



# Investor R&D Briefing

December 1, 2016



Just getting started



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- Introduction & Highlights
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  - Commercial Opportunities
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  - Clinical Development
  - Commercial Opportunities
- Breakthrough Medicines
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  - CSL112 Commercial Opportunities
- Seqirus R&D
- Summary
- Q&A

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Charmaine Gittleson  
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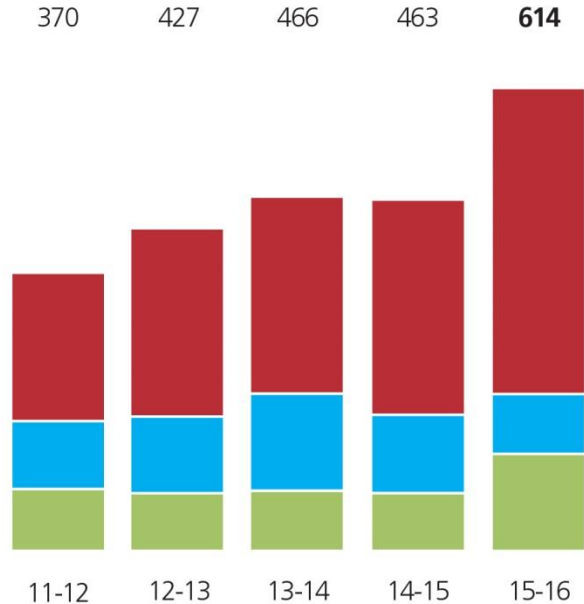
Charmaine Gittleson  
Bob Repella  
Russell Bassar  
Andrew Cuthbertson

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# Introduction and Highlights



Research and Development 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 Management** ensures continuous improvement of existing products.

# Past Launches from the R&D Portfolio

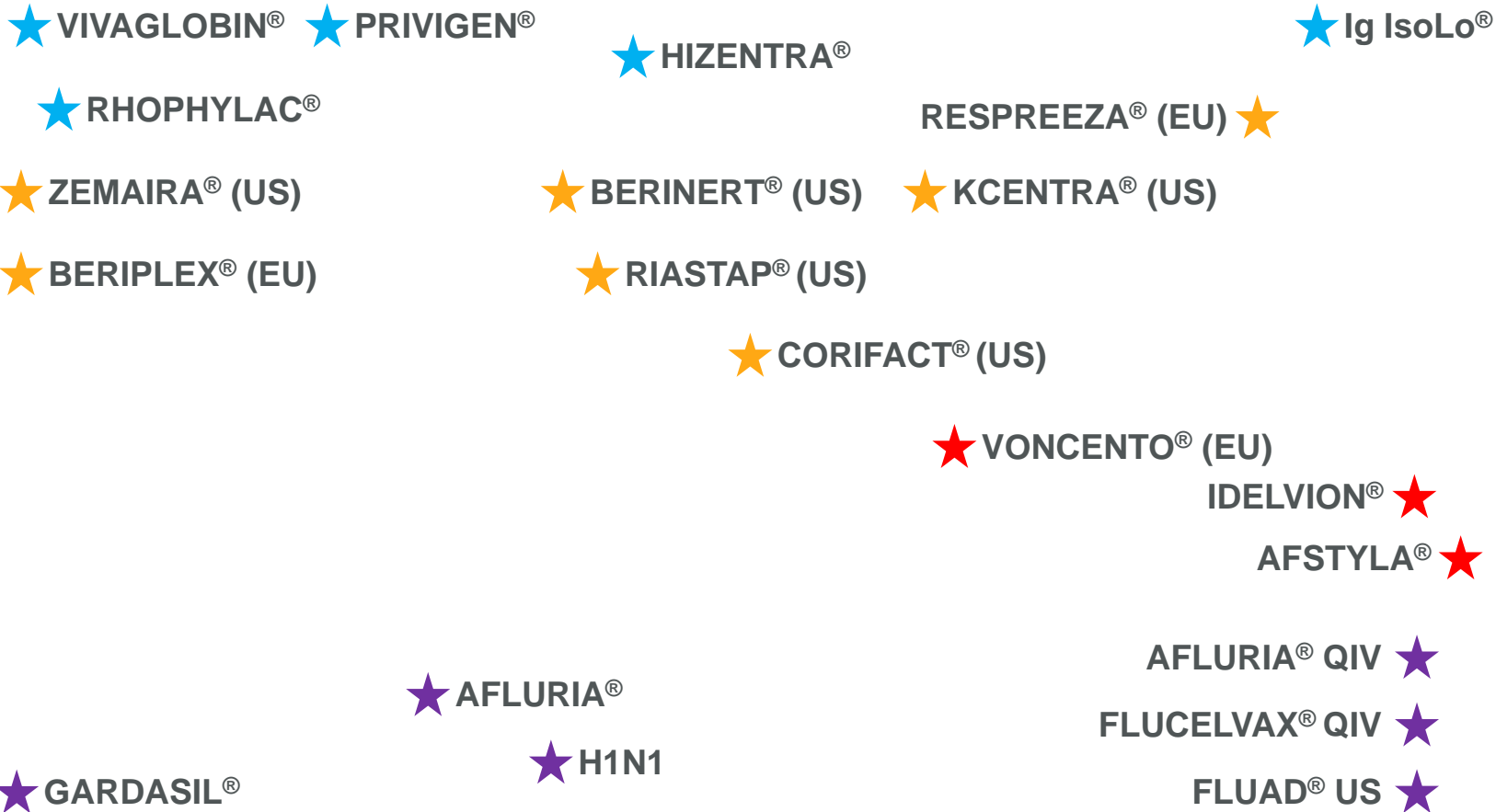


Ig

Specialty

Coag./Heam.

Vaccines



\* First major market launch of new product



# Leveraging Global Capabilities



>1,400 scientists globally

	Research	Pre-clinical	Phase I	Phase II	Phase III	Registration	Commercial/ Phase IV
Life Cycle Management#							Immunoglobulins Haemophilia Specialty Products Influenza Vaccine
Market Development		C1-INH New Indications Fibrinogen New Indications PCC New Indications			HIZENTRA® CIDP PRIVIGEN® Japan BERIPLEX® Japan CSL830 C1-INH subcut		KCENTRA® US Bleeding / Surgery RESPREEZA® EU/US
New Product Development	Ig Formulations Rec Coagulation Factors Partnered Vaccine Programs* P. gingivalis/POD OH-CRC Discovery Projects	Partnered Vaccine Programs* CSL334 IL-13R* ASLAN CSL312 Anti-FXIIa CSL324 G-CSFR CSL346 VEGFB	CSL689 rVIIa-FP Congen Def Partnered Vaccine Programs*	CSL689 rVIIa-FP Inhibitors CSL362 IL-3R* AML Janssen CSL112 reconstituted HDL CAM3001 GM-CSFR –AZ*		CSL654 rIX-FP CSL627 rVIII-SC	

Core Capabilities:

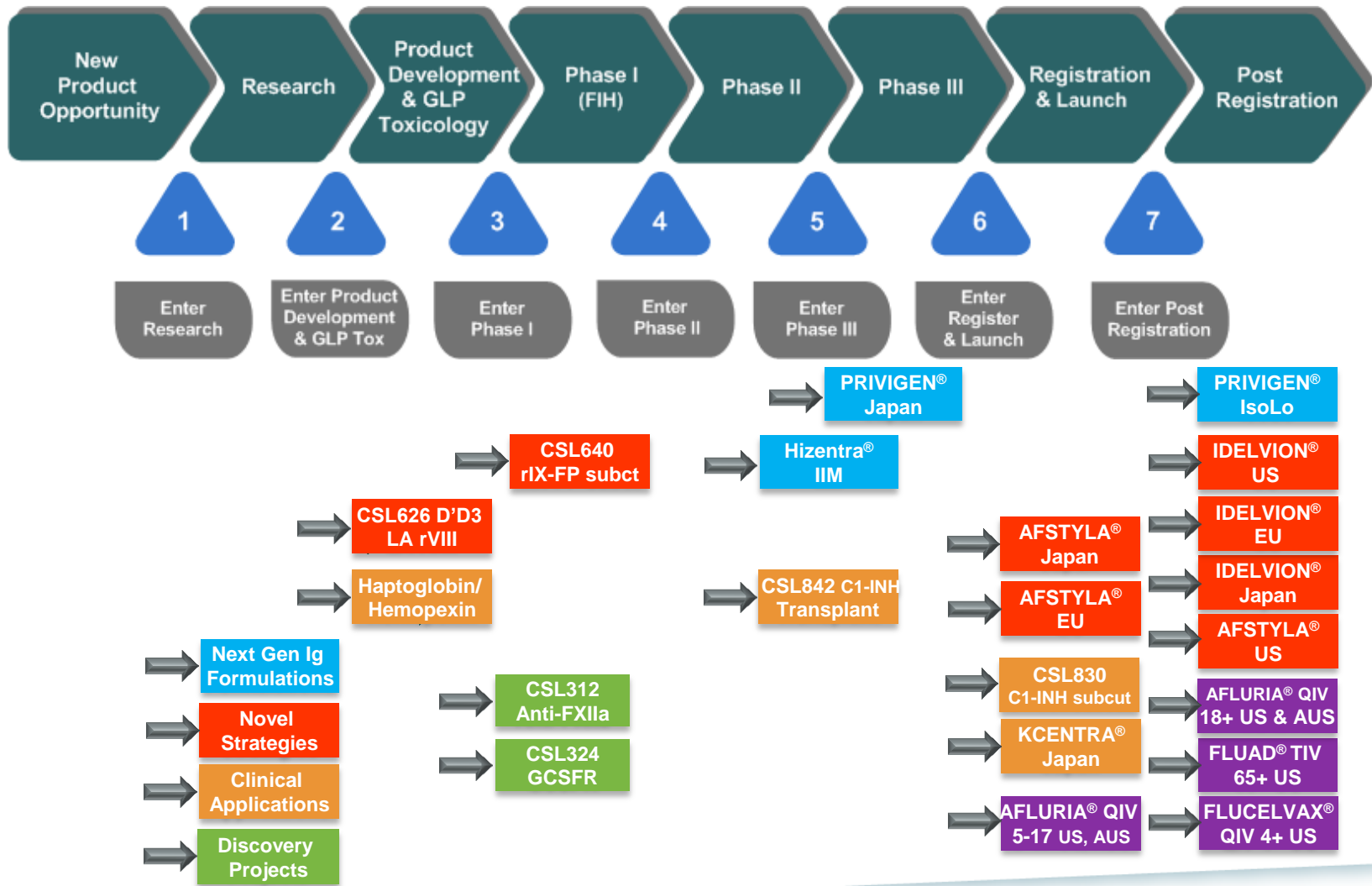
Immunoglobulins
Haemophilia
Specialty Products
Breakthrough Medicines
Vaccines & IP

\*Partnered Projects

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







	Research	Pre-clinical	Phase I	Phase II	Phase III	Registration	Commercial/ Phase IV
Life Cycle Management#							Immunoglobulins Haemophilia Specialty Products Influenza Vaccine
Market Development	PCC New Indications	C1-INH New Indications Fibrinogen New Formulations Haptoglobin/Hemopexin			HIZENTRA® CIDP PRIVIGEN® Japan Hizentra® IIM CSL842 C1-INH Transplant	PRIVIGEN® CIDP US KCENTRA® Japan CSL830 C1-INH subcut	VONCENTO® VWD EU RESPREEZA® EU/US
New Product Development	Next Gen Ig Formulations Rec Coagulation Factors P. gingivalis/POD OH-CRC Discovery Projects	CSL626 D'D3 LA rVIII CSL334 IL-13R* ASLAN CSL346 VEGFB	CSL689 rVIIa-FP Congen Def CSL640 rIX-FP subct CSL312 Anti-FXIIa CSL324 G-CSFR	CSL689 rVIIa-FP Inhibitors Mavri GM-CSFR – AZ* CSL362 IL-3R* AML Janssen CSL112 apo-AI		AFSTYLA® Europe AFLURIA® QIV 5-17 US, AUS	IDELVION® US, EU, Japan AFSTYLA® US AFLURIA® QIV 18+ US & AUS FLUAD® TIV 65+ US FLUCELVAX® QIV 4+ US

Core Capabilities:

Immunoglobulins
Haemophilia
Specialty Products
Breakthrough Medicines
Vaccines & IP

\*Partnered Projects

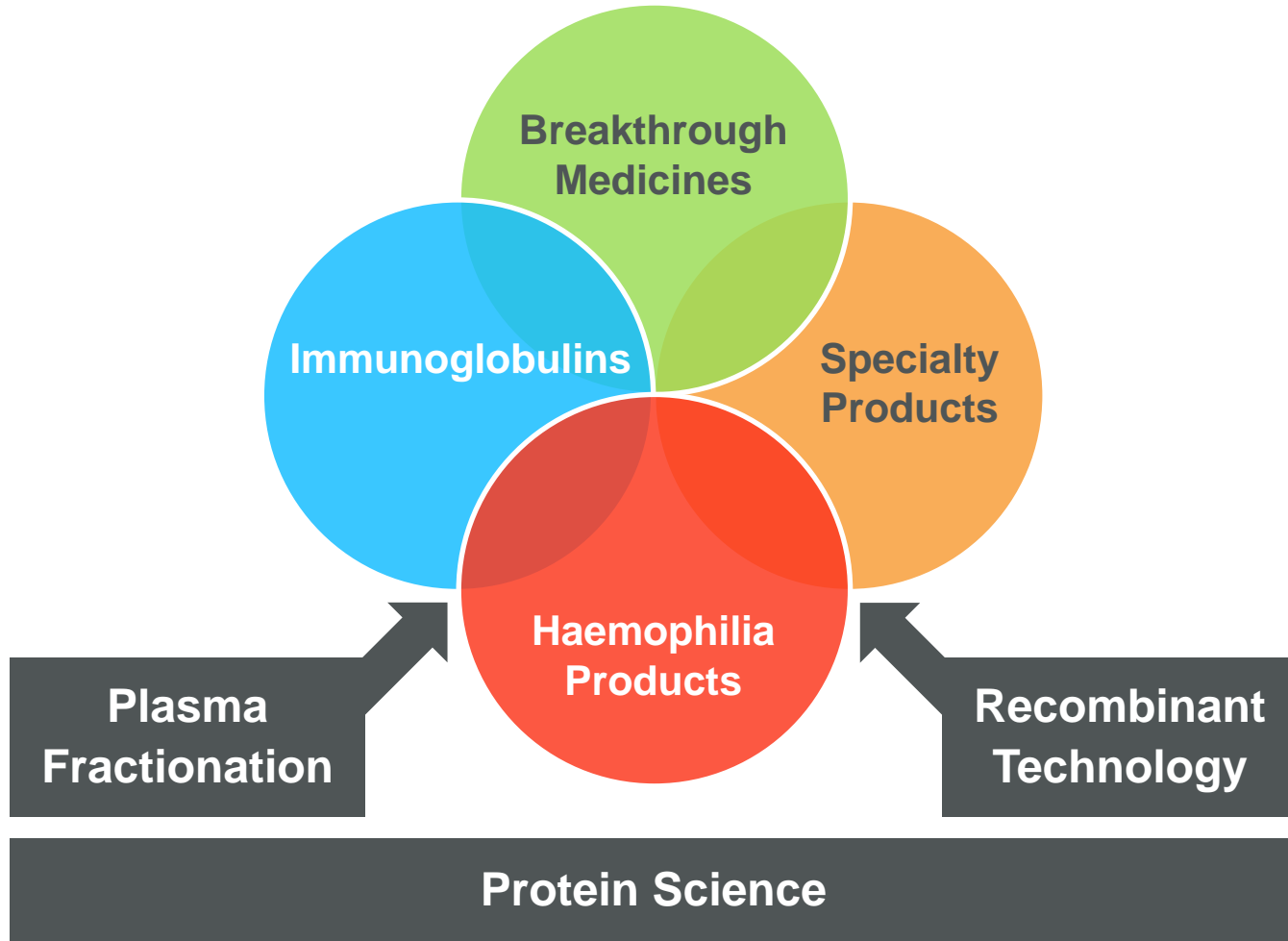
#LCM includes direct post marketing commitments as well as pathogen safety, capacity expansions, yield improvements, new packages and sizes for all registered products



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# CSL Behring R&D Strategy and Focus





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# Research & Early Development



- Coordinated global project portfolio

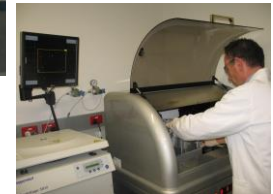
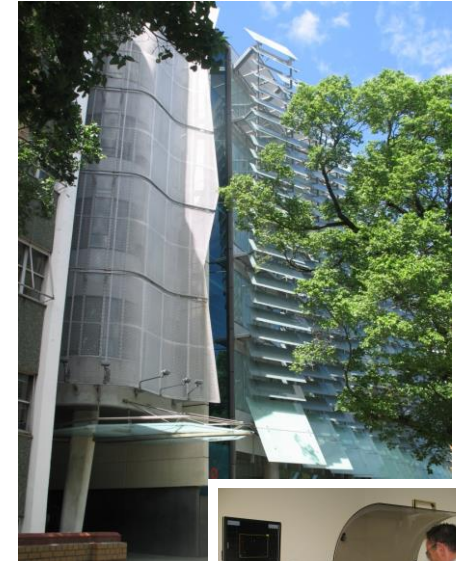
Immunoglobulins

Haemophilia

Specialty  
Products

Breakthrough  
Medicines

- Hub (Bio21, Melbourne) & spoke model
- Bio21 expansion to increase pre-clinical research
- Research excellence in therapeutic proteins
- Plasma and recombinant manufacturing platforms

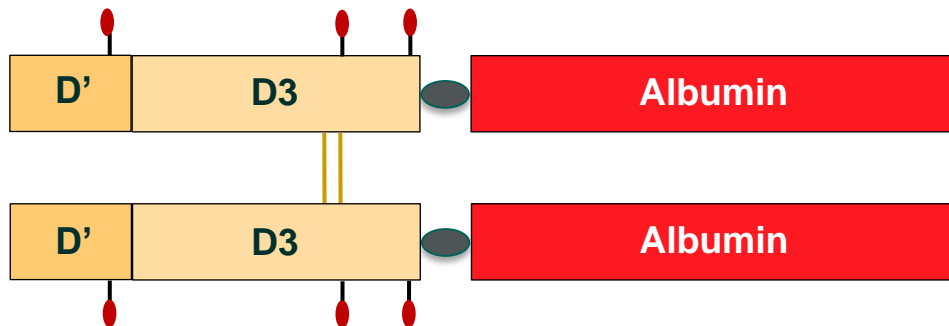




- Major focus on patient Quality of Life
- Extract maximum value and performance from existing assets
- Develop new protein-based therapies and strategies for treating congenital and acquired bleeding disorders
  - LA FVIII
  - Novel delivery technologies
  - Bispecific Abs

- Short FVIII half-life, improved half life = improved prophylaxis
- FVIII half-life regulated by VWF
- Target VWF half-life while minimising thrombosis risk
- CSL626 = VWF D'D3 fragment fused to human albumin

### Von Willebrand Factor

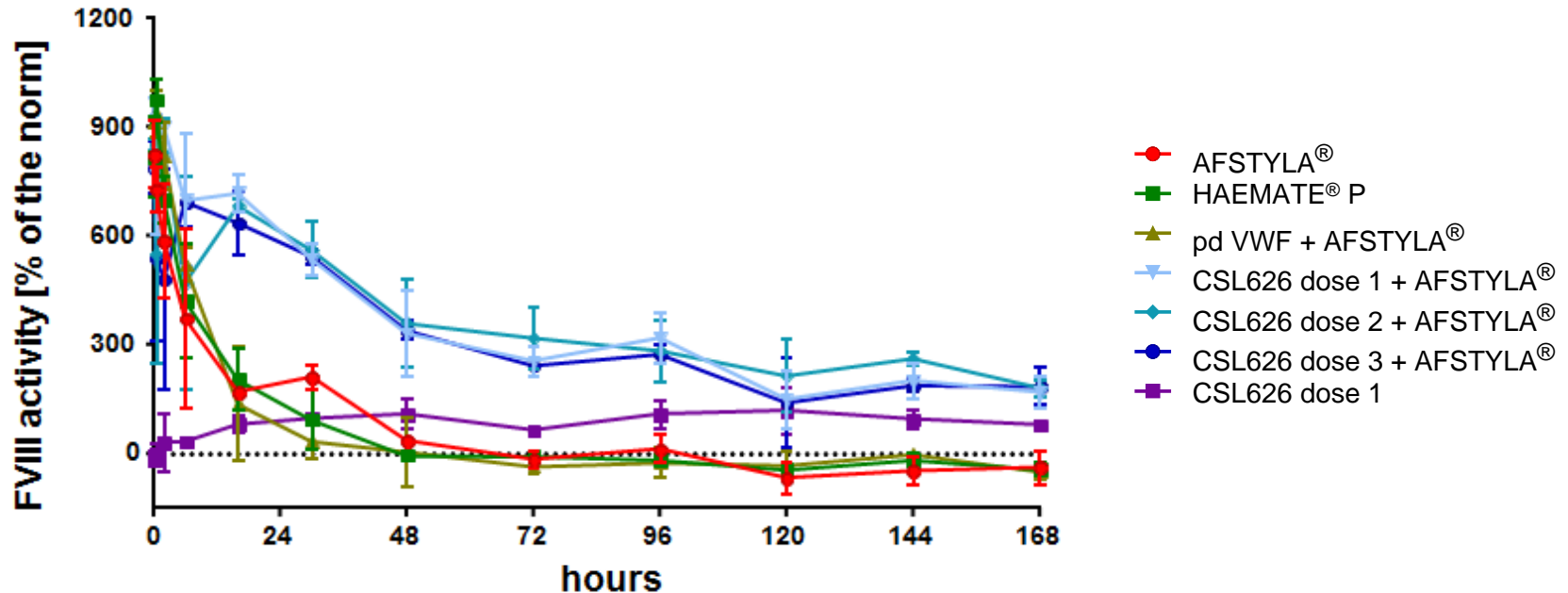


+ AFSTYLA<sup>®</sup>

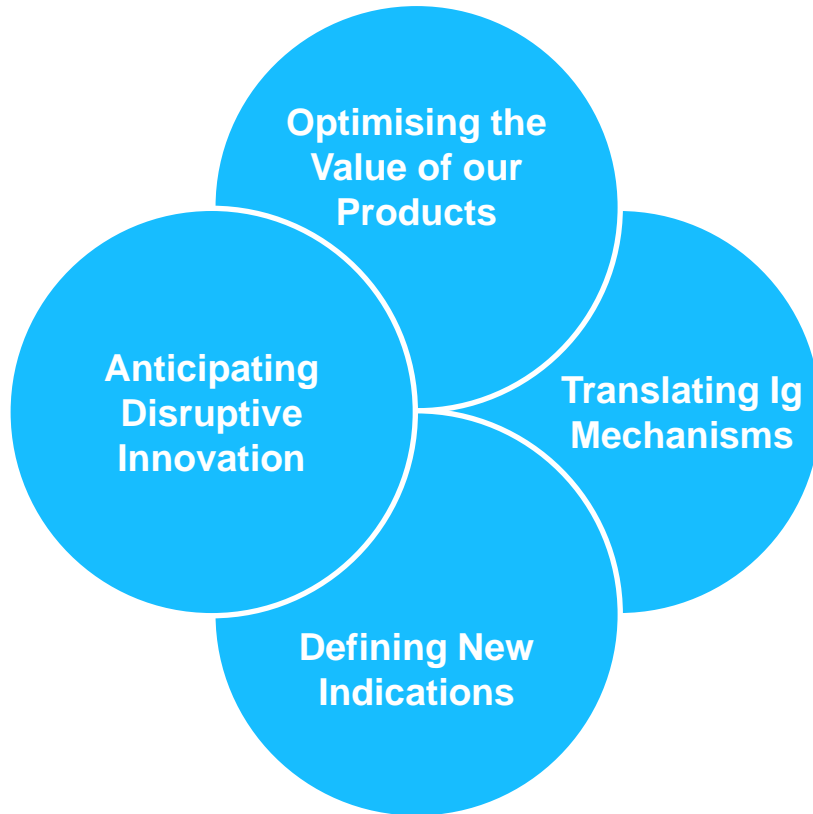
- AFSTYLA<sup>®</sup> bound to CSL626 should have an increased half life (by accessing the FcRn salvage pathway)



