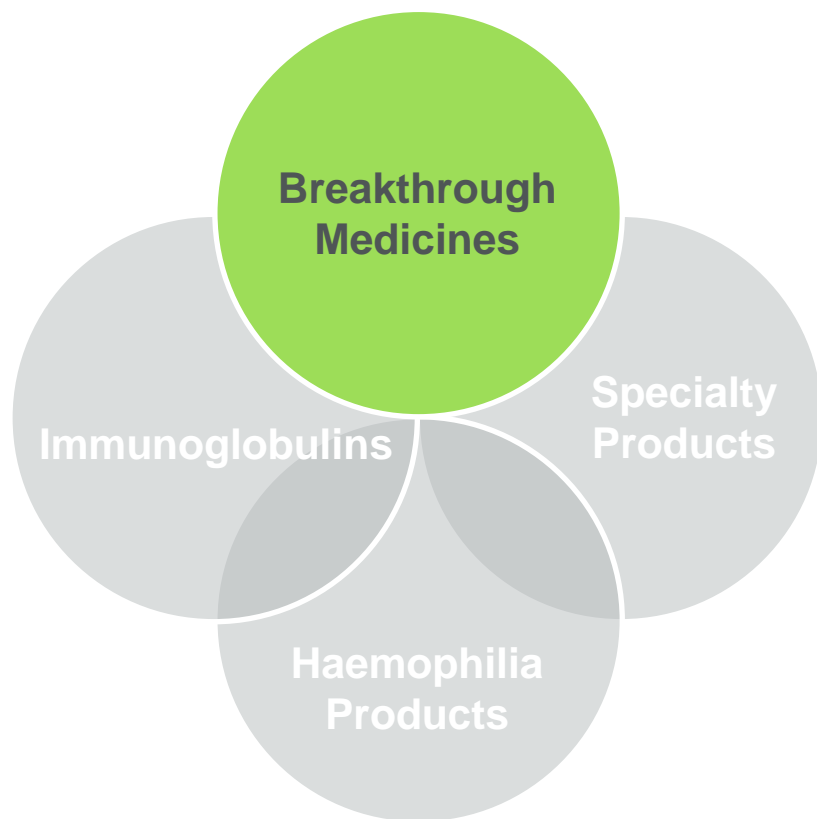
### **Potential Differentiated Profile**

- Fast, effective on-demand treatment in majority of patients
- Therapeutic effect allows for more convenient prophylaxis
- Major improvement to patient care