CSL626 extends the half-life of co-administered AFSTYLA<sup>®</sup> in NHPs



- 4-5 fold increase in AFSTYLA<sup>®</sup> half-life
- GLP toxicology studies in progress
- Phase I planned to commence H1, 2018



- Formulation and purification processes
- Opportunities for new technologies / molecules
- Mechanism driven product design and indication selection
- Identifying new indications for IV/SCIG

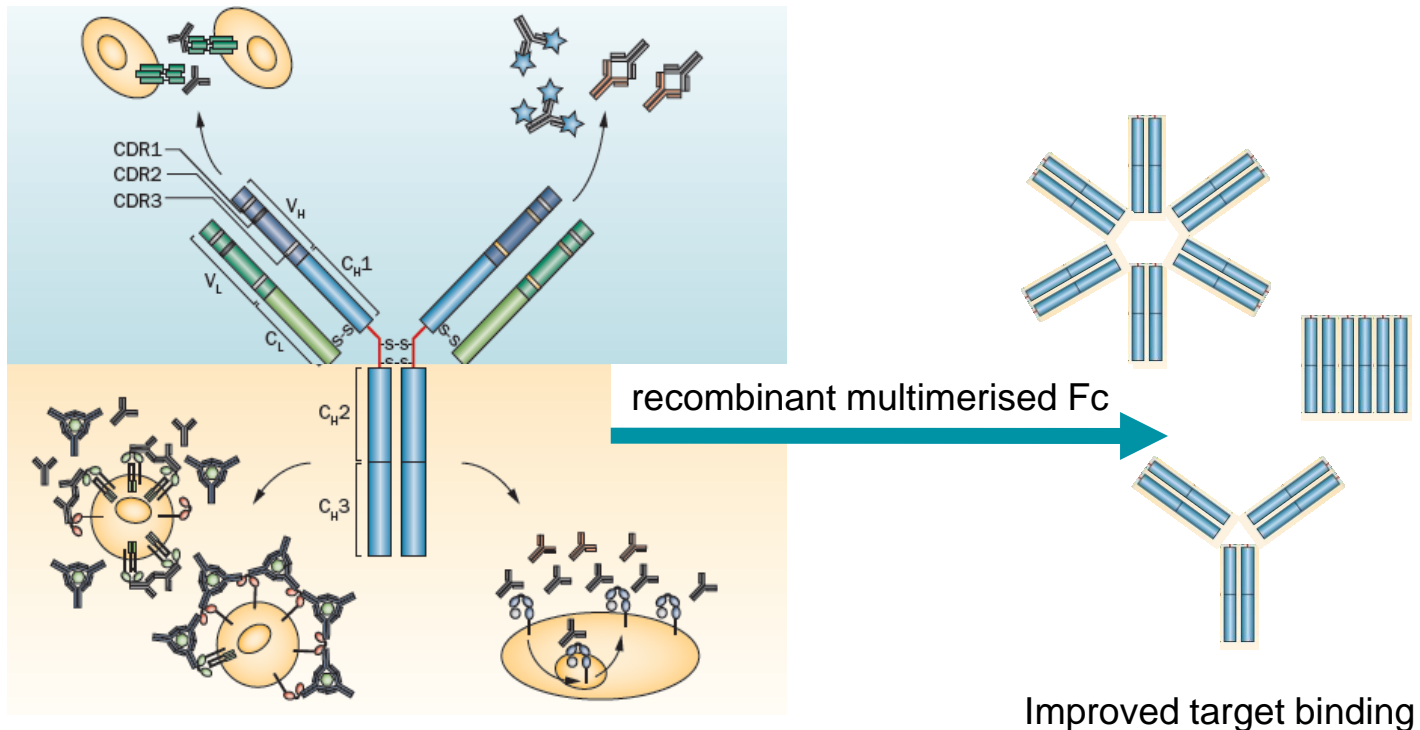
## Immunoglobulin functional domains

### Fab region

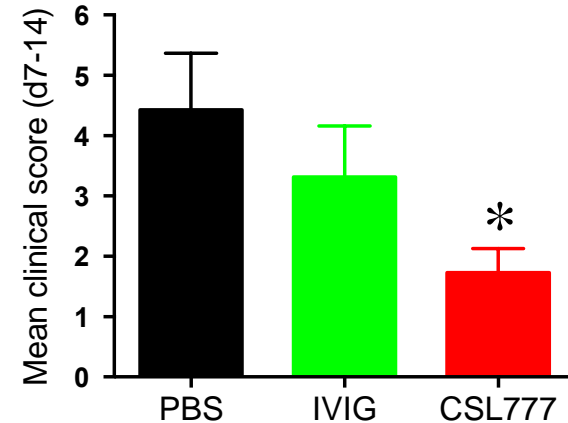
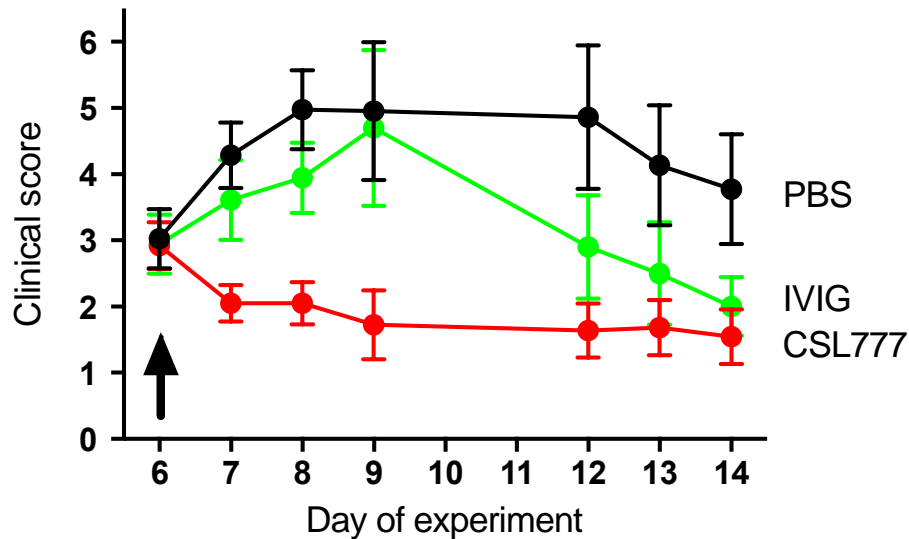
- Immune deficiencies

### Fc region

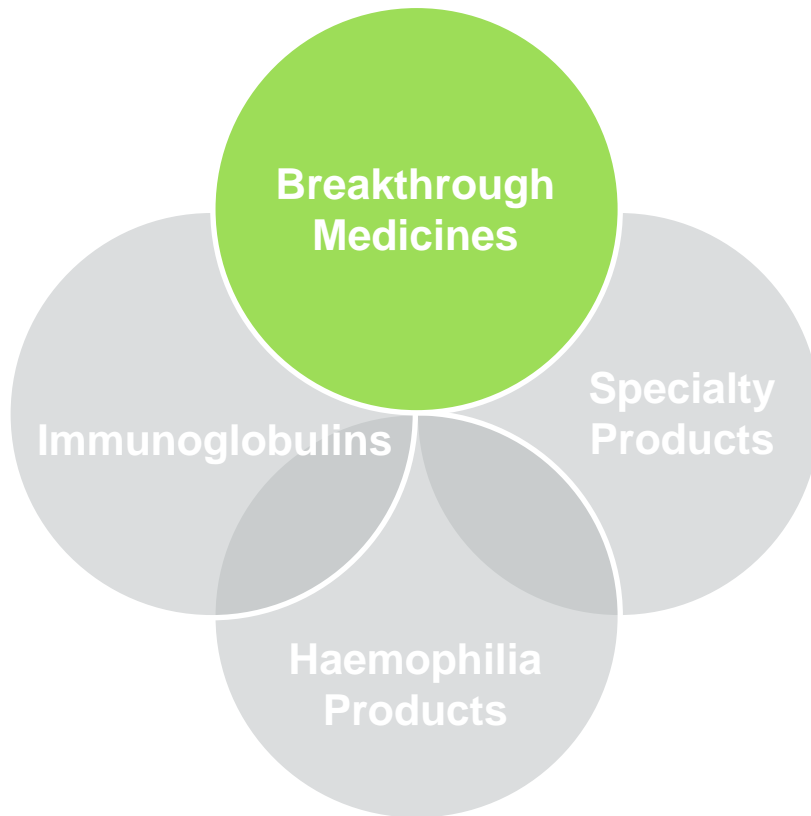
- Autoimmune conditions



CSL777 proof-of-concept in CAblA model of arthritis

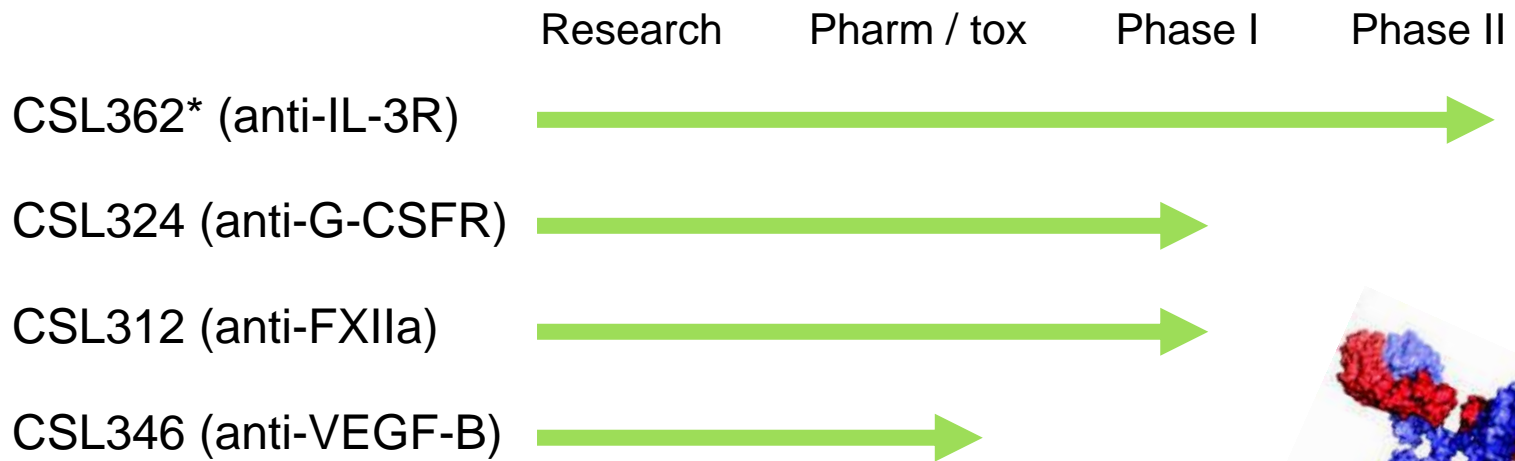


- 200 mg/kg CSL777 or 2 g/kg IVIG, i.p. at day 6
- CSL777 → significantly reduced clinical score (\* $P < 0.05$ ) and joint cell infiltrate
- GLP toxicology planned to commence in 2H, 2017



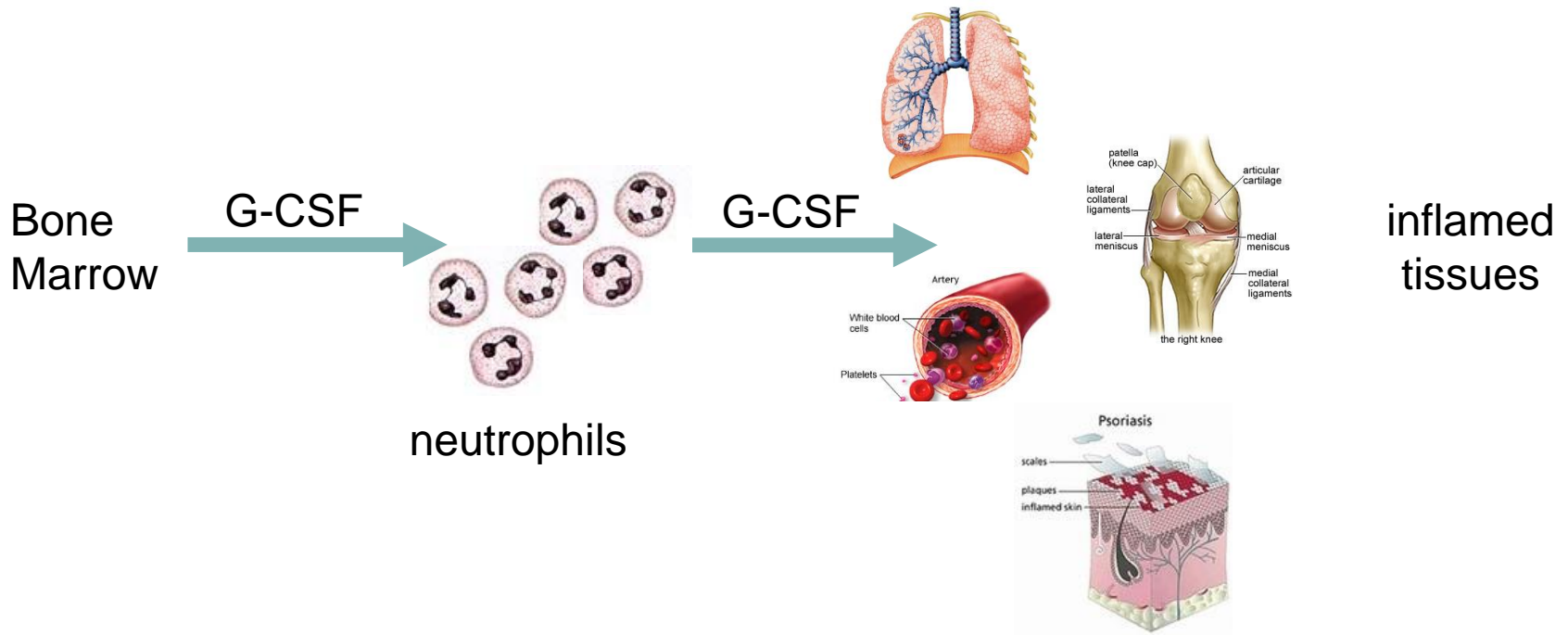
- Leveraging clinical and technical insight in developing novel protein-based therapies
  - Significant unmet need
  - Multiple indications

- Portfolio of preclinical and early-mid stage clinical opportunities consistent with CSL commercial objectives
- Delivery of high quality candidates for clinical development



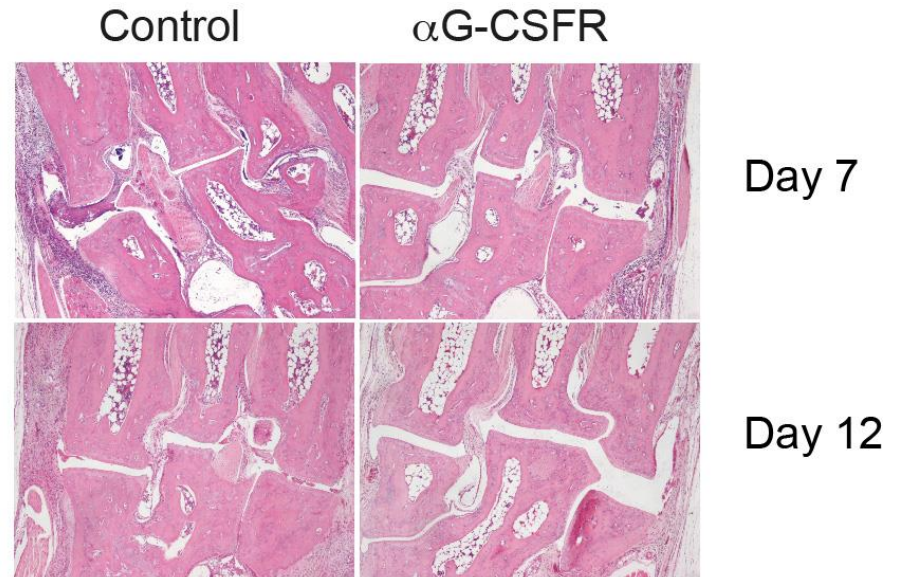
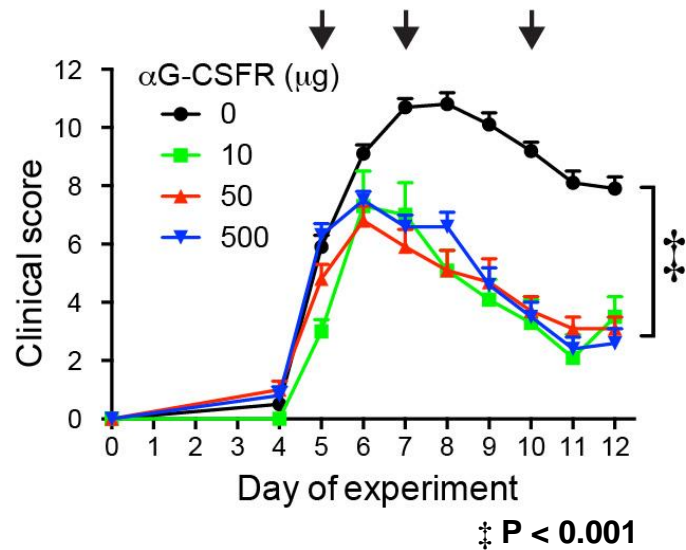
\*Partnered with Janssen Biotech

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



Anti-G-CSFR mAb reverses development of arthritis

- Mouse CAbIA model



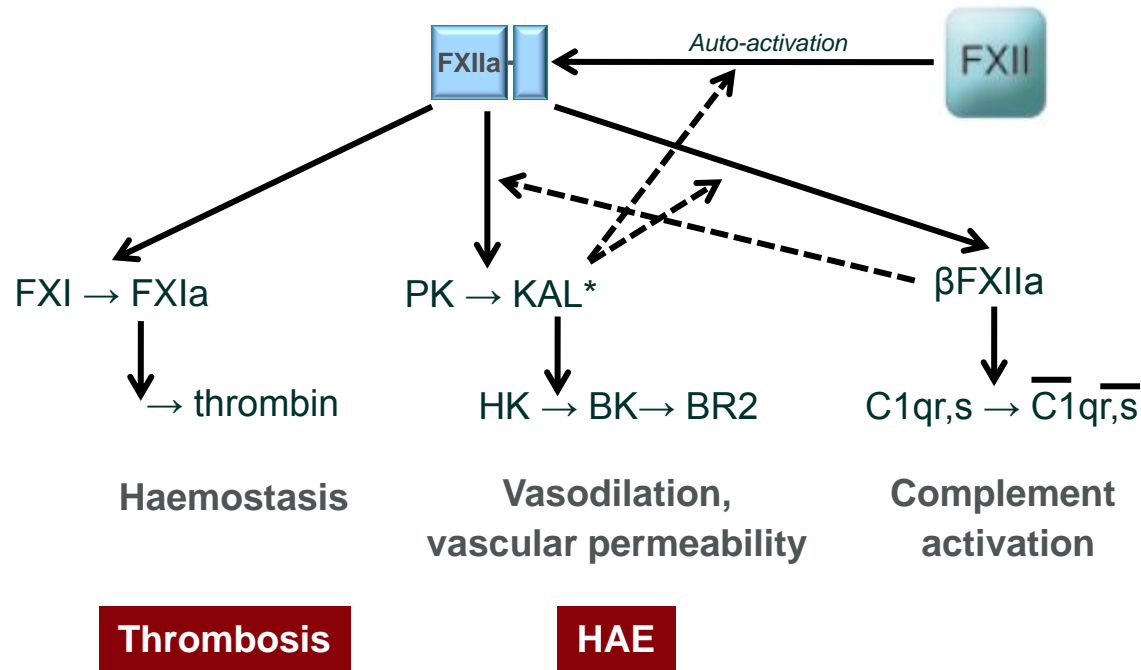
- GLP toxicology completed, CSL324 safe and well tolerated
- Phase I commenced July 2016, Phase II H1 2018

Source: Campbell *et al.*, *J. Immunol.* (in press)



# CSL312 – HAE and Thrombosis

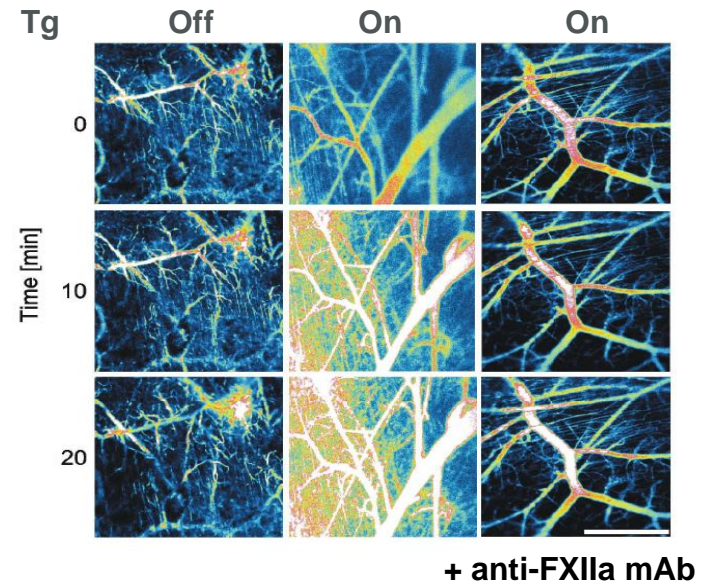
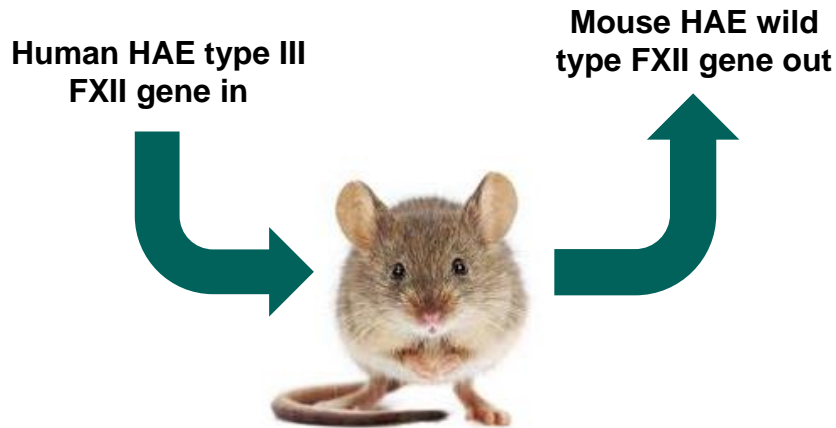
- Targeting FXIIa represents a novel approach to the treatment of hereditary angioedema and contact activated thrombosis
- Efficacy in multiple animal models and translational studies



# CSL312 – HAE and Thrombosis

Anti-FXIIa antibody prevents FXIIa mediated vascular leakage

- Mouse model incorporating a mutant (HAE type III) human FXIIa Tg

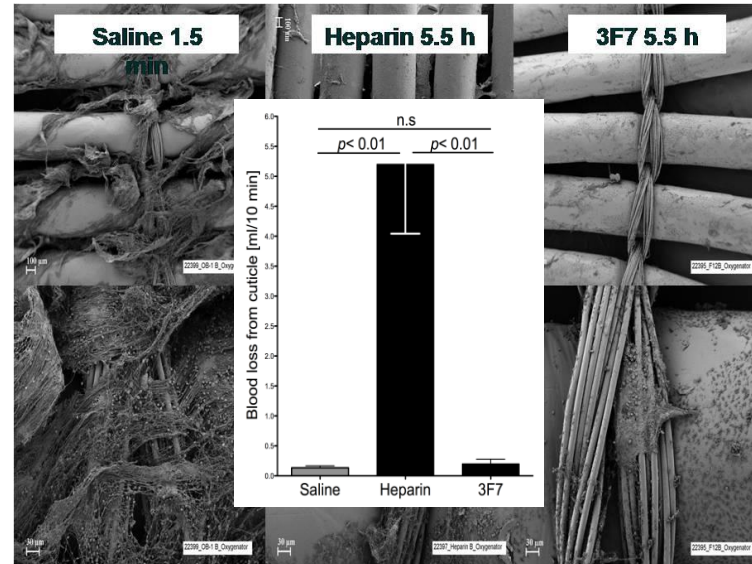
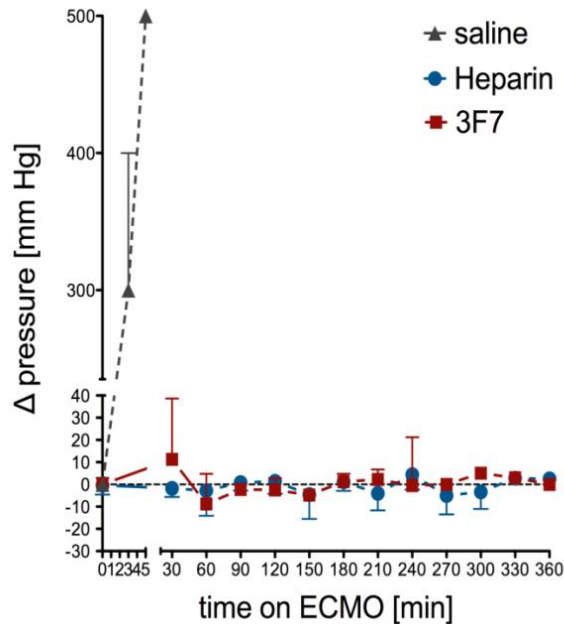


- GLP toxicology completed, CSL312 safe and well tolerated
- Phase I commenced Nov 2016, Phase II H1 2018

Source: Bjorkquist *et al.*, *J Clin Invest.* 2015

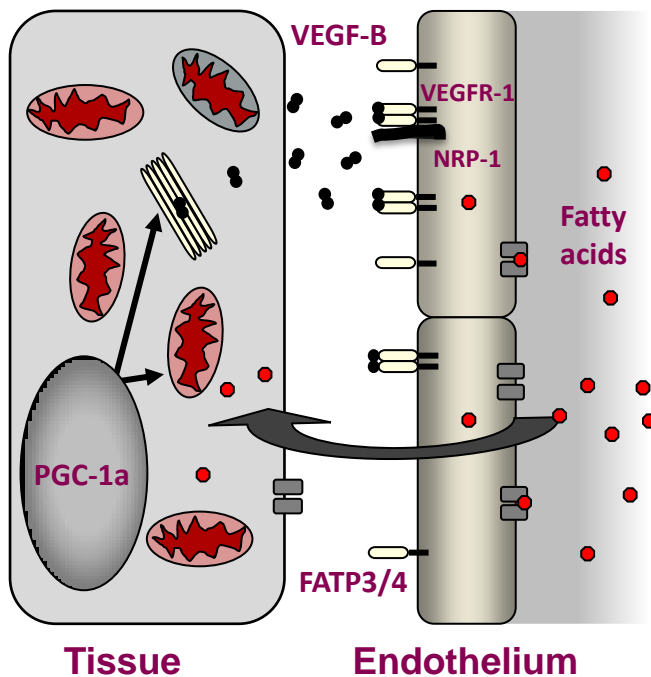
Anti-FXIIa antibody prevents foreign surface activated thrombosis without increasing bleeding risk

- Rabbit ECMO model



Source: Larsson *et al.*, Sci Transl Med, 2014

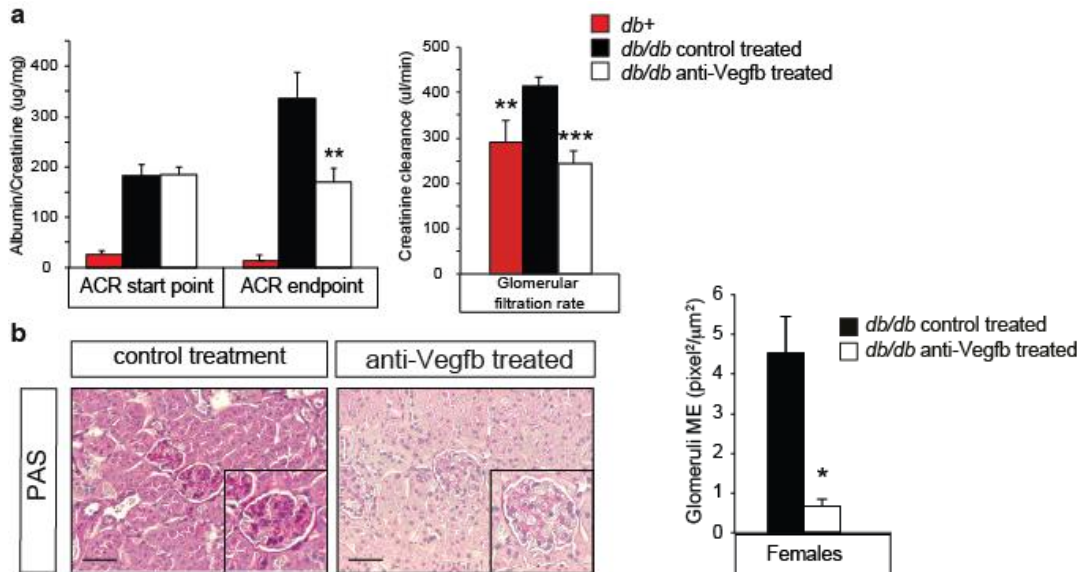
VEGF-B controls tissue uptake of fatty acids via regulation of endothelial fatty acids transport



- Increased VEGF-B leads to lipid accumulation in tissues and lipotoxicity  
➔ diabetes and diabetic complications
- Inhibition of VEGF-B signalling may represent a novel therapeutic strategy for diabetes and associated complications
- CSL346: mAb targeting VEGF-B

Sources: Hagberg *et al.*, *Nature* 2010. Hagberg *et al.*, *Nature* 2012

Anti-VEGF-B antibody prevents development of nephropathy in db/db//BLKS mice



- GLP toxicology studies in progress
- Phase I planned to commence in 2H, 2017

- Expanding capacity and capability across global research sites
- Innovating in key areas of business strength

Immunoglobulins

Haemophilia

Specialty  
Products

- Developing new opportunities in important areas of unmet medical need
  - Three novel mAbs entering the clinic in 12-18 month timeframe

Breakthrough  
Medicines

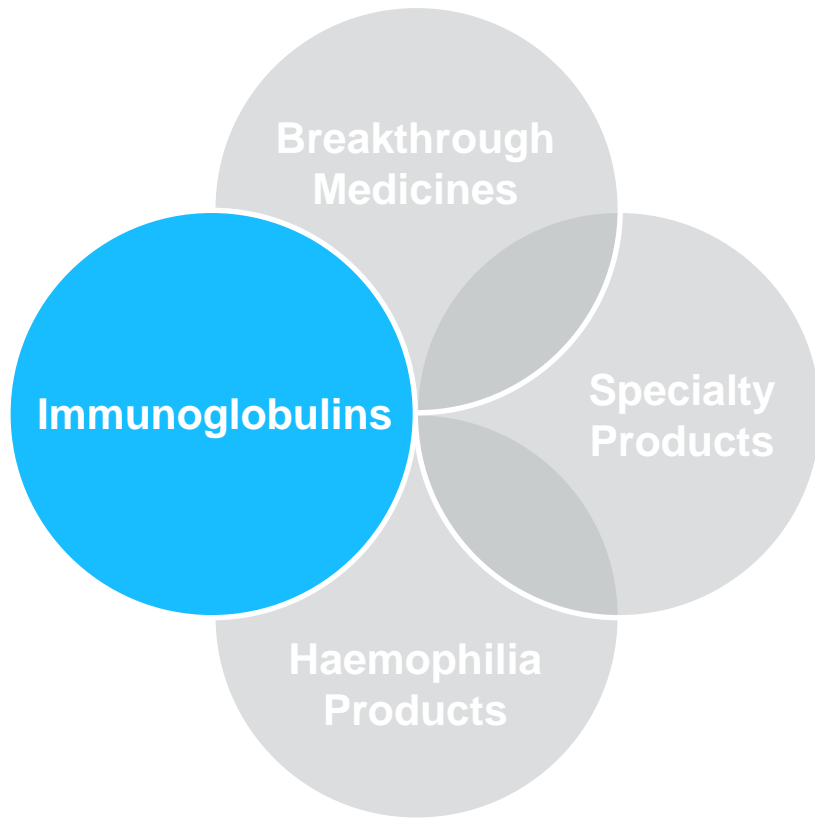
- Creating a sustainable pipeline for future growth

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# Immunoglobulins

CELEBRATING  
**100**  
CSL  
Just getting started

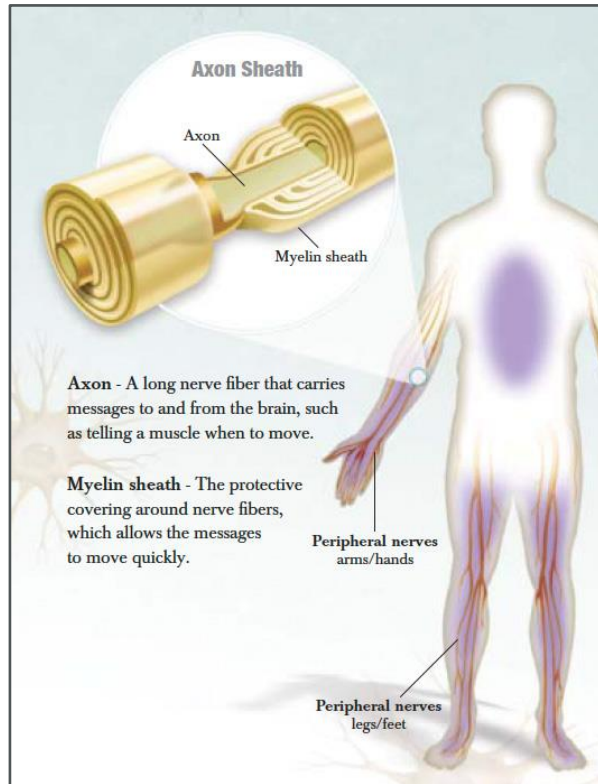
**CSL™**



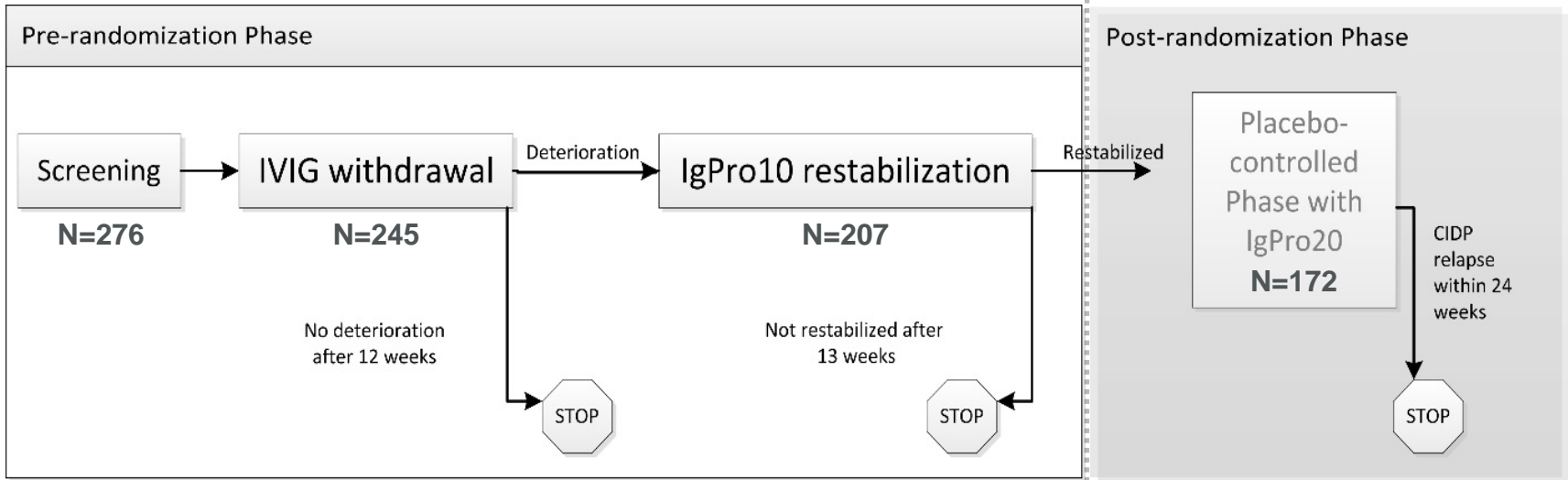
- Maintaining leadership position through focus on:
  - New Indications
  - Geographic expansion
  - Delivery options
- Key Focus
  - HIZENTRA®
  - PRIVIGEN®



### Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

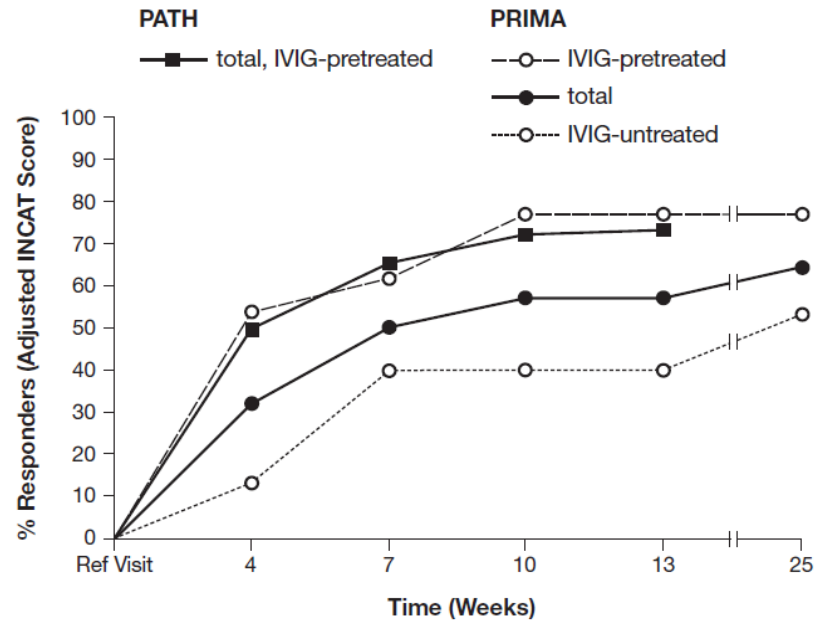


- Progressive weakness and impaired sensory function in the legs and arms
- New cases per year ~1-2 per 100,000 people
- Occurs at any age, in both genders, more common in young adults and in men
- Course varies widely among individuals. Left untreated, 30% of CIDP patients will progress to wheelchair dependence
- IVIG as first line therapy



- Largest placebo controlled study in CIDP
- Data base locked
- HIZENTRA<sup>®</sup> CIDP FDA submission mid 2017 and EMA submission 2H 2017

Source: 1. Von Schaik et al. Trials 016 Jul 25;17(1):345



- 73% PATH subjects responded with improvement in INCAT score
- PATH and PRIMA represent largest CIDP cohort studied
- FDA submission sBLA November 2016

Source: 1. Leger, JM et al. J Peripher Nerv Syst 2013 Jun;18(2):130-40



- Expand on our commitment to rare diseases
- Rigorous review of science and prioritisation
- Commence study in idiopathic inflammatory myopathies 2H 2017

- New generation IVIG products are associated with low, but relevant, risk of haemolysis



- Due to isoagglutinins
- Regulatory release specifications for maximum IVIG isoagglutinin titre are  $\leq 1:64^2$
- All Ig products manufactured by CSLB already meet these standards

Sources: 1. Bellac CL, et al. *Transfusion*. 2015;55(Suppl 2):S13–S22. 2. European Pharmacopea

### Methods to Reduce Isoagglutinin Levels

#### Cold ethanol fractioning

Cohn method includes a precipitation step that reduces isoagglutinin levels<sup>2</sup>

#### Donor screening

The levels of isoagglutinins can be reduced by 1 titre step<sup>2</sup> with exclusion of ~5% of donors<sup>3</sup>

#### Immunoaffinity chromatography (IAC)

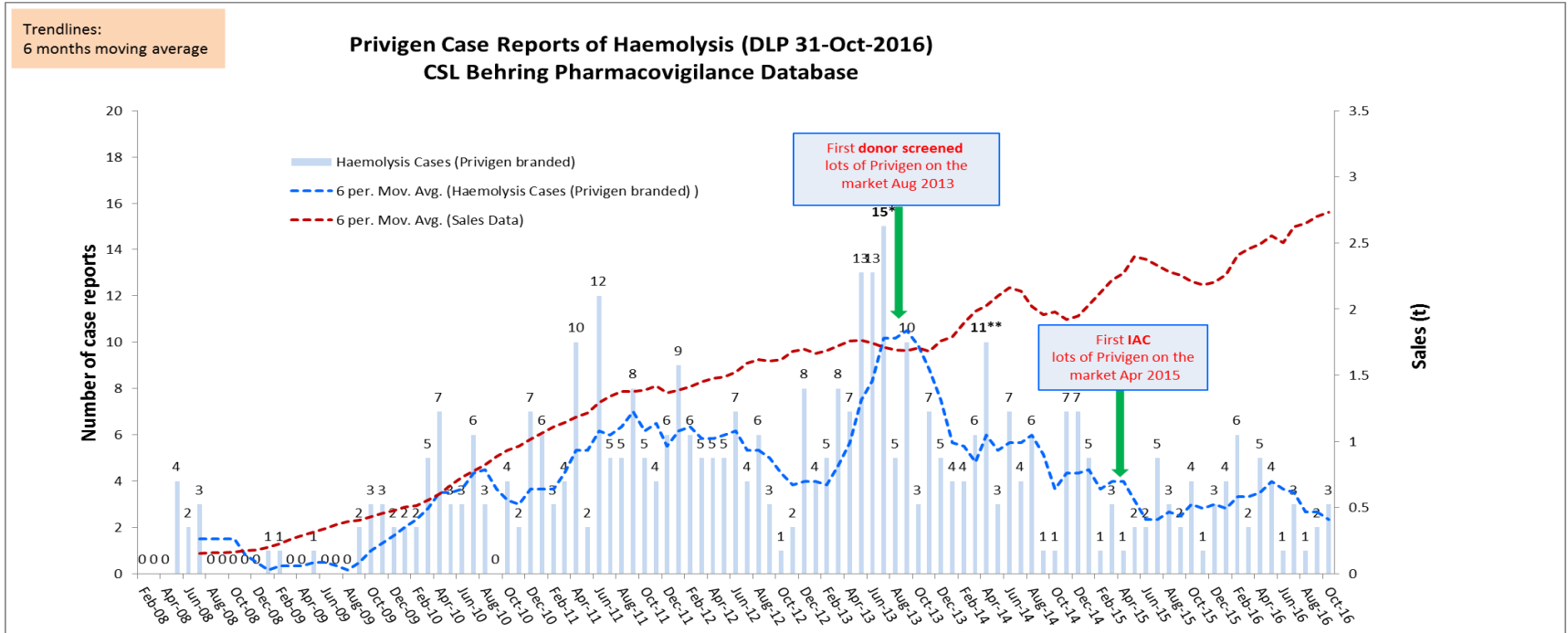
Isoagglutinin levels in PRIVIGEN® can be reduced by 2–3 titre steps, or 75–88%<sup>4-6</sup>

PRIVIGEN® median isoagglutinin titres are now 1:8 for anti-A and 1:4 for anti-B



**Sources:** 1. CSL Behring. *Data on File*. 2. Romberg V, et al. *Transfusion*. 2015;55(Suppl 2):S105–S109. 3. Siani B, et al. *Transfusion*. 2015;55(Suppl 2):S95–S97. 4. Gerber S, et al. *Manuscript submitted*. 5. Hoeffler L, et al. *Transfusion*. 2015;55(Suppl 2):S117–S121. 6. Hubsch AP, et al. [Poster]. 2016 AAAAI, LA, CA.

CSL Behring proactively introduced an isoagglutinin reduction strategy that reflects our strong commitment to continue to deliver safe and effective therapies to patients



- PRIVIGEN® IsoLo® approved in US, Europe, Canada, Australia, Switzerland and other selected countries

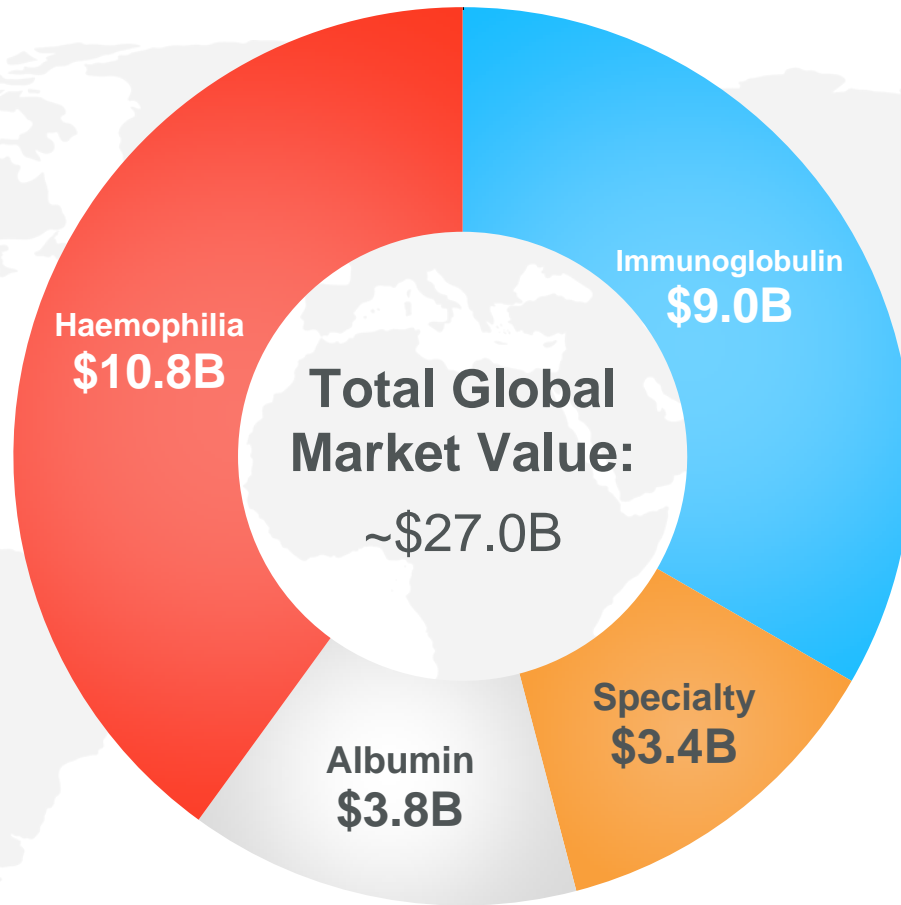
Source: ENCePP: Privigen PASS. Available at: <http://www.encepp.eu/encepp/viewResource.htm?id=6515>. Accessed 14 April 2016

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# Commercial Market Overview







**Sources:** Company 3Q 2016 reports/financial schedules, MRB global Coagulation Factors Concentrate Market 2015 & 2016, MRB WW Plasma Fractionation Market 2015 interim report, CSL Actuals FY16