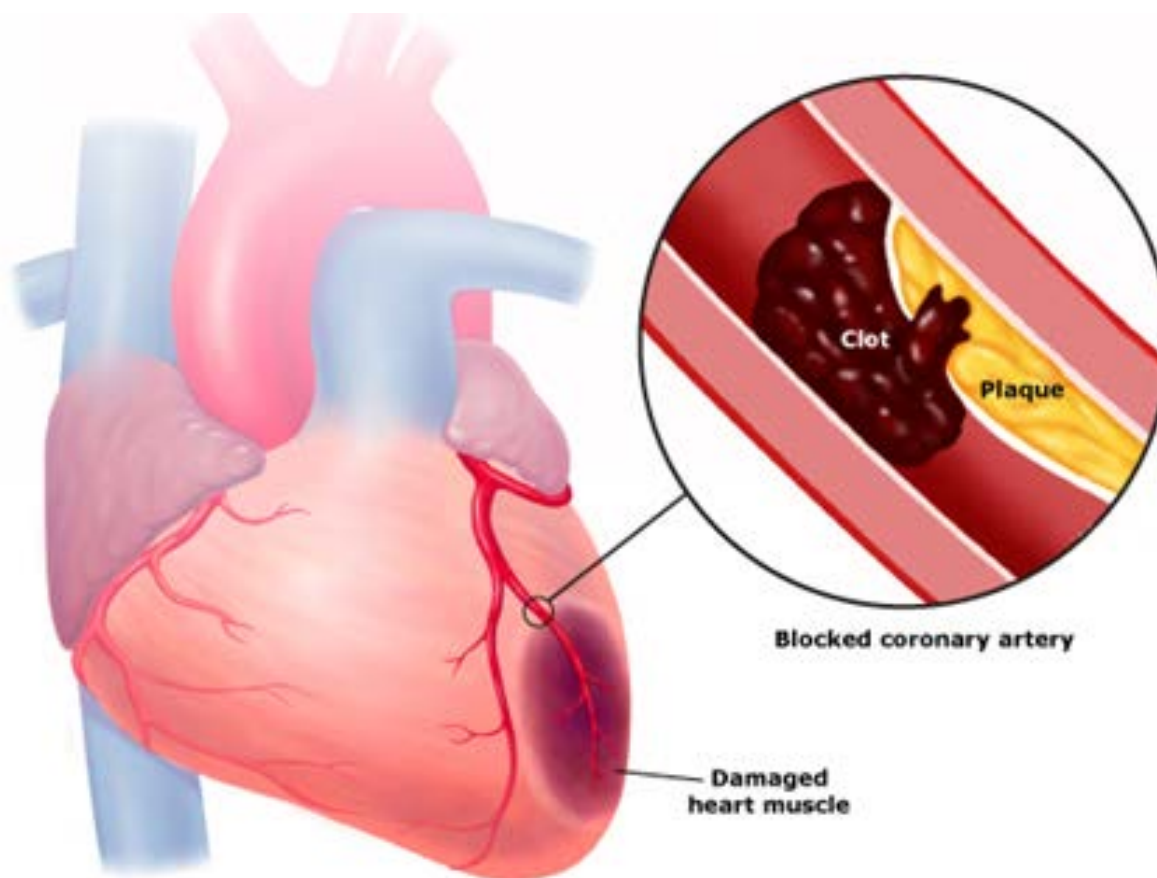
A dark teal world map is centered in the background of the slide. The continents are visible in a slightly lighter shade of teal.

# **Breakthrough Medicines**



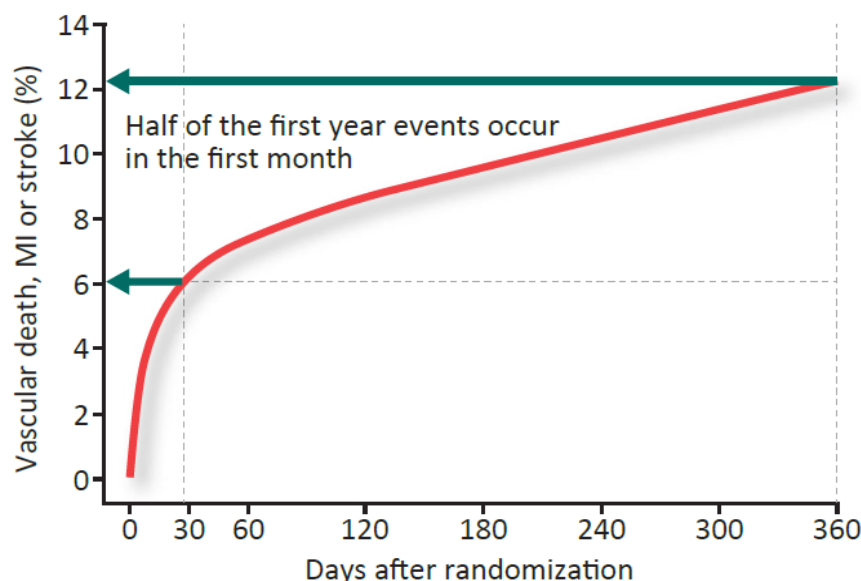
- Leveraging clinical and technical insight in developing novel protein-based therapies
  - Significant unmet need
  - Multiple indications
- Key Focus
  - CSL112 (Apo AI)
  - CSL324 (anti-G-CSFR mAb)
  - CSL346 (anti-VEGFB mAb)
  - CSL312 (anti-FXIIa mAb)

# Acute Coronary Syndrome (ACS)



### Reduction of Early Recurrent Cardiovascular Events – A High Unmet Medical Need in ACS

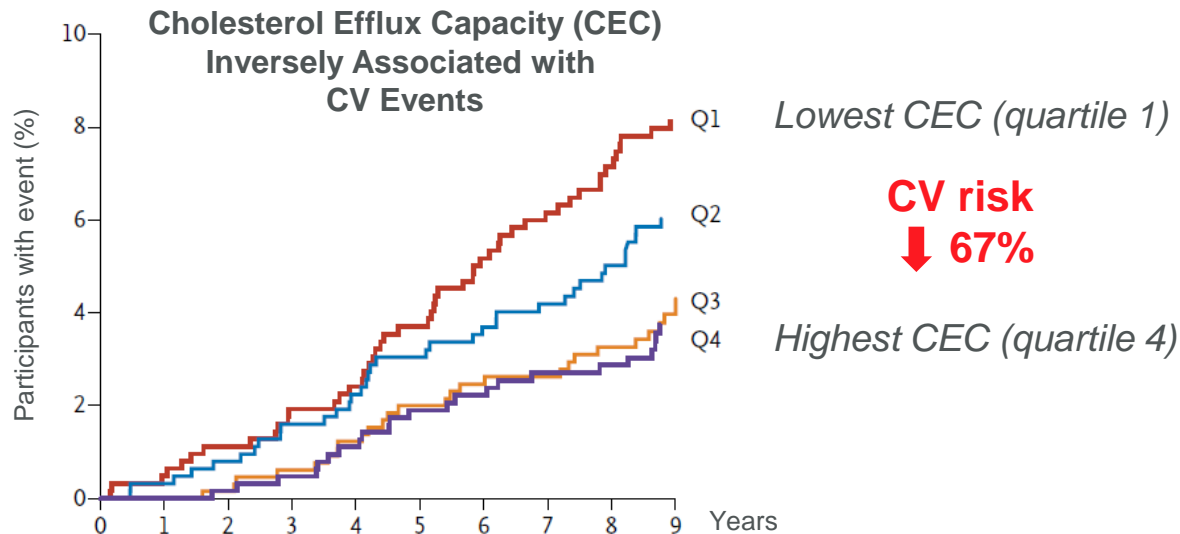
- Recurrent CV events occur early, are associated with high mortality and are inadequately addressed by available therapies



**References:** Figure adapted from PLATO Trial, Kohli P et al. *Circulation* 2013;127:673-680

## Cardioprotective Role of High Density Lipoprotein

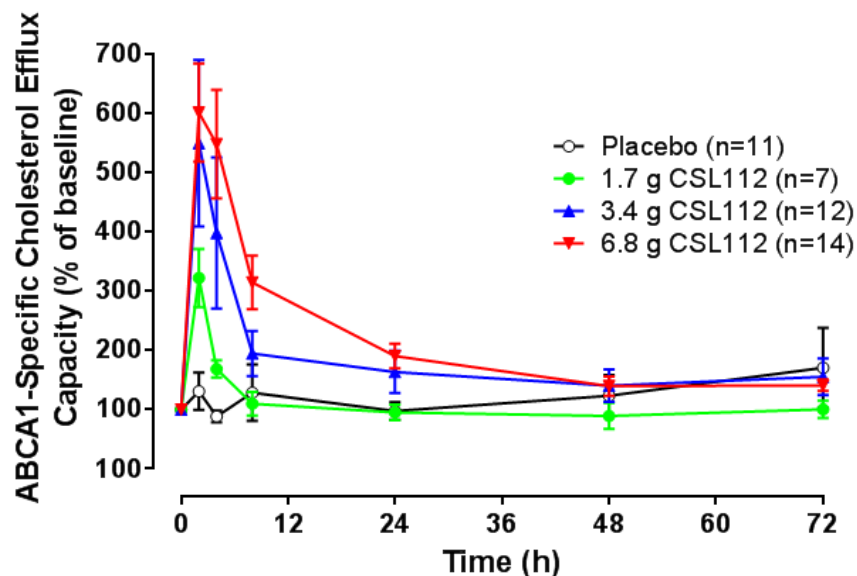
- HDL exerts cardio protective effect through cholesterol efflux
  - movement of excess cholesterol from arterial-wall macrophages
  - leads to reduction in plaque size and risk of rupture