# Key Segment Opportunities

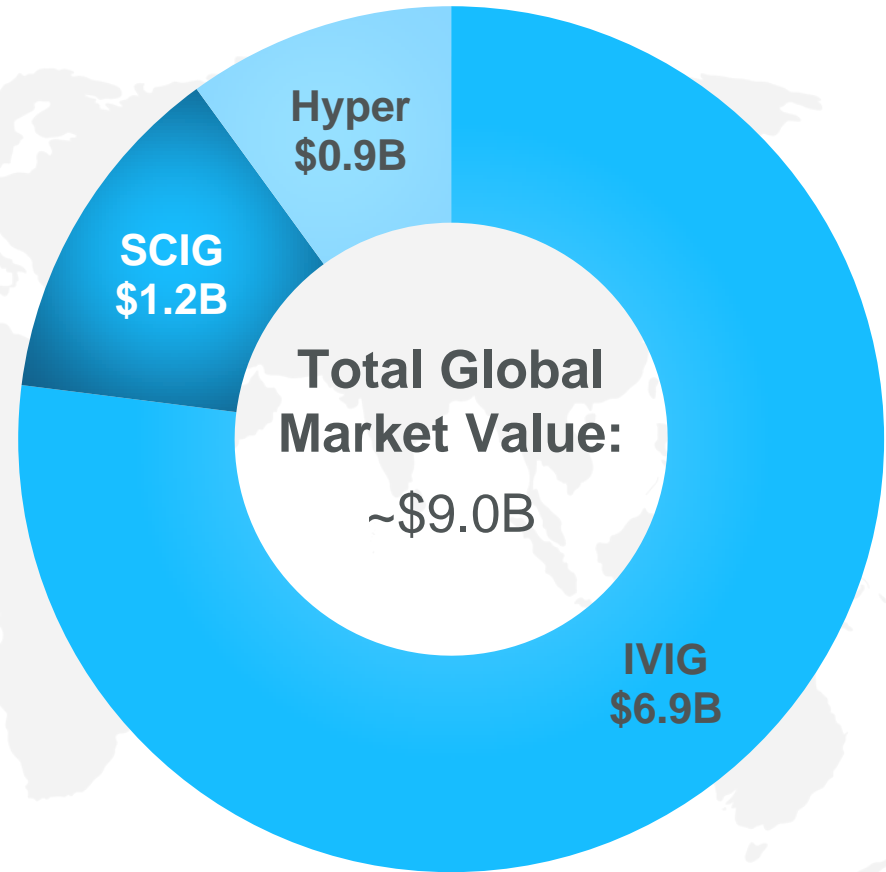


# Immunoglobulins

Commercial Opportunities and Activities

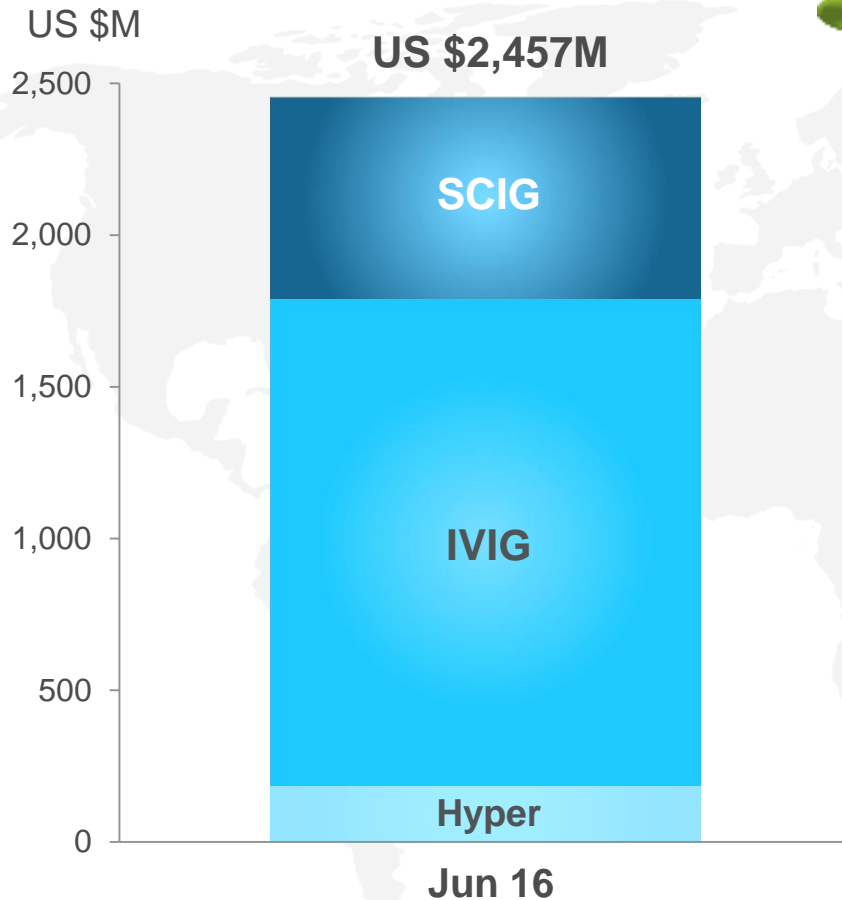


- Global market volume growth projected at 5-7% in 2017
- Demand driven by medical education and brand promotion
- Growing patient acceptance of subcutaneous delivery in developed and emerging markets
- Evidence-based opportunities for future indications



Sources: Company 3Q 2016 reports, Markets and Markets Plasma Fractionation Report 2016, based on 2015 data, CSL Actuals FY16

# Immunoglobulins



Reported sales for the 12-month period

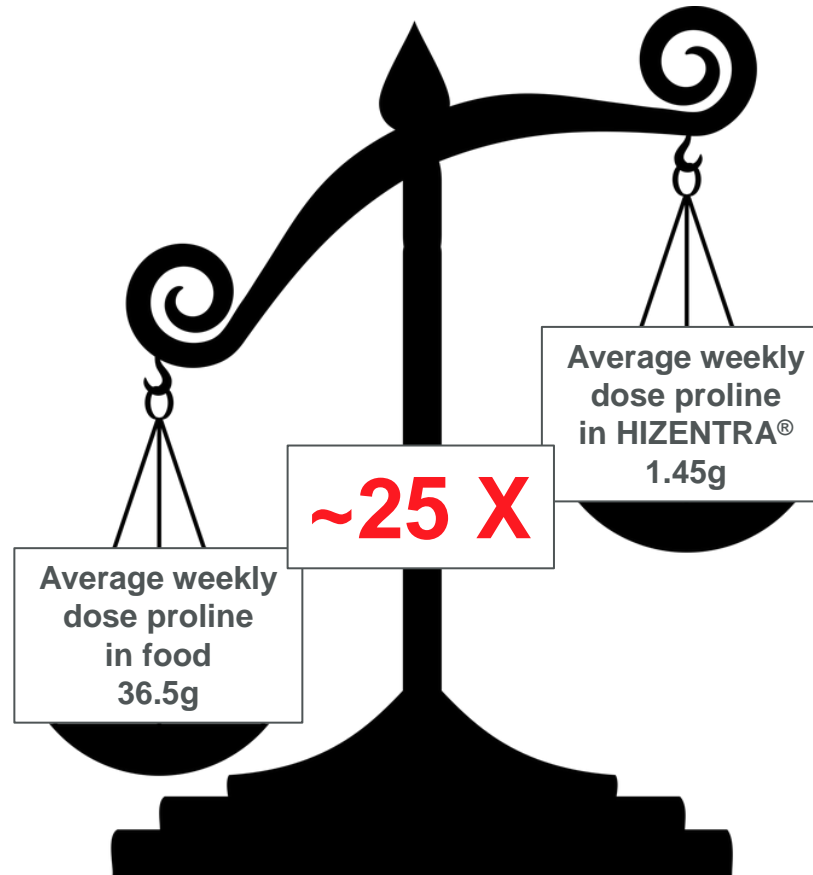


privigen®

- Global revenue +7%
- CIDP & SID indications in the EU
- Reliability of supply
- Geographic and market expansion
- Introduction of PRIVIGEN® IsoLo®

Hizentra®

- Global revenue +31%
- Significant increase in new patient starts in US and EU
- Patient preference for at home treatment



[http://www.nutritionvalue.org/foods\\_by\\_Proline\\_content\\_page\\_1.html](http://www.nutritionvalue.org/foods_by_Proline_content_page_1.html)  
HIZENTRA® dose 1 X 50ml vial (10g) – average weekly adult dose



### GROW

our Current Franchise by:

- Maximising current indications globally: continue geographic expansion; accelerate subcutaneous growth; launch 5 & 10 ml PFS in 2017



### BUILD

a Leading Neuro Franchise by:

- Focusing on CIDP: PRIVIGEN® today, HIZENTRA® in the near term; new neurology indications such as myositis in the future



### EXPAND

the Global Franchise by:

- Continue to invest in a broad range of potential new indications, product innovations and disruptive technologies

Category Leadership



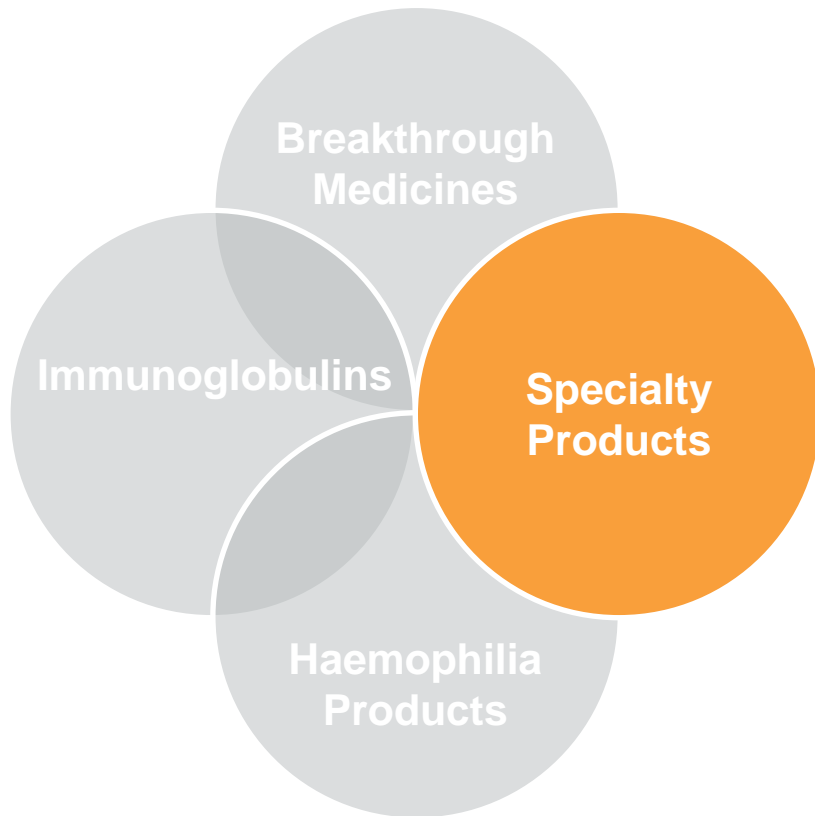
CSL Behring  
is *the* world  
renowned  
leader in Ig  
therapy  
delivering  
innovations  
that enhance  
patients' lives



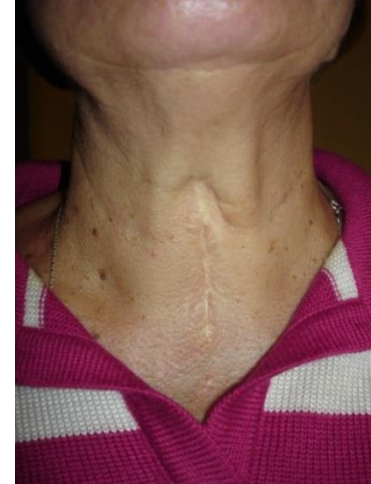
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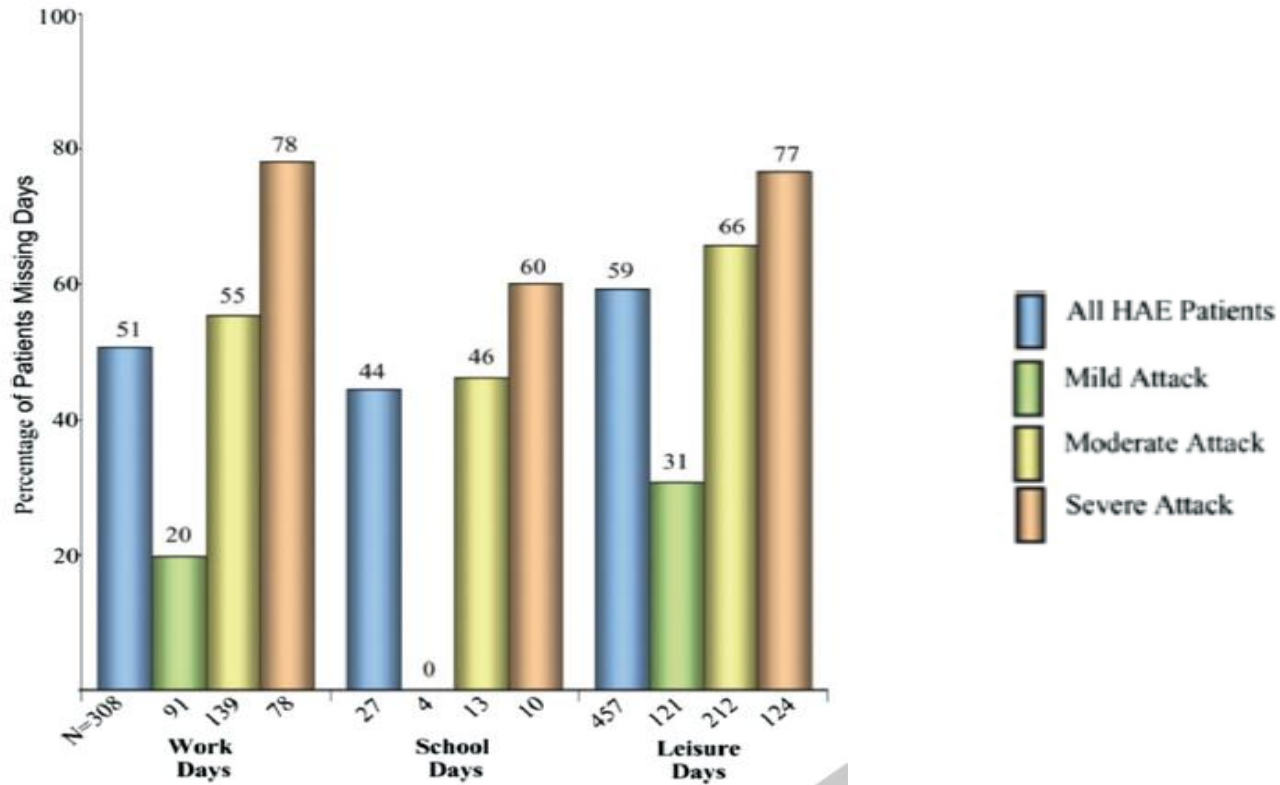
# Specialty Products





- Leveraging high quality broad product portfolio through:
  - New markets
  - Novel indications
  - Novel modes of administration
- Key Focus
  - HAEGARDA™/BERINERT®
  - BERIPLEX®/KCENTRA®
  - ZEMAIRA®/RESPREEZA®





### Work Productivity Activity Impairment (WPAI)<sup>1</sup>

\*QOL – Quality of Life

Source: 1. Lumry WR, et al. Allergy Asthma Proc 2010; 31(5):407–14.

## **Phase III COMPACT Study**

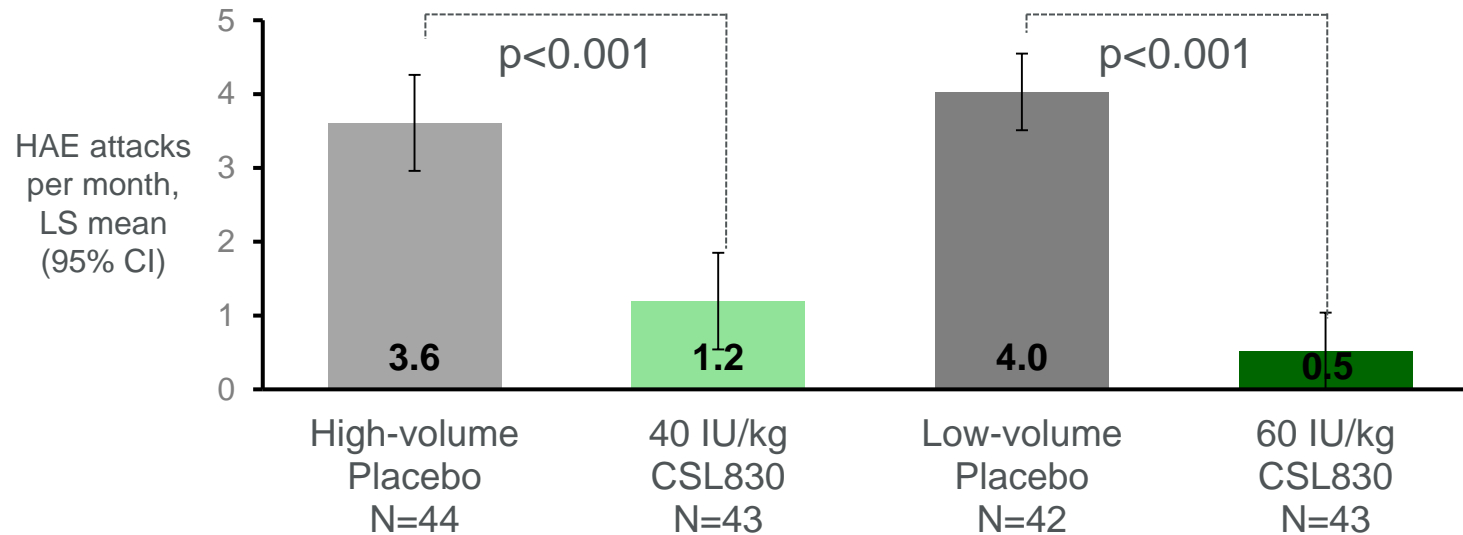
**C1-INH (SC)**, CSL830, a low volume self-administered, subcutaneous C1-inhibitor preparation, is well tolerated and efficacious for preventing attacks in patients with HAE<sup>1</sup>

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



**Source:** 1. Zuraw et al. Oral Presentation American College of Allergy Asthma and immunology. Manuscript submitted

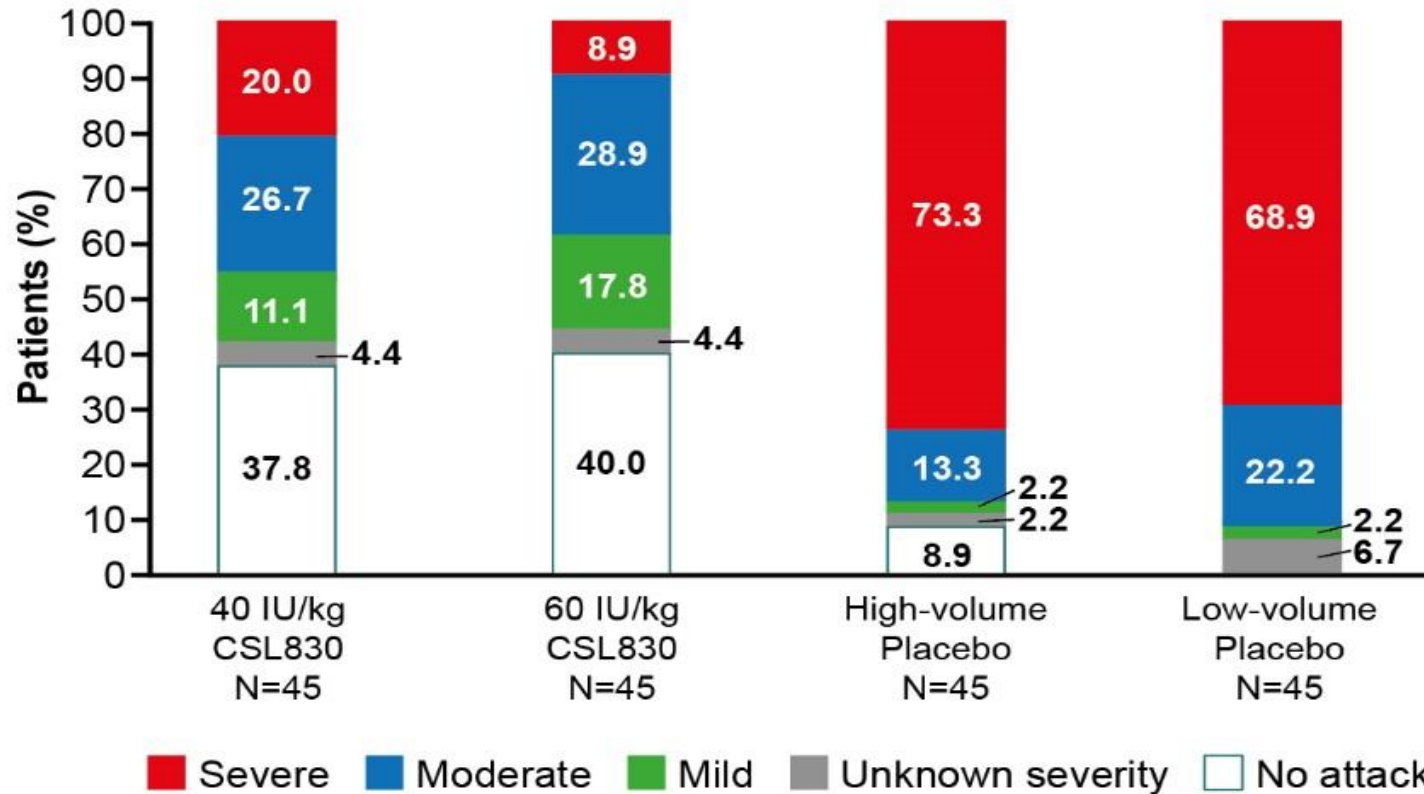
- Primary endpoint met:
  - 40 IU/kg reduced attack rate 88.6% (median,  $p < 0.001$ )
  - 60 IU/kg reduced attack rate 95.1% (median,  $p < 0.001$ )



**COMPACT**

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

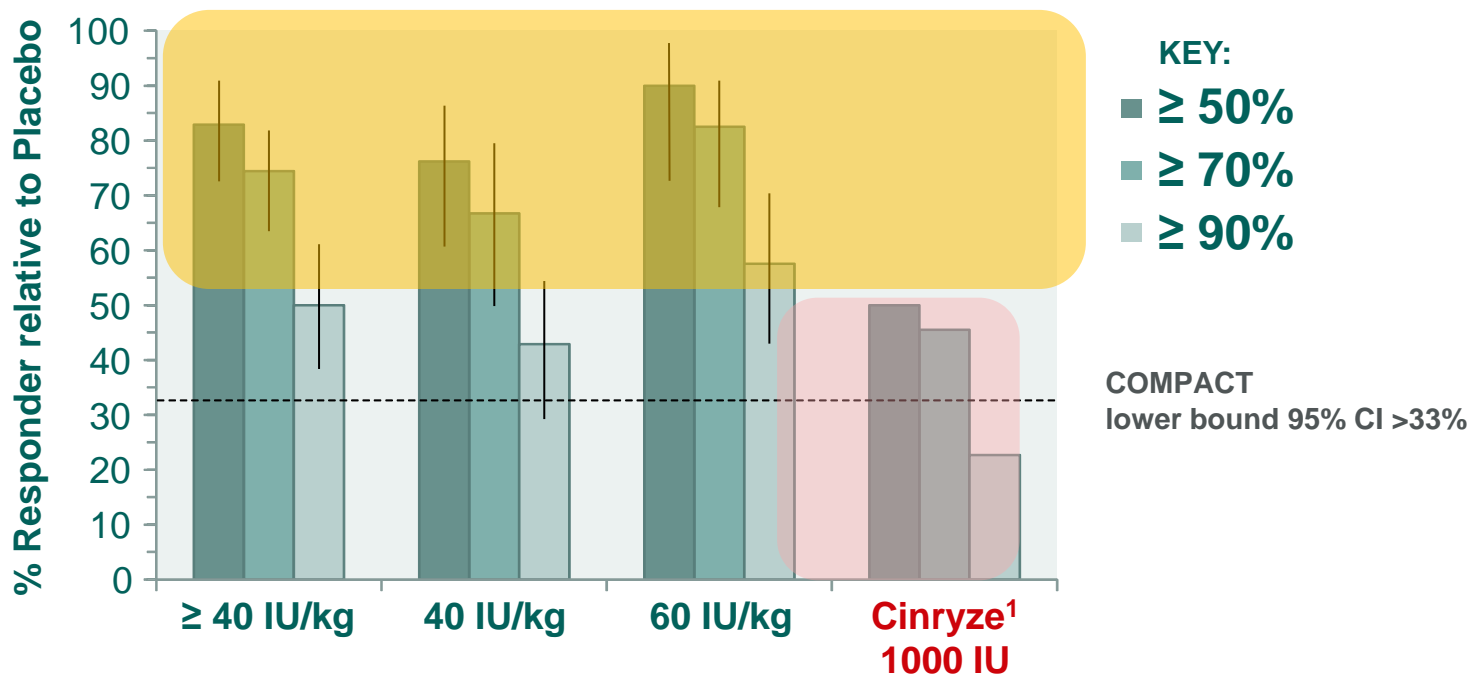
# HAEGARDA™ Reduces Attack Severity



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

- FDA definition of a responder is a subject with  $\geq 50\%$  reduction of attacks