**References:** Dallas Heart Study, New England Journal of Medicines, Nov 2014

## CSL112 raises ABCA1 Cholesterol Efflux Capacity

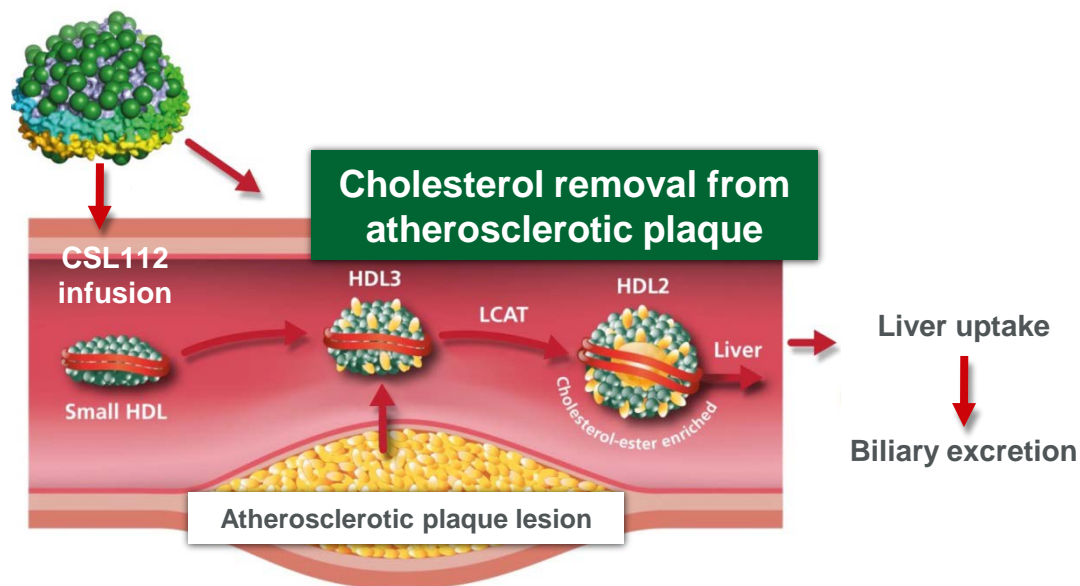
- Impaired cholesterol efflux, inflammation and plaque rupture, all exist in the setting of ACS
  - Contribute to the high incidence of early recurrent cardiovascular events
- CSL112 results in a profound, immediate and sustained rise in ABCA1 specific cholesterol efflux capacity



Phase 2a Study in patients with stable atherosclerotic disease

References: Gille et al. (2014) presented at AHA.

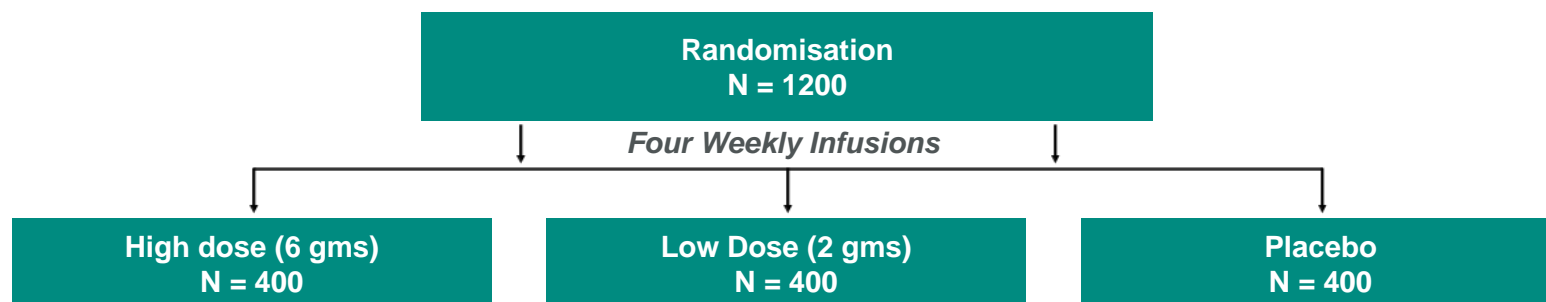
## CSL112 – A Novel Therapy for Acute Coronary Syndrome



**CSL112 has the potential to rapidly reduce the high rate of early recurrent CV events, addressing a significant unmet medical need in ACS.**

**References:** Modified from Kingwell & Chapman. *Circulation* 2013;128:1112-1121

*Proof of mechanism and demonstration of safety*



- 1,258 patient post myocardial infarction trial fully recruited
- Data Monitoring Committee has confirmed safety to date
- Biomarker data to confirm mechanism of action – 2H 2016



## Phase 2b Dose-ranging / POC

- ACS population
- Safety, efflux biomarker, pop PK
- Normal and mild RI
- Enrollment completed LPLV Q2 2016

## Moderate RI safety (Ph2)

- Higher risk ACS population
- Safety, pop PK
- Start up stage

## Phase 3 Pivotal Trial

- ACS treatment target population
- CV event benefit (MACE) and safety risk
- 1<sup>o</sup> endpoint: MACE
- Design and planning stage

- Planning for Phase 3 commenced
  - Strategy in place for inclusion of high risk patients in Phase 3
  - Anticipating commencement in 2H 2017

A dark teal world map is centered in the background of the slide. The continents are visible in a slightly lighter shade of teal.

## Influenza Vaccines R&D



- Differentiated, adjuvanted influenza vaccine for 65yr+ and young children
- Elderly indication approved in >30 countries (US approval Nov 2015)
- Paediatric indication in Canada



- World's first cell-culture flu vaccine
- Currently registered for 18yr+
- QIV 4yr+ anticipated in 2016



- Traditional egg-based vaccine
- Currently indicated for 5yr+
- QIV 18yr+ anticipated in 2016



- First and only intravenous influenza anti-viral
- Currently registered in the US for 18yr+
- Plans for global rollout<sup>1</sup> and paediatric indication