Indirect Cross-study Comparison



Source: 1. Zuraw BL, et al: Results of a randomized double-blind placebo controlled study of nanofiltered C1-inhibitor for the treatment of HAE attacks. American College of Allergy, Asthma & Immunology; Dallas, Texas 2007



## Adverse Events in Study Safety Population

n (%)	40 IU/kg CSL830 N=43	60 IU/kg CSL830 N=43	Combined placebo N=86
Patients reporting ≥1 AE	29 (67.4)	30 (69.8)	57 (66.3)
Adverse drug reactions, number of patients (%)			
Injection site reactions*	12 (27.9)	15 (34.9)	21 (24.4)
Nasopharyngitis	1 (2.3)	8 (18.6)	6 (7.0)
Hypersensitivity**	2 (4.7)	3 (7.0)	1 (1.2)
Dizziness	4 (9.3)	0	1 (1.2)

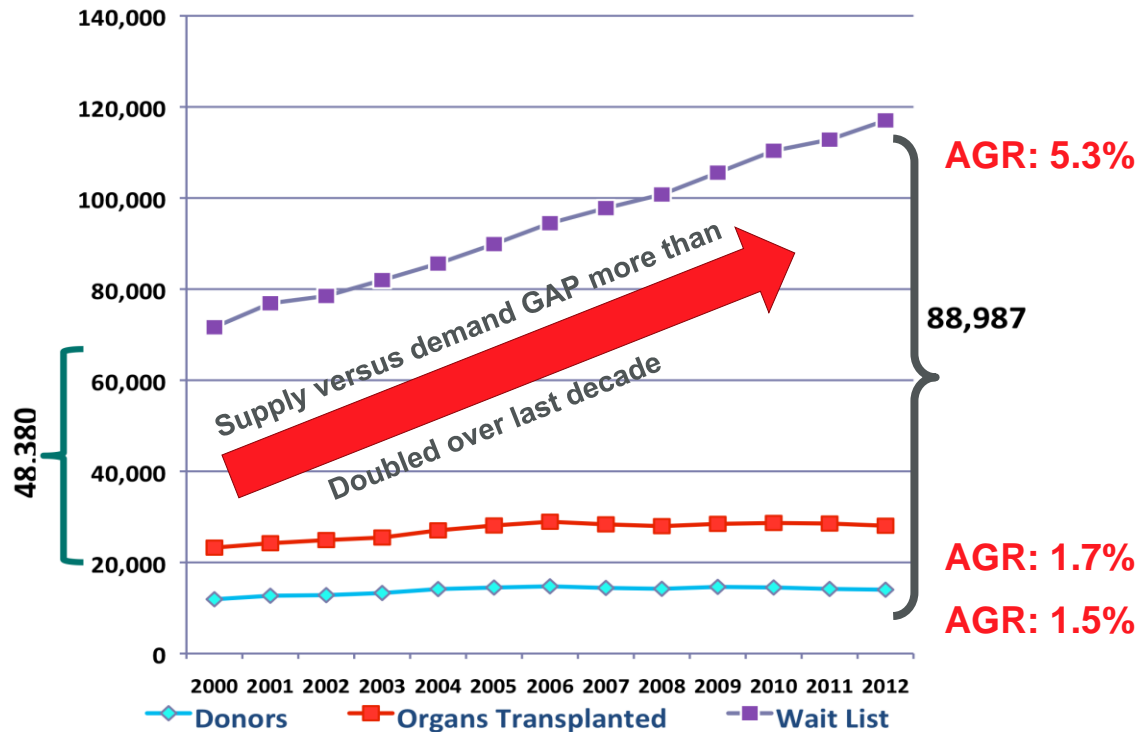
- Injection site reactions were the most commonly reported AEs
- 95% of injection site reactions were mild, most occurred and resolved within 24 h after injection
- No injection site reactions were serious or led to discontinuation of treatment

\*Injection site reactions include: injection site bruising, coldness, erythema, and similar

\*\*Hypersensitivity includes: pruritus, rash, and urticaria

- COMPACT trial demonstrated dose-dependent efficacy of HAEGARDA™ for the prevention of HAE attacks
  - Reduction in median attack rate: 89–95%
  - Response rate ( $\geq 50\%$  relative attack reduction): 76–90%
  - 60 IU/kg consistently showed higher efficacy
- BLA accepted by FDA 30 August 2016
- Submission to EU anticipated early 2017

- Increasing global demand for organ transplantation associated with limited supply<sup>1</sup>

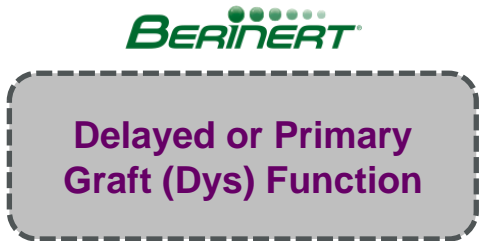
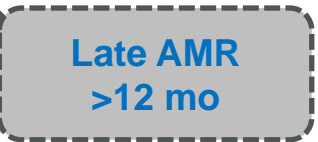
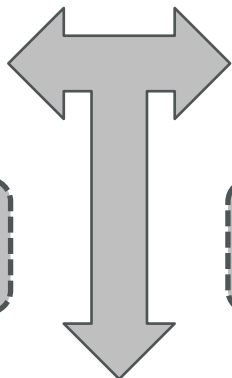


Source: 1. OPTN Database May 2016 (Note: Deceased donors may donate multiple organ)

## Normal Kidney



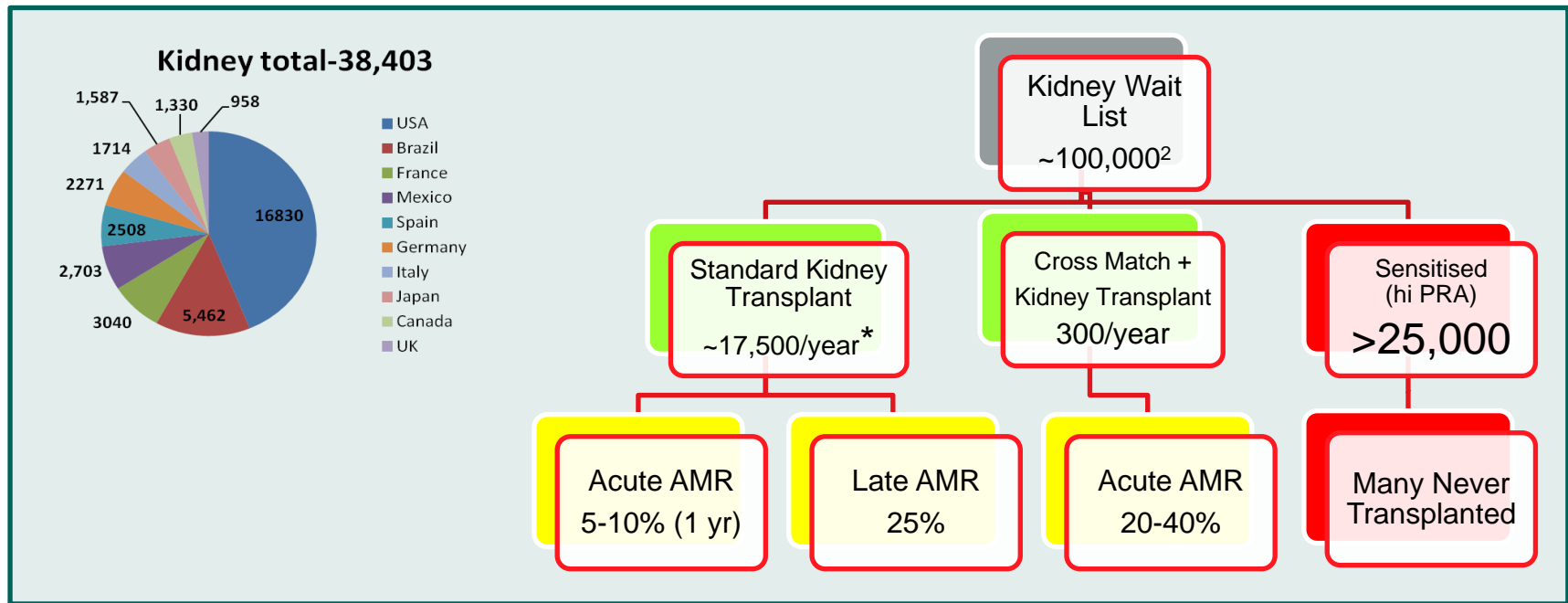
HLA reduction /  
Desensitisation /  
Improve viability



## Rejected Kidney



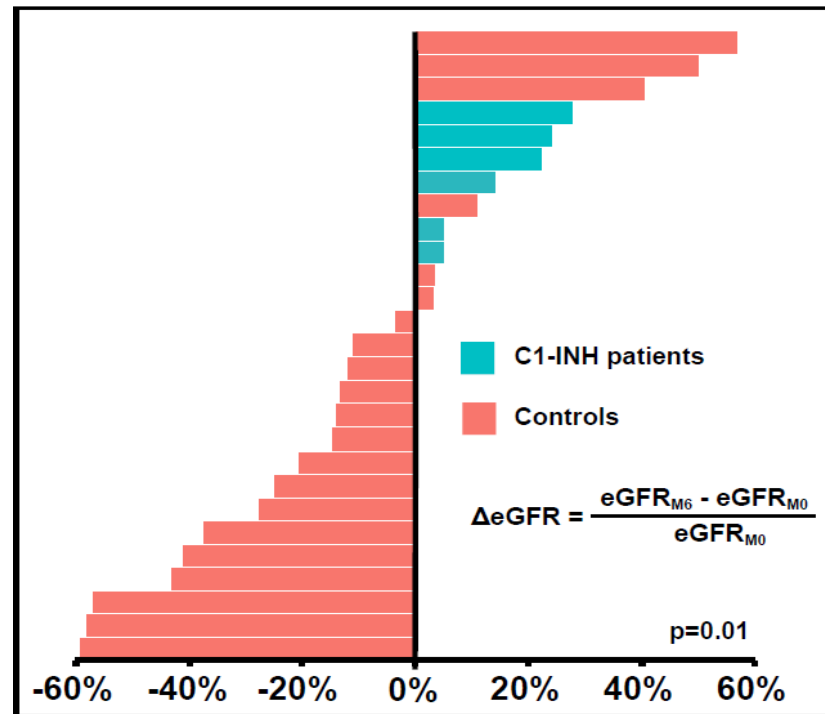
- Lack of donors, organ unsuitability
- Long-term graft survival still poor, graft loss after 1 year is 5% per year<sup>1</sup>



AMR – Antibody Mediated Rejection

Sources: 1. Lamb, KE et al, *Am J Transplant* 2011 Mar;11(3):450-62. 2. OPTN Database May 2016 (Note: Deceased donors may donate multiple organ)

- Patients treated with BERINERT® demonstrated an improvement in renal function (GFR - glomerular filtration rate)



\* Refractory AMR (acute or late) patients who have not responded to 3 months standard of care

- Source: Viglietti et al. *Am J Transplant* 2016 May;16(5):1596-603

- Program will test ability to increase donor compatibility and improve long and short-term graft survival
- First program of C1 inhibition in renal transplant in 2H 2017, pending regulatory interactions
- Ongoing interactions with high quality collaborators and regulators which will inform further CSL sponsored programs

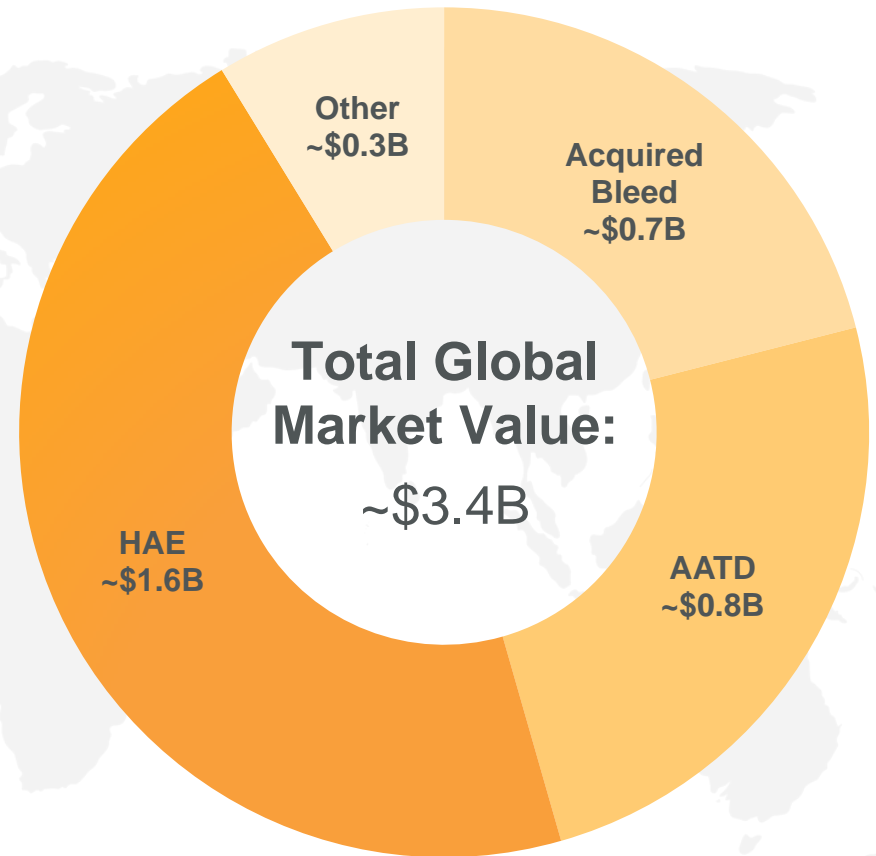
# Specialty Products

Commercial Opportunities and Activities





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

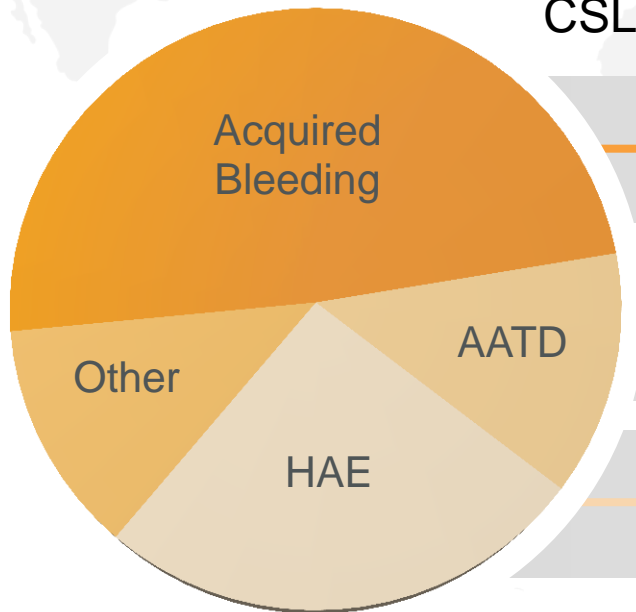


**Sources:** Company annual reports/financial schedules, based on 3Q 2016 data, MRB WW Plasma Fractionation Market 2016 interim report, CSL Actuals FY16

- KCENTRA®/BERIPLEX® usage growing across multiple specialties
- BERINERT® geographic and market expansion continues
- Launch of RESPREEZA® in EU
- EU growth of HAEMOCOMPLETTAN® P

CSL FY16 Sales \$983M

Key Brands:



**Kcentra®**  
**Beriplex® P/N**

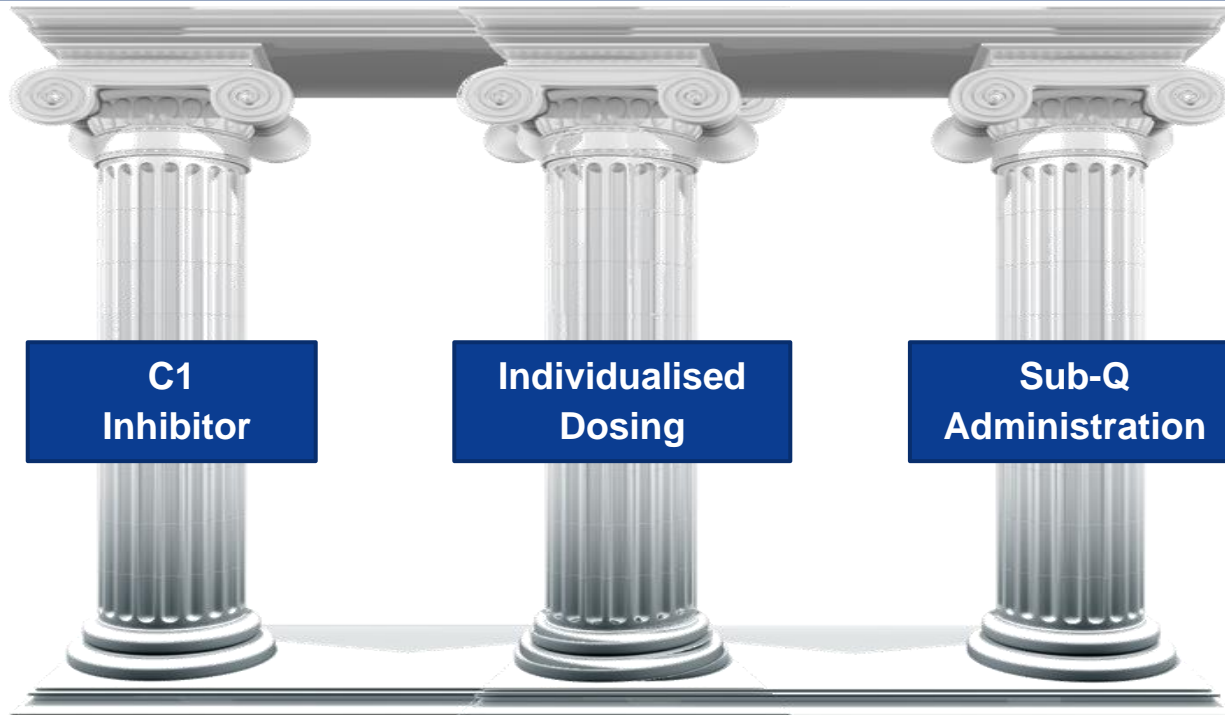
**Zemaira®**  
**Respreeza®**

**BERINERT®**

- AATD market in Europe approximately ~\$200M
- Majority of treated patients are in Germany and France
- RESPREEZA® differentiation:
  - Indicated for maintenance treatment, and to slow the progression of emphysema in adults
  - Highly purified formulation provides lower volume for faster infusion speed

Reimbursement Achieved	Reimbursement Pending
Czech Rep	Austria
France	Belgium
Germany	Denmark
Greece	Finland
Italy	Norway
Portugal	Poland
Slovakia	Sweden
Spain	United Kingdom
Switzerland	

Most effective in preventing HAE attacks



### HCP

- HAEGARDA™ has two key perceived advantages over current options:
  1. More efficacious in reducing frequency of HAE attacks
  2. Only subcutaneous agent for HAE prophylaxis
- All physicians noted that efficacy is their primary goal when recommending prophylactic therapy

### Patients

- The core value proposition HAEGARDA™ offers is greater efficacy (reduced number of attacks) with prophylaxis therapy
- Subcutaneous administration is a life-transforming advantage, but secondary to efficacy

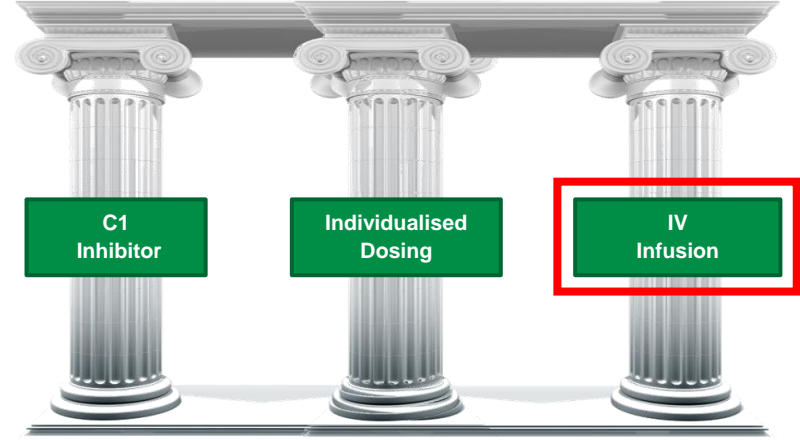
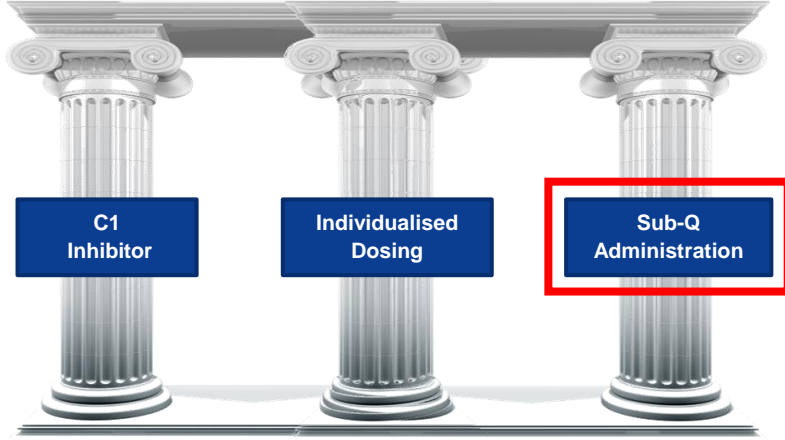
Revenue Potential of \$0.75M – \$1B p.a.

HAEGARDA™

BERINERT®

*Most effective in preventing HAE attacks*

*Most effective in stopping HAE attacks*



PK data to reinforce consistent levels for Sub-Q



# Q&A



Just getting started



A dark teal world map is centered in the background of the slide.