1. Seqirus rights exclude Japan, South Korea, Taiwan, Israel and US Government stockpile



TIV

Filed

- Expanding age indication to 4yr+

Cell culture QIV

Filed

- Filed for US approval  
Anticipate launch in 2016

Adjuvanted QIV

Phase III

- Filing in 2016



QIV

Filed

- Age  $\geq$  18 yrs  
Anticipate soft launch in 2016

QIV

Phase III

- Age  $\geq$  5yrs, filing 2016



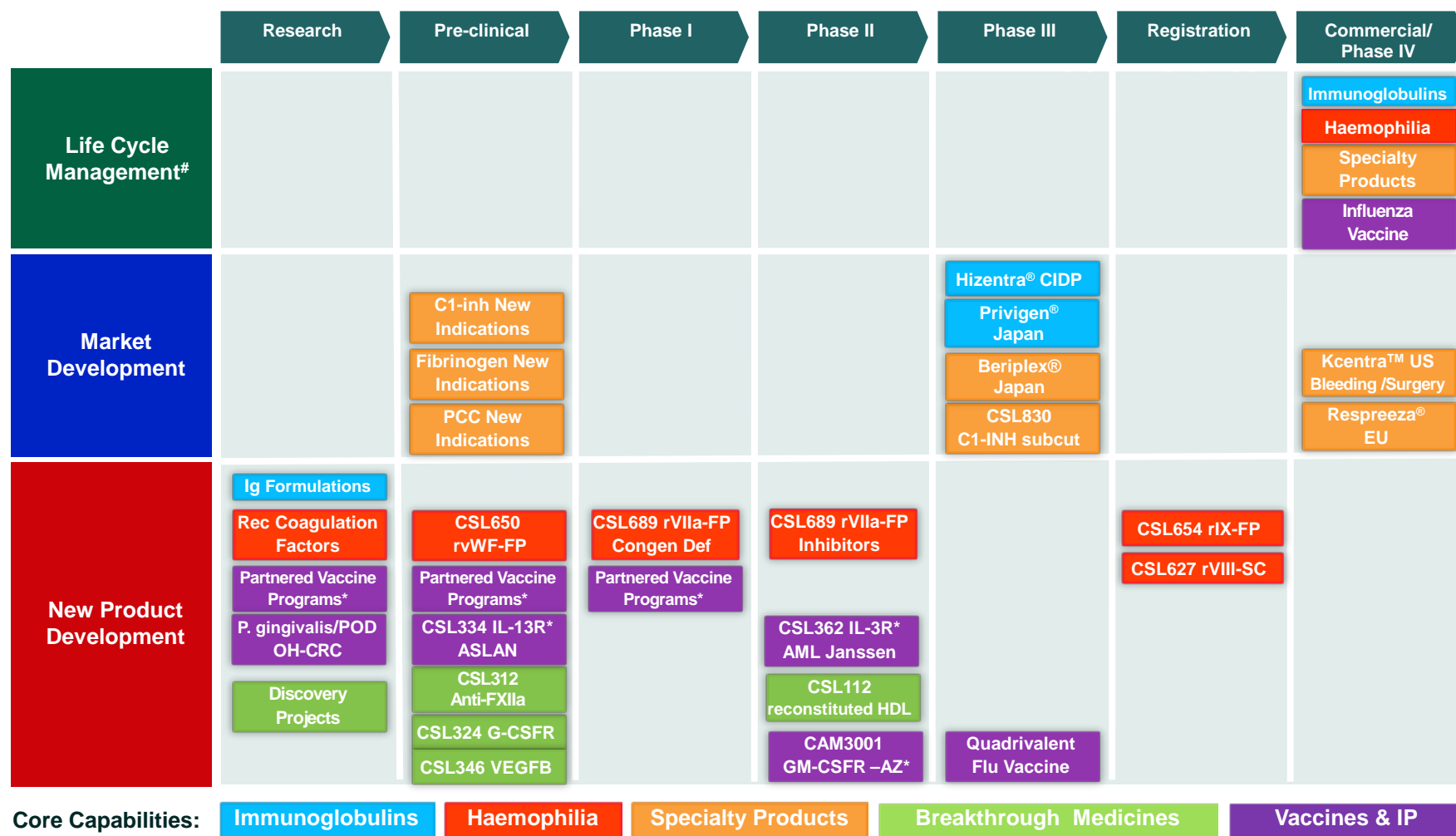
QIV

Phase III

- Age  $\geq$  6mo, filing 2017

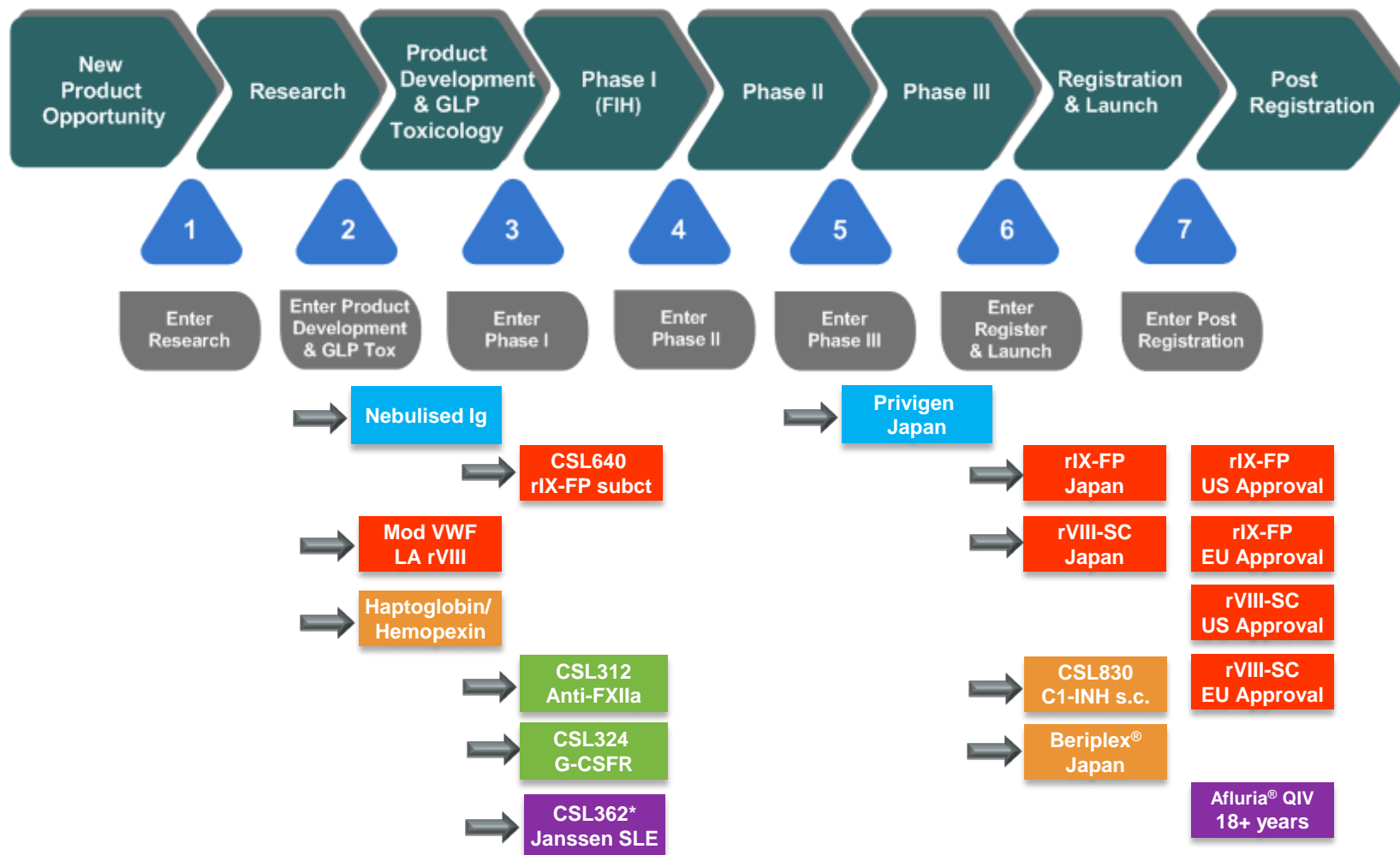
A dark teal world map is centered in the background of the slide. The word "Summary" is written in white, bold, sans-serif font, centered over the map.

# Summary



\*Partnered Projects

<sup>#</sup>LCM includes direct post marketing commitments as well as pathogen safety, capacity expansions, yield improvements, new packages and sizes for all registered products



## Significant Target Launch Dates

2015	2016	2017	2018	2019	2020
Voncento™ V WD EU	CSL654 rIX-FP US CSL654 rIX-FP EU CSL627 rVIII-SC US	CSL654 rIX-FP Japan CSL627 rVIII -SC EU/Japan			CSL689 rVIIa-FP Inhibitors
Respreeza® EU		CSL830 C1-INH SubCut Beriplex® Japan			
Fluad US Elderly+	Cell Culture QIV Afluria/Fluvax QIV 18+		Hizentra® CIDP Privigen® Japan PID/SID Adjuvanted QIV		

Core Capabilities:

Immunoglobulins

Haemophilia

Specialty Products

Vaccines & IP

\* Calendar Years

### Immunoglobulins

- Hizentra® flexible dosing registration in US
- Hizentra® CIDP pivotal study recruitment completed

### Specialty Products

- Respreeza® registration in Europe
- Berinert® s.c. pivotal Phase III recruitment completed

### Haemophilia

- rIX-FP effective in 7-14 day dosing regimens & MAA submitted
- rVIII-SingleChain effective 2x weekly prophylaxis & MAA submitted
- rVIIa-FP inhibitor Phase I/II commenced

### Breakthrough Medicines

- CSL112 (Apo A-1) Phase IIb study recruitment completed
- Anti-FXIIa mAb pre-clinical development completed

### Licensing & Vaccines

- Fludac registration in the elderly in the US
- CSL362 Phase II AML study commenced by Janssen

A dark teal world map is centered in the background of the slide. The continents are visible in a slightly lighter shade of teal.

# Q&A

R&D Briefing

## **Presentation Playback**

A playback of the Research and Development presentations will be available for a period of two weeks following R&D Briefing. Investors wishing to listen to these presentations should contact CSL Investor Relations to arrange access.

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