Break



Just getting started

**CSL™**





# Investor R&D Briefing

December 1, 2016

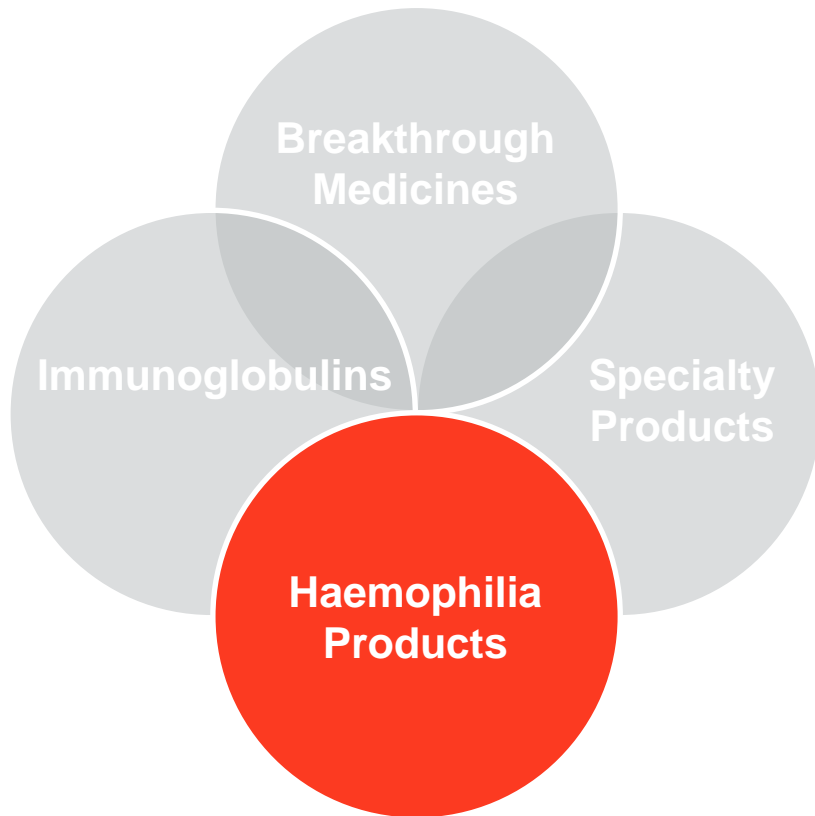
CELEBRATING  
**100**  
**CSL**  
Just getting started

**CSL**<sup>TM</sup>



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# Haemophilia Products





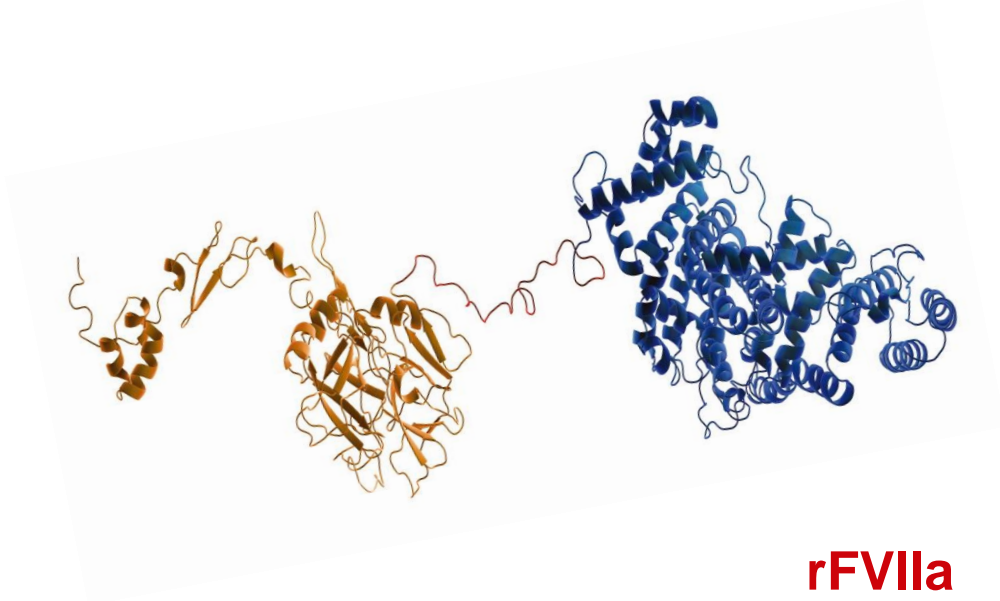
- Supporting and enhancing plasma products and developing novel recombinant portfolio with focus on:
  - Scientific and product innovation
  - Patient benefit
- Key Focus
  - IDELVION® (rIX-FP)
  - AFSTYLA® (rVIII-Single Chain)
  - Long acting rVIIa-FP

	Achieved 2016	Anticipated 2017
 <p><b>IDELVION</b><sup>®</sup> Coagulation Factor IX (Recombinant), Albumin Fusion Protein</p>	<p>Australia Canada EU Japan Switzerland USA</p>	<p>Hong Kong Israel New Zealand Taiwan</p>
 <p><b>AFSTYLA</b><sup>®</sup> Antihemophilic Factor (Recombinant), Single Chain</p>	<p>Canada USA</p>	<p>Australia EU <i>(positive opinion Nov 2016)</i> Japan New Zealand Switzerland</p>

AsBR Extension Study		7-Day Regimen (n=19)	10-Day Regimen (n=7)	14-Day Regimen (n=21)	21-Day Regimen (n=10)
Adults	Median (IQR)	0.85 (0,2.9)	0 (0,0)	0 (0,0)	0 (0,0)
	Estimated Mean AsBR (95% CI) <sup>†</sup>	1.91 (1.09-3.36)	0.31 (0.4-0.7)	0.88 (0.47-1.65)	0.45 (0.07-0.98)
	Duration	309	650	491	442
		7-Day Regimen (n=20)	10-Day Regimen (n=6)	14-Day Regimen (n=8)	Not tested
<12 years	Median (IQR)	0 (0,5.6)	0 (0-3,06)	1.16 (0-2.63)	
	Estimated Mean AsBR (95% CI) <sup>†</sup>	0.7 (0.3-1.6)	2.12 (0.56-8.02)	1.19 (0.56-2.54)	
	Duration	415	501	483	

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

<sup>†</sup>Assuming Poisson distribution



rFVIIa

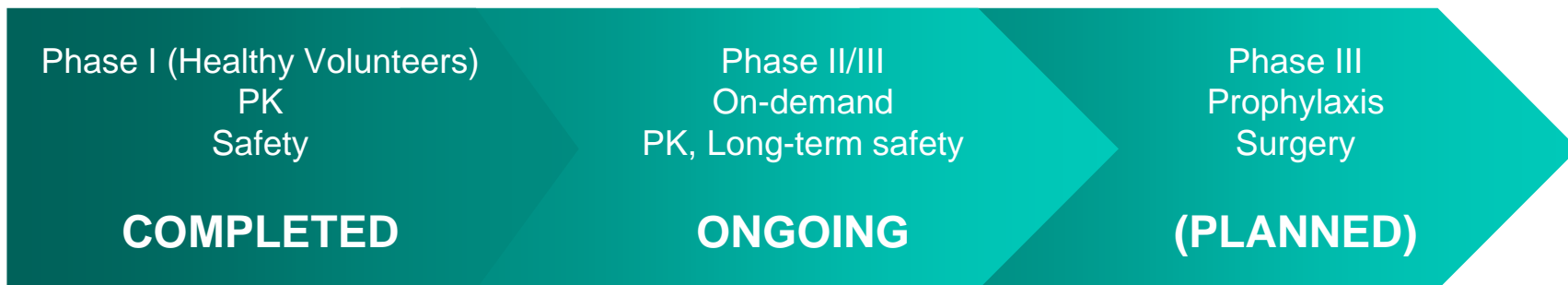
Linker

rAlbumin



PROLONG **7** FP

### Congenital Haemophilia A or B with Inhibitors (CHwI)



### Congenital Haemophilia Factor VII Deficiency



PROLONG 7 FP

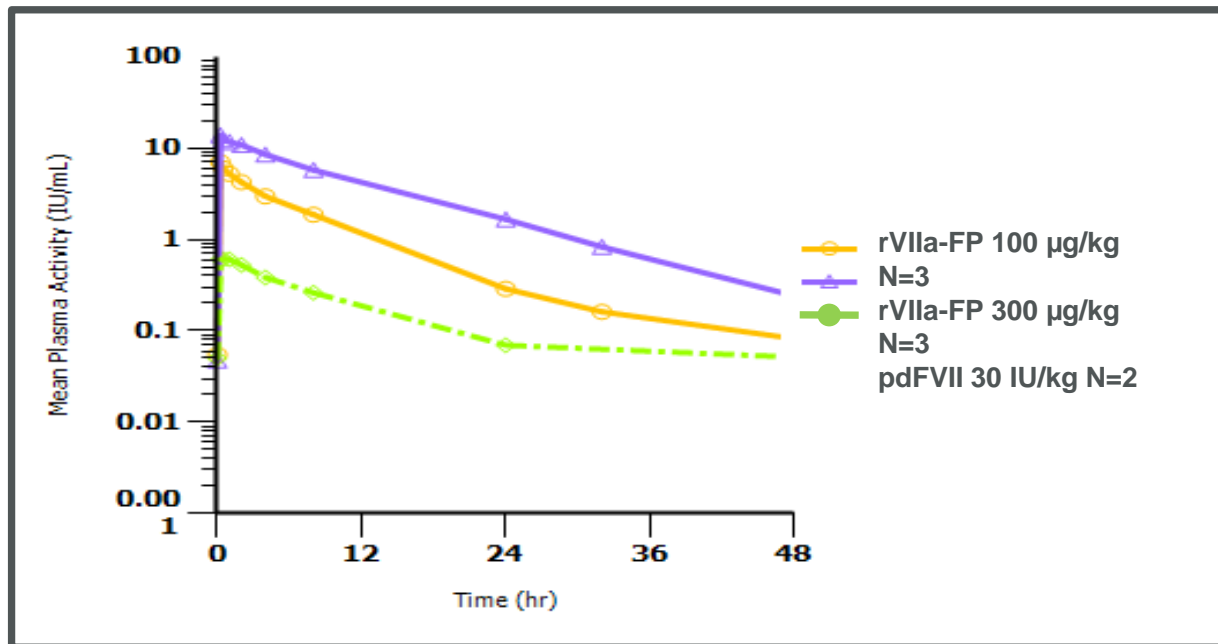
- rVIIa-FP is efficacious and safe in treating bleeding events
  - 47 bleeds in 10 subjects
  - 77% of bleeds controlled with 1 infusion
  - 100% of bleeds controlled with 2 infusions
  - No thrombo-embolic adverse events experienced
- NOVOSEVEN<sup>®</sup>
  - 10% of bleeds controlled with 1 infusion
  - 27% of bleeds controlled with 2 infusions (published data\*)

\*S.R. Lentz et al. *Journal of Thrombosis and Haemostasis*, 12: 1244–1253

- CSL689 was not studied head to head with NOVOSEVEN<sup>®</sup>



- Phase I study confirms rVIIa-FP has measurable FVIIa levels up to 48 hrs
- Supports testing once to twice weekly dosing in Phase II
- Phase II to commence 2H 2017

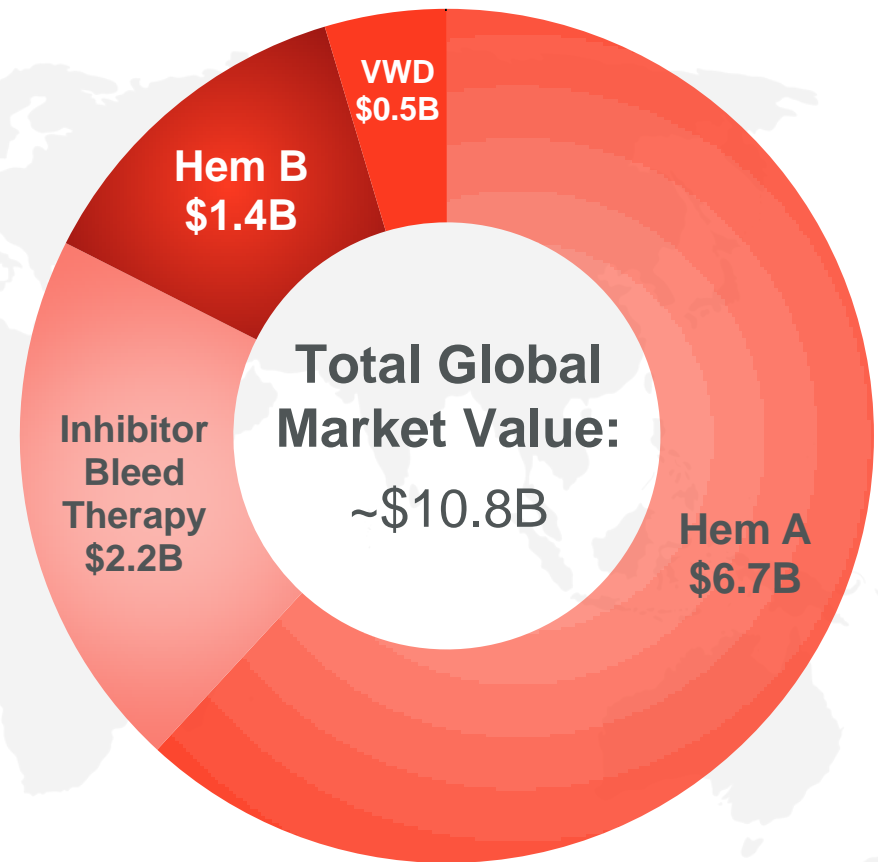


# Haemophilia

Commercial Opportunities and Activities



- Trend toward recombinants in developed markets
- 75% of patients with bleeding disorders are under/un-treated
- Launches of multiple longer-acting products in Hem-A space
- Payers contemplating active category management
- Rapid transition of Hem-B category



**Sources:** Company 3Q 2016 reports/financial schedules, based on 2016 data, MRB global Coagulation Factors Concentrate Market 2015 & 2016, Haemophilia World, December 2013, Vol 20. No 3, CSL Actuals FY16

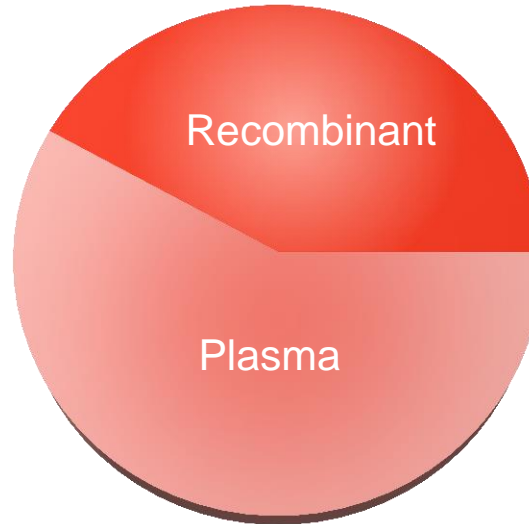
**HUMATE-P®**  
Antihemophilic Factor/von Willebrand  
Factor Complex (Human)

**Monoclante-P®**  
Factor VIII:C Pasteurized, Monoclonal Antibody Purified  
Antihemophilic Factor (Human)

CSL FY16 Sales \$1B

 Beriate® P

**Helixate®FS**  
Antihemophilic Factor (Recombinant)  
Formulated with Sucrose





**Mononine®**  
MONOCLONAL ANTIBODY PURIFIED  
Coagulation Factor IX (Human)

 **STIMATE®**  
(desmopressin acetate) Nasal Spray, 1.5 mg/mL

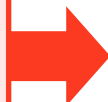
 **VONCENTO®** ▼  
(Human Coagulation Factor VIII/  
Von Willebrand Factor Complex)

Revenue Potential of \$0.7 – \$1B p.a. in 4-5 years

		US	EU	Japan
 <p>Coagulation Factor IX (Recombinant), Albumin Fusion Protein</p>	<ul style="list-style-type: none"> <li>• Unique albumin fusion protein</li> <li>• New SOC for haemophilia B</li> <li>• Increased protection and convenience</li> </ul>	Launched	Launched	Launched
 <p>Antihemophilic Factor (Recombinant), Single Chain</p>	<ul style="list-style-type: none"> <li>• Unique single chain design</li> <li>• Longer acting (2-3x weekly dosing)</li> <li>• Increased vWF affinity</li> </ul>	Launched	Q1'17	Q1'18

### Single Dose:

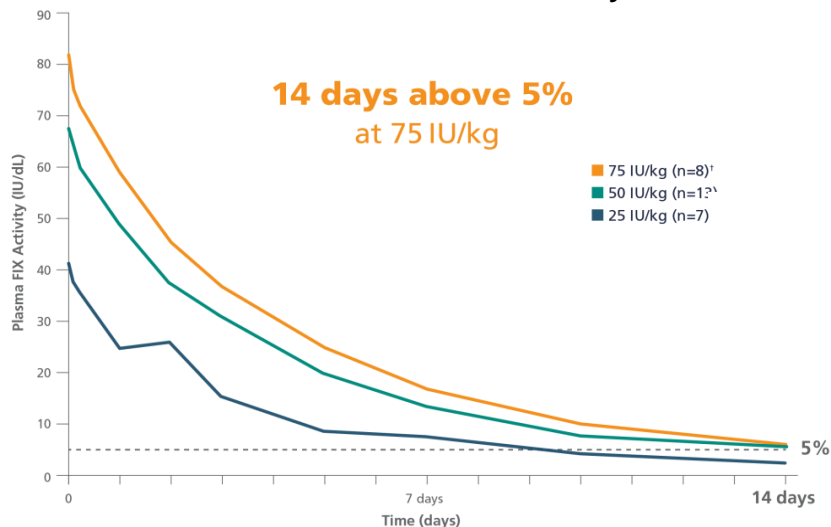
IDELVION® maintains high trough levels (>5%) for protection from bleeds between treatments



### Steady-State:

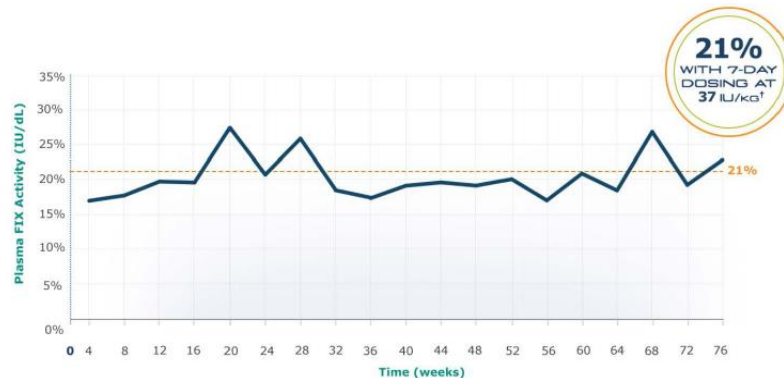
IDELVION® delivers steady-state mean FIX levels of 21% with 7-day prophylaxis (patients <12 years) and 13% with 14-day prophylaxis (patients ≥12 years)

Baseline-corrected FIX activity\*1

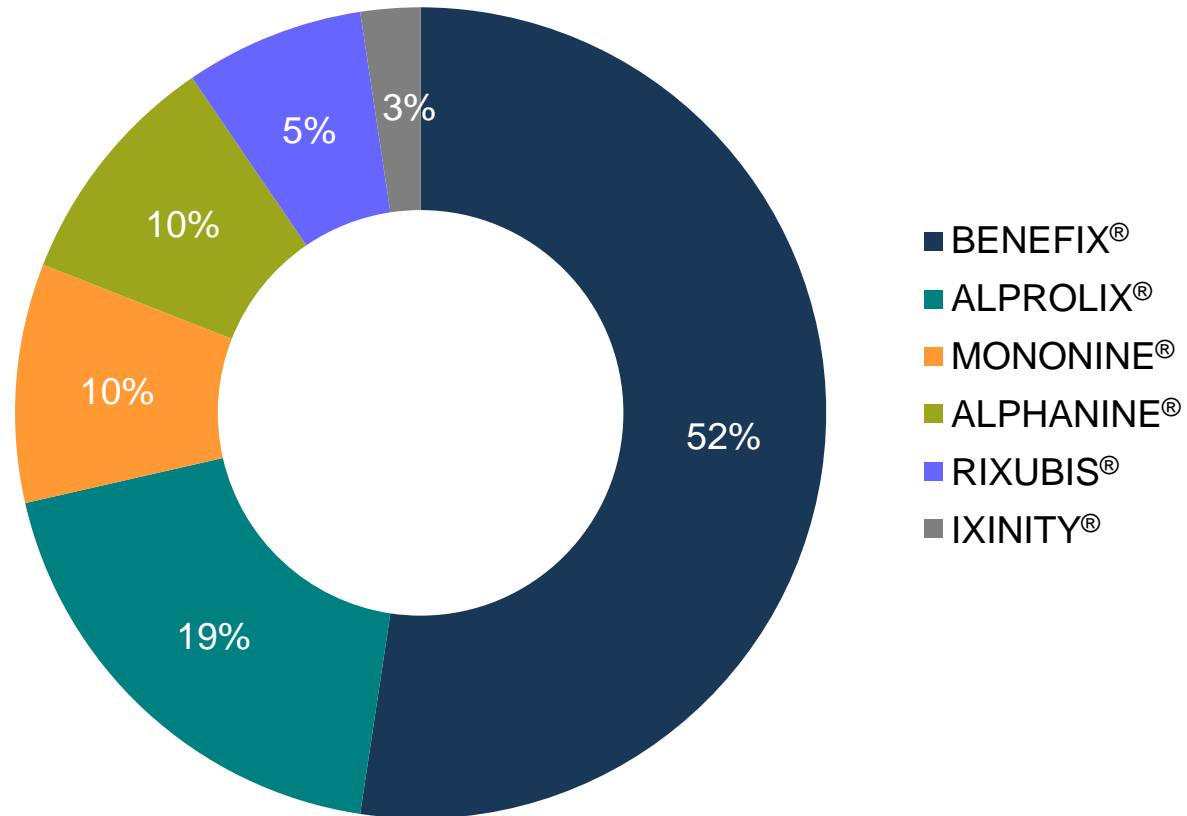


\*After administration of a single infusion of IDELVION. Data from Phase 1 clinical study.

1. Santagostino E, Negrier C, Klamroth R, et al. Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients. *Blood*. doi:10.1182/blood-2012-05-429688.

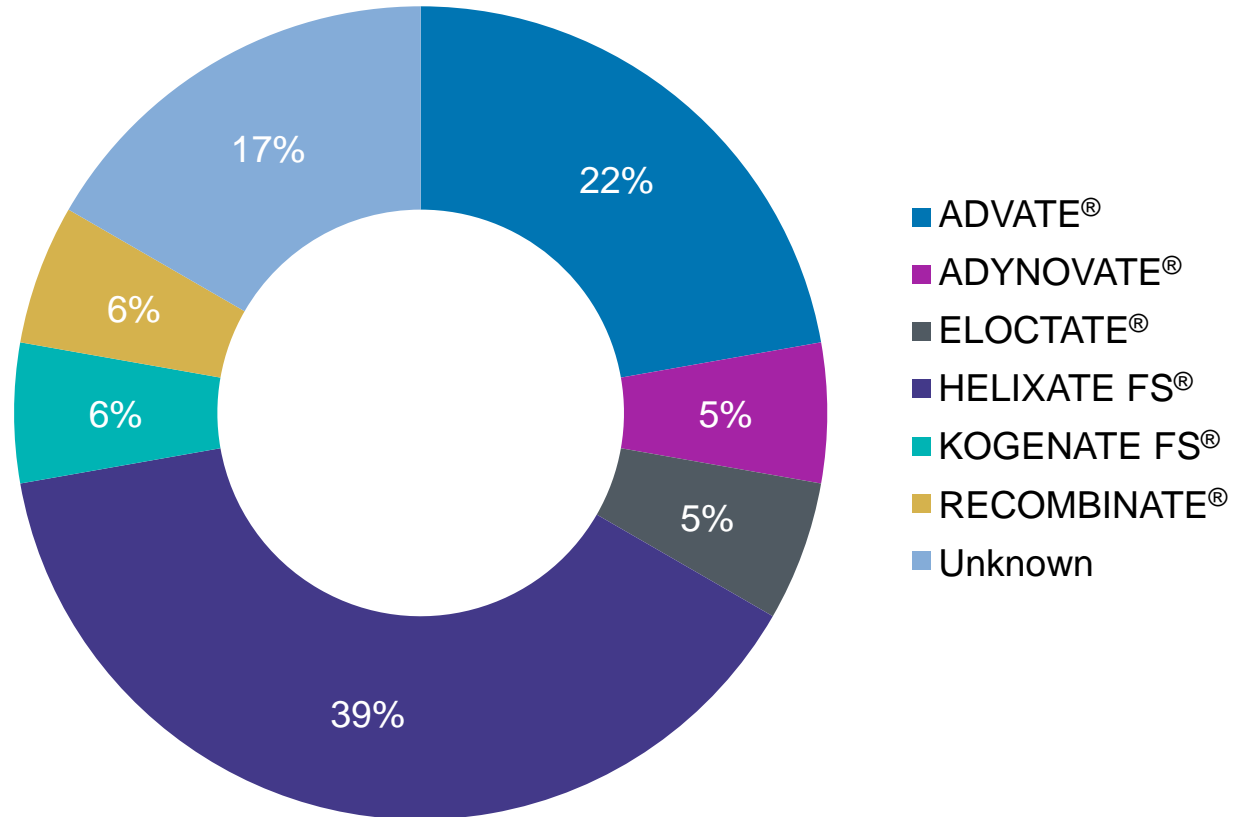


## Conversions to IDELVION®



Source: My Source weekly reporting as of October 25. Based on data from U.S. Hub Services Provider

## Conversions to AFSTYLA®



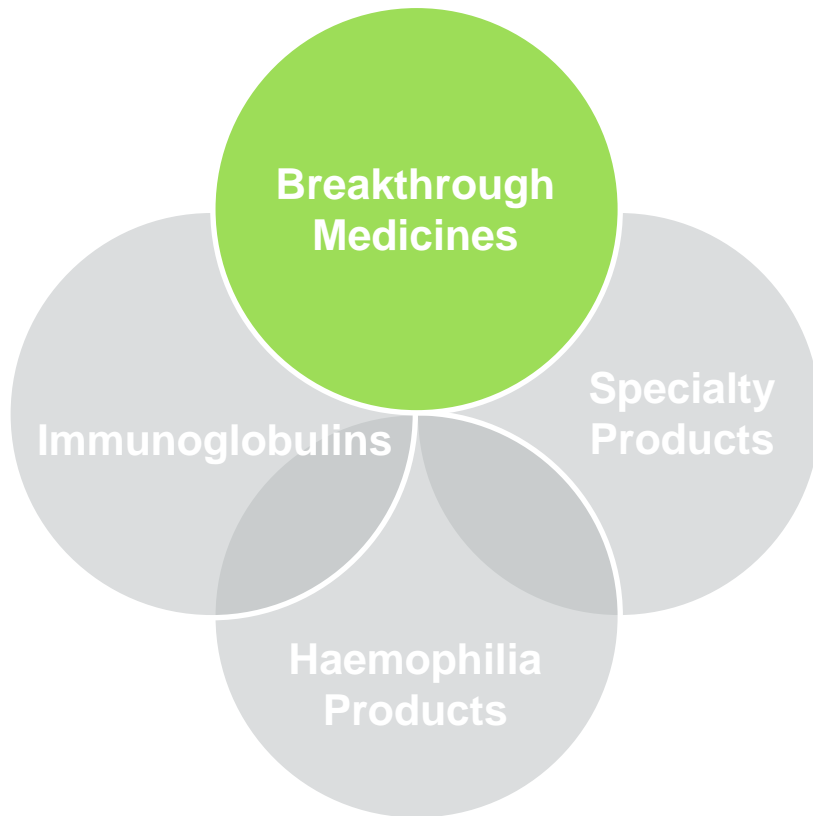
Source: My Source weekly reporting as of October 25. Based on data from U.S. Hub Services Provider



A dark teal world map is centered in the background of the slide.

# Breakthrough Medicines

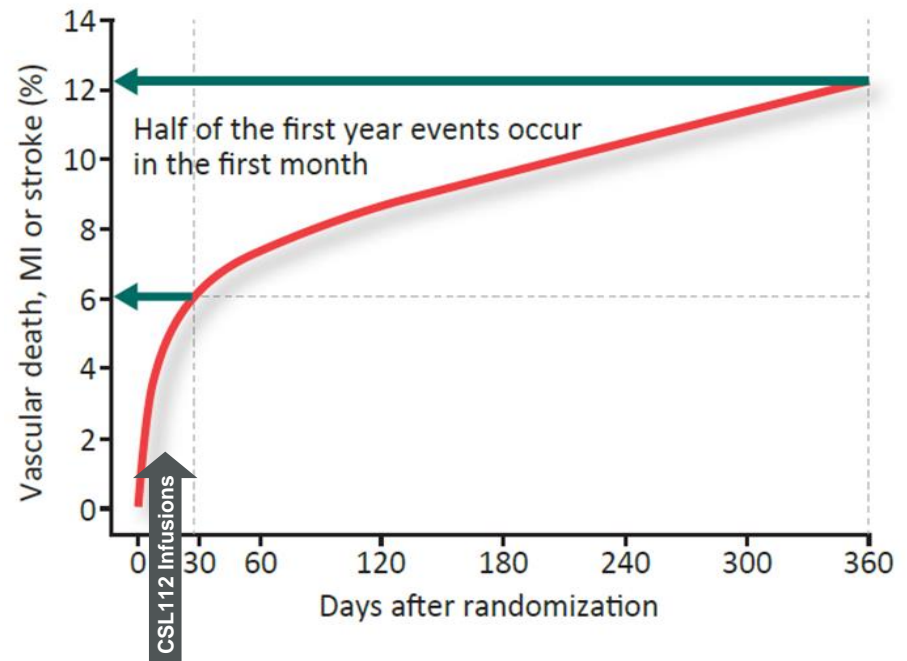




- Leveraging clinical and technical insight in developing novel protein-based therapies
  - Significant unmet need
  - Multiple indications
- Key Focus
  - CSL112 (Apo AI)
  - CSL324 (anti-G-CSFR mAb)
  - CSL346 (anti-VEGFB mAb)
  - CSL312 (anti-FXIIa mAb)

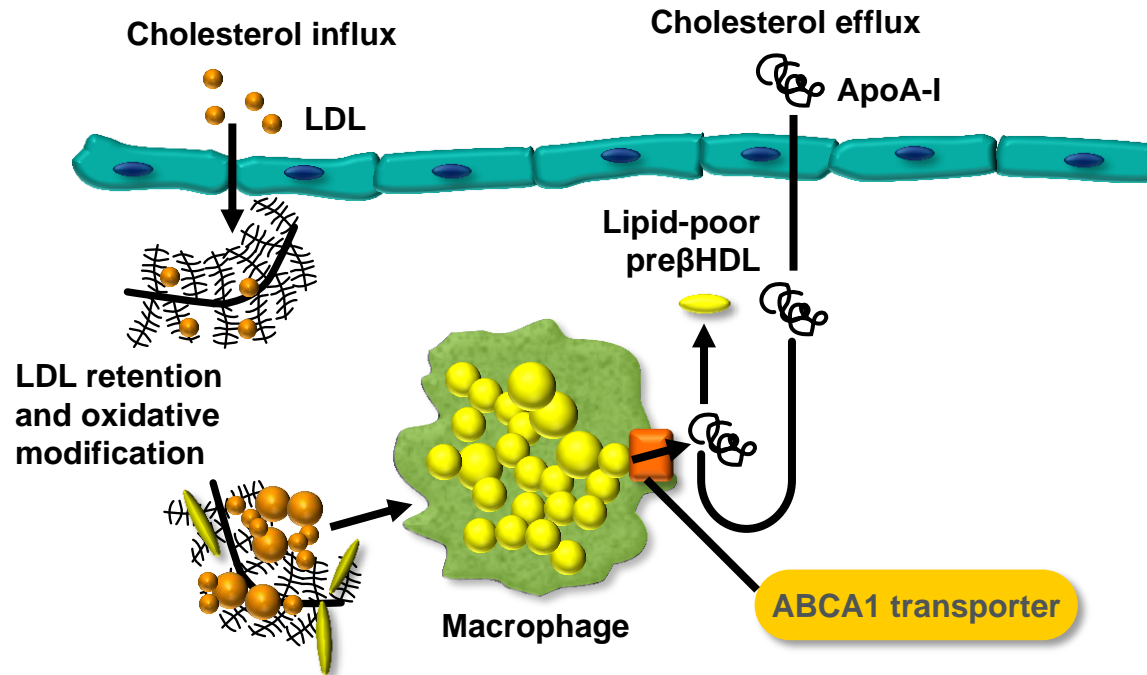
- In 2012, CVDs are the **leading cause of death globally (31%)**
  - ~7.4 million were due to coronary heart disease
  - ~6.7 million were due to stroke<sup>1</sup>
- In the European Union, coronary heart disease, is the **single most common cause of death**
  - 681,000 deaths each year

**ACS patients experience a high rate of recurrent cardiovascular events in the sub-acute period**



Sources: 1. <http://www.who.int/mediacentre/factsheets/fs317/en/> 2. Nichols et al, 2012  
 Figure adapted from the PLATO Trial. Wallentin et al. *N Engl J Med* 2009;361:1045-57

## Cholesterol Influx and Efflux Imbalance

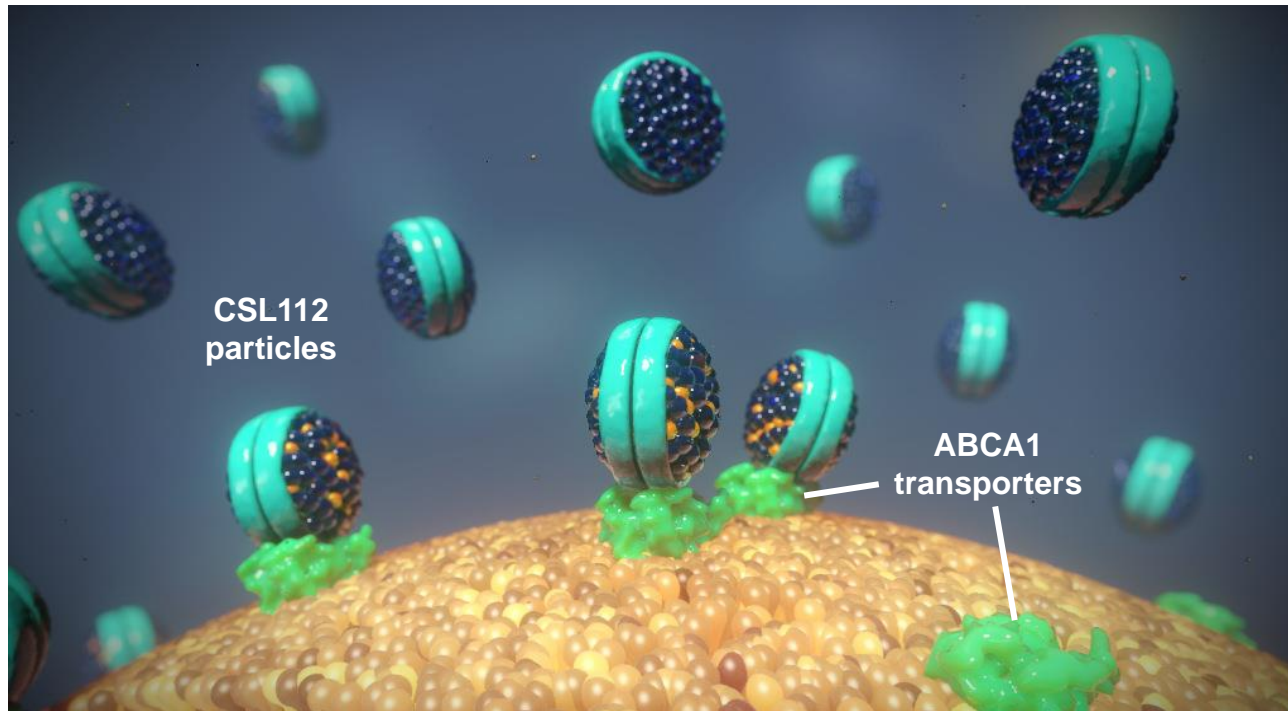


ABCA1=ATP-binding cassette transporter 1; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

**Sources:** 1. Curtiss LK, et al. *Arterioscler Thromb Vasc Biol.* 2006;26:12-19. 2. Linton MF, et al. The role of lipids and lipoproteins in atherosclerosis. In: De Groot LJ, et al, eds. *Endotext [Internet]*. Dartmouth, MA: MDText.com, Inc.; 2000. <http://www.ncbi.nlm.nih.gov/books/NBK343489>. Accessed May 24, 2016.

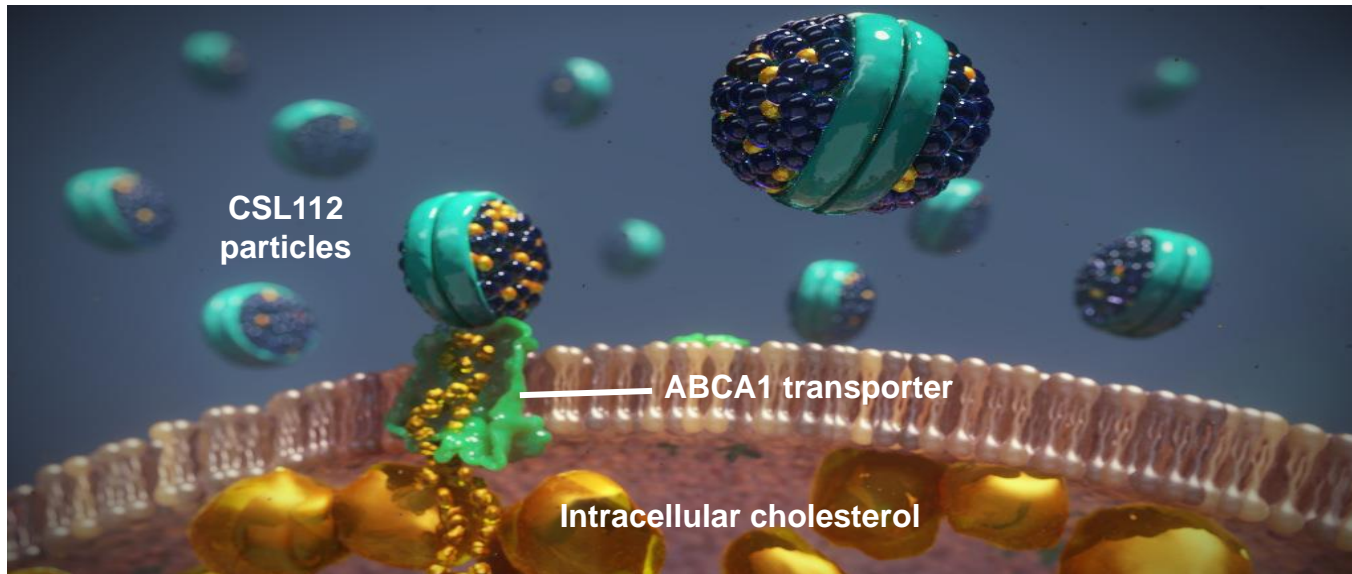
## Removal of Cholesterol From Unstable Plaque

Upon infusion, CSL112 immediately produces a significant increase in circulating lipid-poor apoA-I particles...



## Removal of Cholesterol From Unstable Plaque

...accompanied by a marked increase in ABCA1-dependent cholesterol efflux capacity



*CSL112 holds the potential to rapidly stabilise plaque and reduce the high rate of early recurrent cardiovascular events*

# AEGIS-I

The Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Human ApoA-I, After Acute Myocardial Infarction: The **A**poA-I **E**vent reducin**G** in **I**schemic **S**yndromes **I** Trial (AEGIS-I)

Infusion of aopA-I (CSL112) in addition to standard of care in subjects following ACS can safely and rapidly elevate cholesterol efflux capacity

Source: Gibson, M et al. Circulation. 2016;134 – In press



# AEGIS-I Primary Endpoint Met

	CSL112 2g N=415	CSL112 6g N=416	Placebo N=413
<b>Liver</b>			
Confirmed elevated markers of liver injury	4 (1.0%)	2 (0.5%)	0 (0.0%)
<b>Kidney</b>			
Confirmed elevated markers of kidney injury	0 (0.0%)	3 (0.7%)	1 (0.2%)

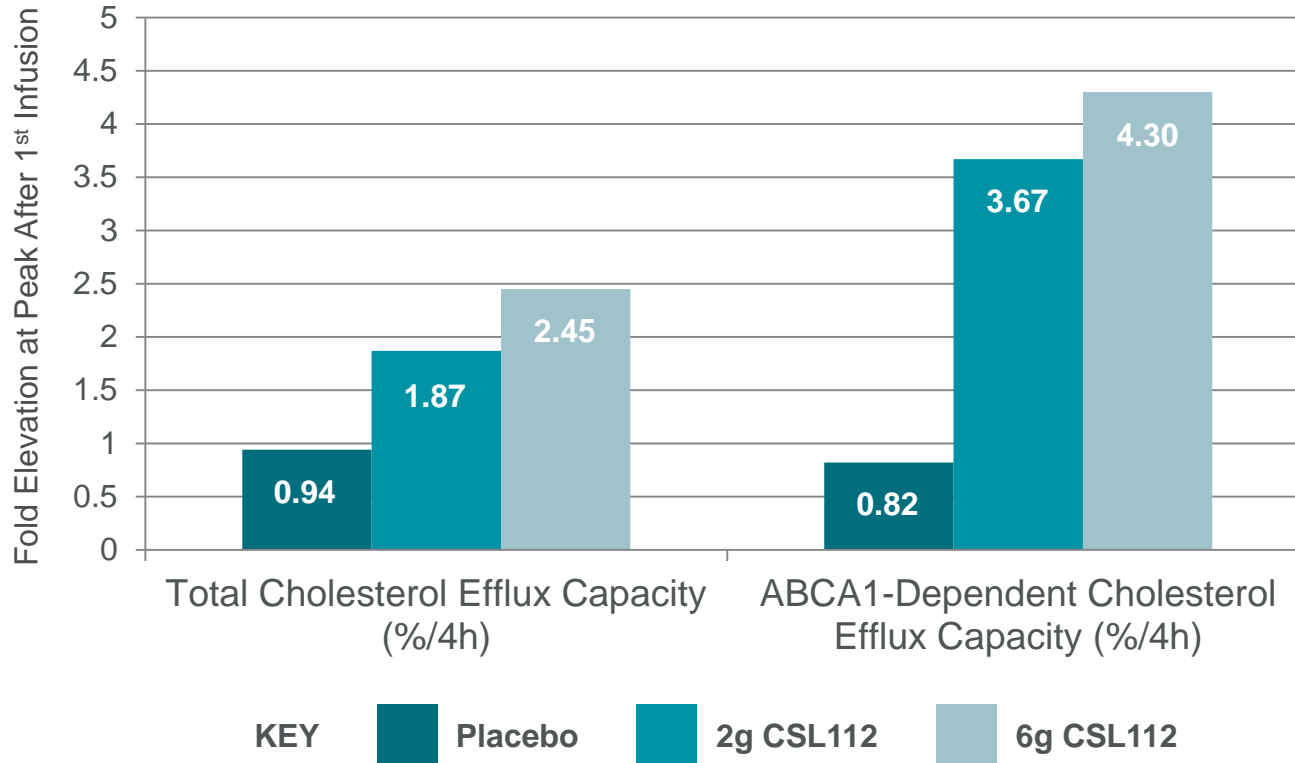
- Percentages are based on the number of subjects with data
- A hepatic endpoint of interest is defined as any subject recording one of the two following results: ALT > 3x ULN, Total bilirubin > 2x ULN, confirmed by a consecutive repeat test after at least 24 hours but within 1 week of the original test
- A renal event is defined as a serum creatinine increase of  $\geq 1.5X$  the baseline value, confirmed by a repeat test after at least 24 hours but within 1 week, or the need for renal replacement therapy

Source: Gibson, M et al. Circulation. 2016;134 – In press



# Proof of Mechanism Demonstrated

- Cholesterol efflux capacity increased after Infusion of CSL112 in AMI patients



AMI- acute myocardial infarction  
Fold elevation at peak compared with baseline  
All analyses were performed using patients with available data.

## AEGIS-I Exploratory Endpoint (MACE)

- Major Cardiovascular Events (MACE) collected to inform Phase III
  - Comprised cardiovascular death, non-fatal myocardial infarction, stroke, hospitalisation for unstable angina
- Low event rate was expected in this study population
  - Study not powered to detect an efficacy signal
- Data available in *Circulation*, 2016\*

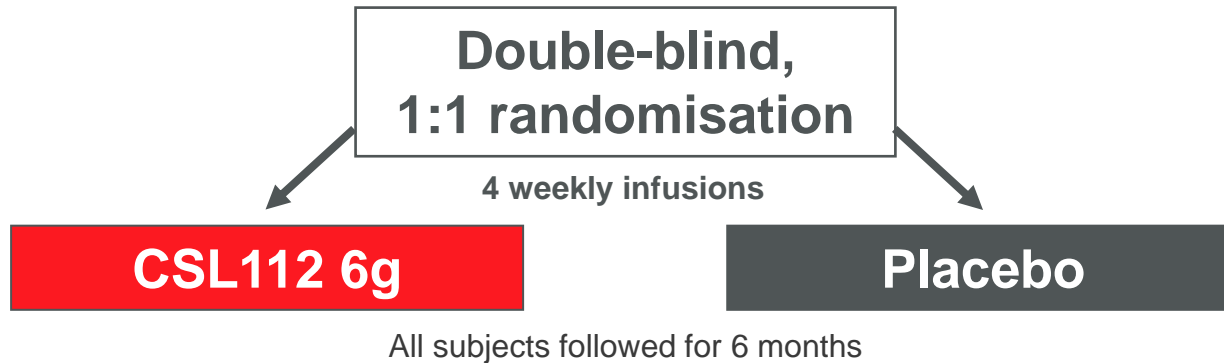
\*American Heart Association. Heart Disease and Stroke Statistics—2016 Update. *Circulation*. 2015;132:000-000. DOI: 10.1161/CIR.0000000000000350

## **AEGIS-I Summary**

- AEGIS-I study positive
- Four weekly infusions of CSL112 following MI was feasible and did not have any safety concerns
- CSL112 rapidly elevates cholesterol efflux in a dose dependent fashion in the acute MI setting
- Based on the current assessment of the data, the 6g dose is recommended for further study in Phase III

## Proposed Phase III Study Design

**A Phase III, Multicenter, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Investigate the Efficacy and Safety of CSL112 in Subjects with Acute Coronary Syndrome**



- Primary endpoint: Time-to-first occurrence of any component of the composite MACE, ie, CV death, MI, or stroke, from the time of randomisation through 90 days
- Enriched Study Population: Multi-vessel disease +  $\geq 65$  years of age or previous MI or peripheral artery disease or diabetes mellitus

## **AEGIS Planning for Phase III**

- Regulatory agency consultations have commenced
- Results of safety study in moderate renal impaired ACS patients anticipated 2H 2017
- Study planned to start Dec 2017 / early 2018, pending outcome of above activities
- Study likely to run over a 3-4 year period



# Breakthrough Medicines

Commercial Opportunities and Activities



## **Unmet Medical Need:**

- Approximately 20% of patients that survive a heart attack will experience a recurrent CV event within one year
- About half of these will occur in the first month post index event

## **Potential Clinical Benefit:**

Significant reduction in early, recurrent CV events (CV death, Recurrent MI, stroke) in high-risk ACS patients

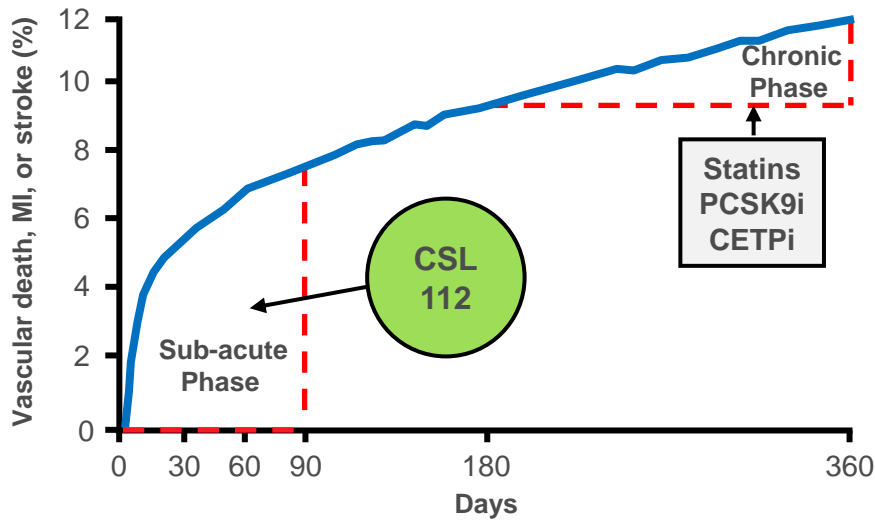
## **MOA:**

Rapidly removes cholesterol from atherosclerotic lesions/plaque via significantly enhanced cholesterol efflux

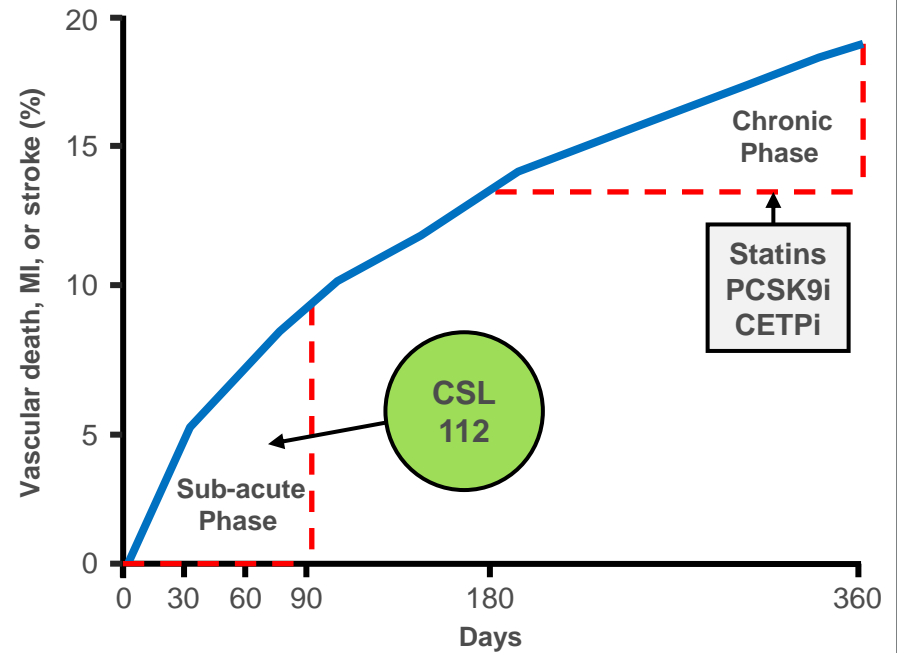
Source: WHO 2013 Update; CDC Heart Disease Fact Sheet August 2014

## Uncontested sub-acute market space

### PLATO STUDY<sup>1</sup>



### SWEDISH REGISTRY STUDY<sup>2</sup>



Sources: 1. Figure adapted from Wallentin L, et al. *N Engl J Med.* 2009;361:1045-1057.

2. Figure adapted from Jernberg T, et al. *Eur Heart J.* 2015;36:1163-1170.



### **Third-party Payers**

Payer perspective on key Phase 3 design variables

### **Access and Reimbursement**

HEOR endpoints / HTA / Value demonstration

### **Product Labeling**

Claims prioritisation and treatment guidelines placement

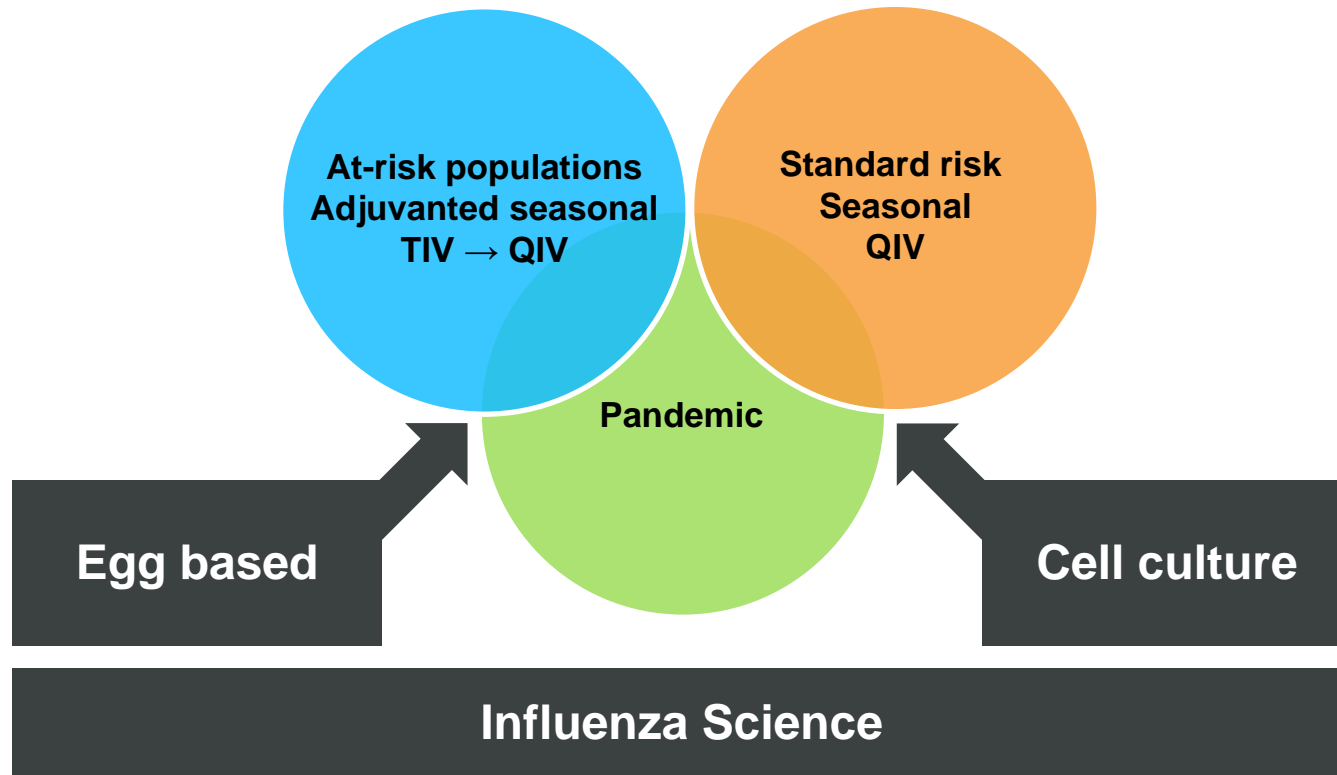
A dark teal world map is centered in the background of the slide.

# Seqirus R&D



Just getting started

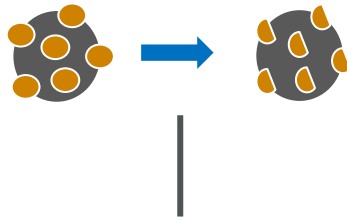
# Seqirus Influenza Vaccine Platform



*TIV = trivalent influenza vaccine (3 strains)*  
*QIV = quadrivalent influenza vaccine (4 strains)*

# Influenza Changes Constantly

## Antigenic drift



Small mutations

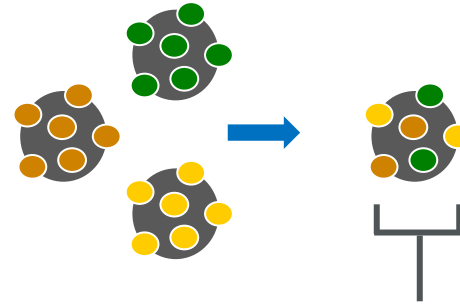


## Epidemic

Yearly seasonal vaccine  
3-4 circulating strains  
(2 "A", 1 or 2 "B" strains)

May vary season to season, SH vs NH

## Antigenic shift



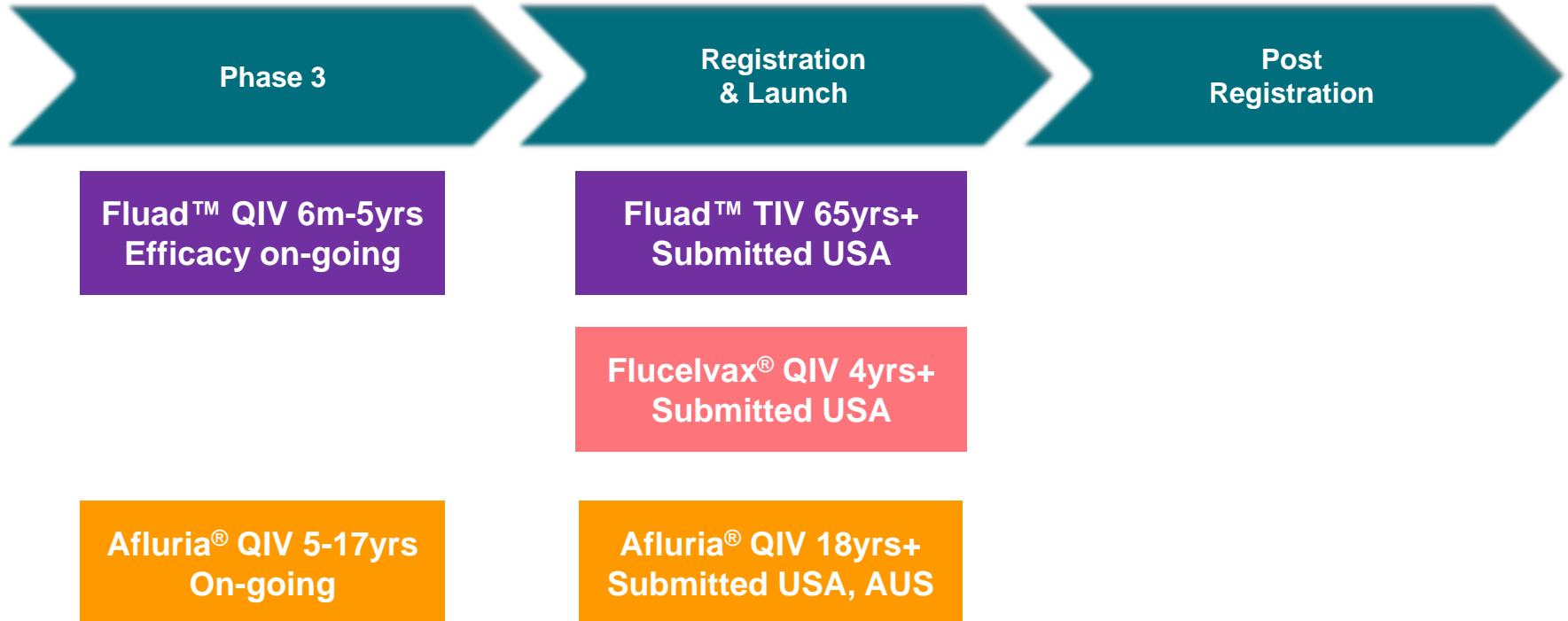
New strain



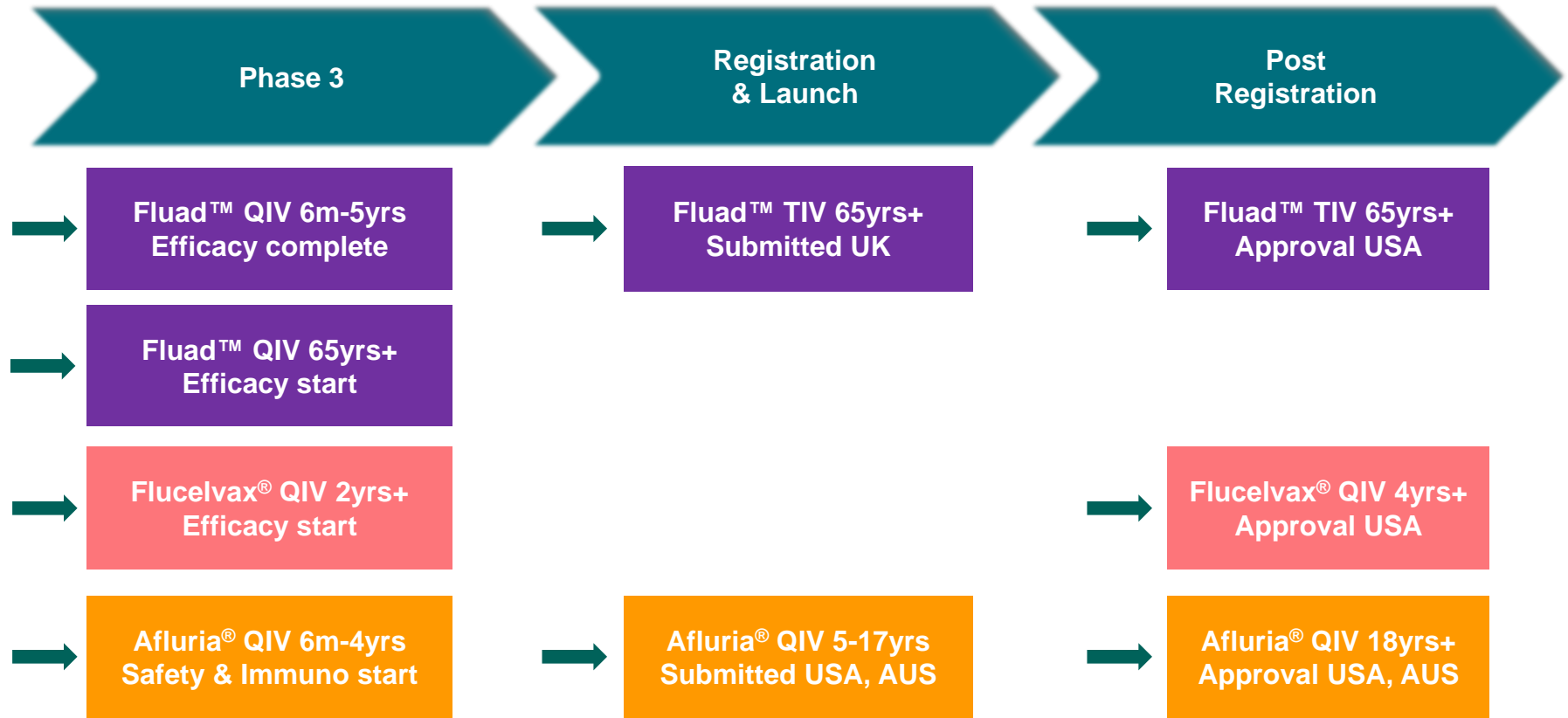
## Pandemic

Occasional vaccine  
Single strain








# Programs at Time of Acquisition



# Delivery of all Milestones during Integration



# Differentiated Product Portfolio - Current and Future Indications

Brand	Age Indication Today	Planned Future Age Indication	Target Offer
 FLUAD™ influenza vaccine, adjuvanted	6 months to 2 years 65 years +	6 months to 5 years 65 years +	QIV
 FLUCELVAX. Influenza Vaccine	4 years +	2 years +	QIV
 afluria. INFLUENZA VACCINE	18 years +	6 months +	QIV
 AGRIPPAL® INFLUENZA VACCINE (SURFACE ANTIGEN, INACTIVATED)	6 months +		TIV
 Influenza Virus Vaccine Fluvirin®	4 years +		TIV
 AFLUNOV® FOCLIVIA		Pandemic preparedness	
 Rapivab™ peramivir injection	18 years +	5 years +	i.v.



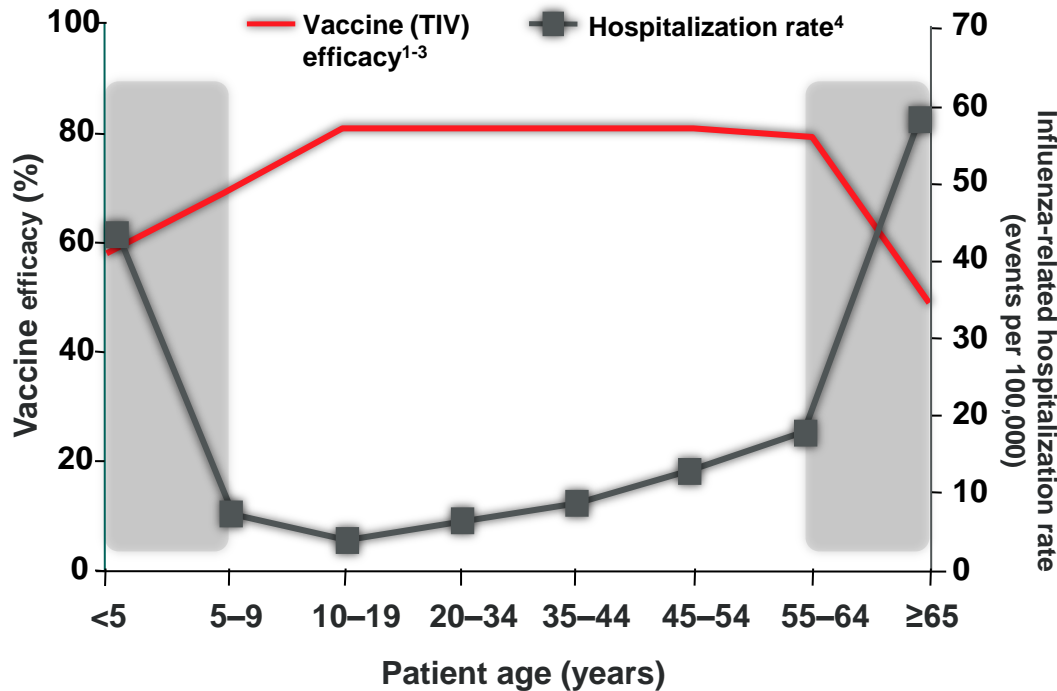
## **FLUAD™**

**Differentiated (MF-59 adjuvanted) influenza vaccine for vulnerable populations**



# Why FLUAD™?

## Age-related hospitalisations and TIV efficacy rates



- MF59 adjuvant strengthens and potentially broadens the immune response
- >100 million doses of MF59 adjuvanted vaccines distributed – excellent safety
- ***Developing QIV for at risk paediatric and elderly age groups***

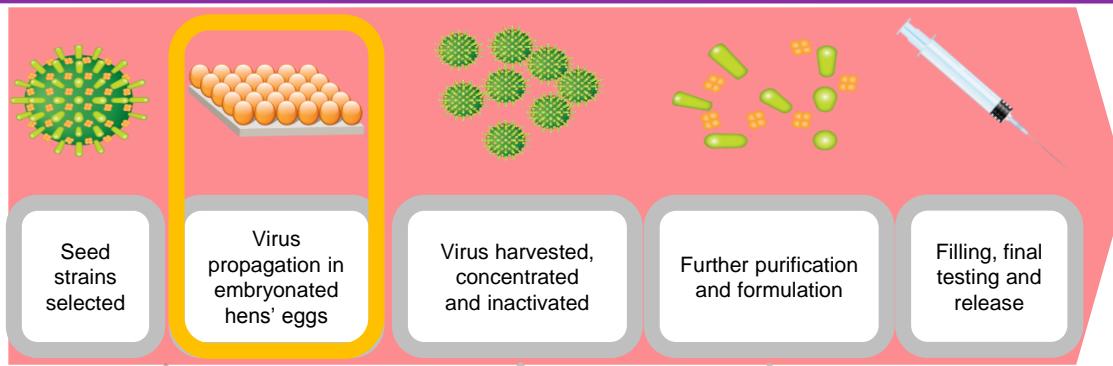
1. Nichol KL, et al. *Vaccine*. 2003;21:1769-1775; 2. Goodwin K, et al. *Vaccine*. 2006;24:1159-1169; 3. Grubeck-Loebenstien B, et al. *Nat Med*. 1998;4:870; 4. Glezen WP, et al. *Am Rev Respir Dis*. 1987;136:550-555.



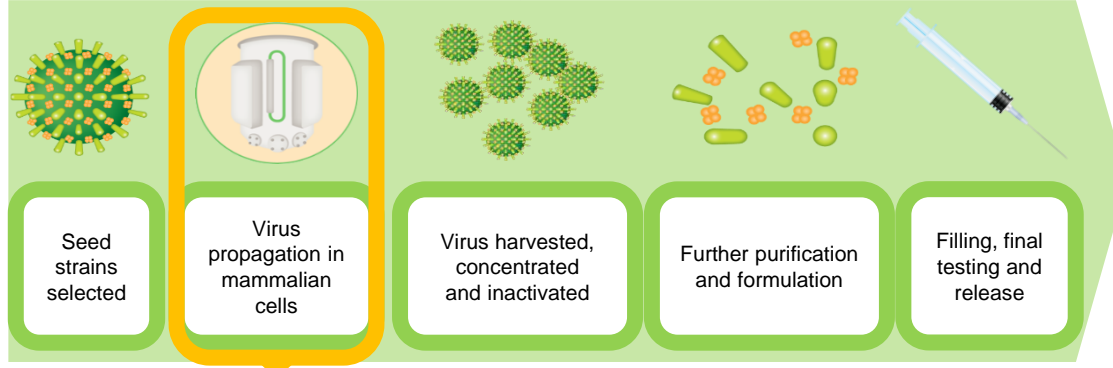
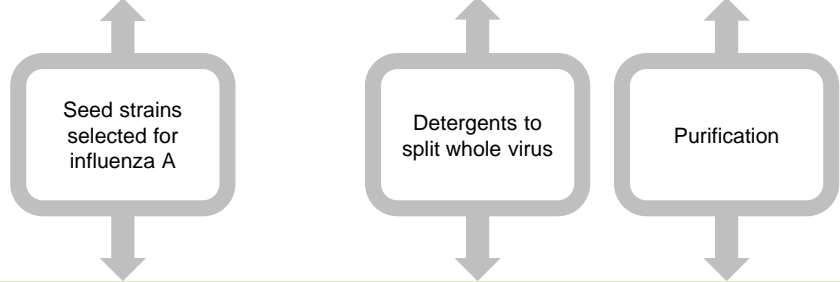
## **FLUCELVAX®**

**Developing a cell culture-derived QIV for the  
general population in global markets**

# Cell-culture offers potential benefits over egg-derived influenza vaccine



- EGG-DERIVED**
- Process well established and understood
  - Long track record of safety and efficacy
  - Efficient



- CELL CULTURE**
- Removes reliance on eggs
  - Potential to increase capacity
    - substantial process improvements
    - greater scalability
  - Improvements in seed selection
  - Enhanced responsiveness, ie in a pandemic

Sterile closed-system bioreactors, antibiotic-free vaccine production

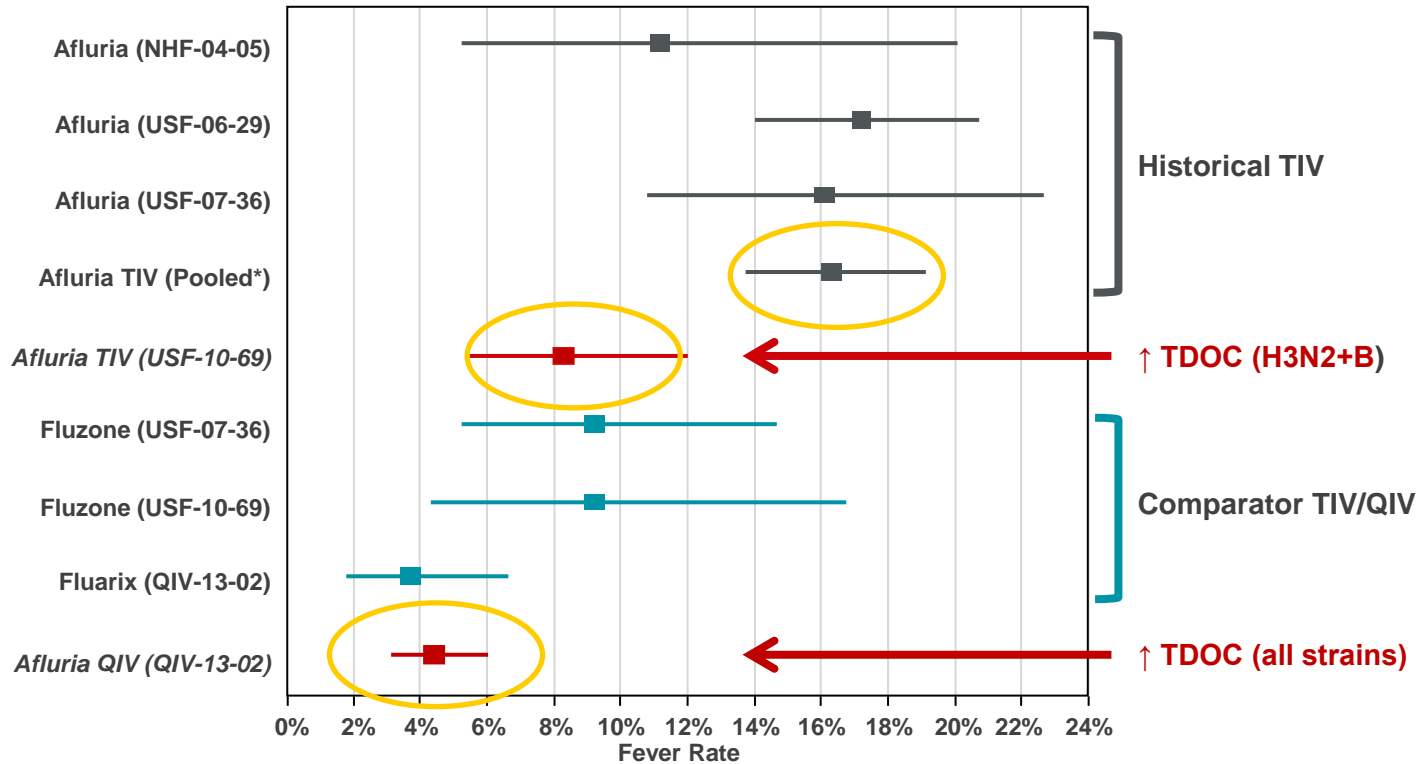


## **AFLURIA®**

**Developing an egg-derived QIV for the  
general population in global markets**

# Reduced fever rate with Afluria® QIV in children

Comparison with Historical Fever Rates  
5 - 8 years age group

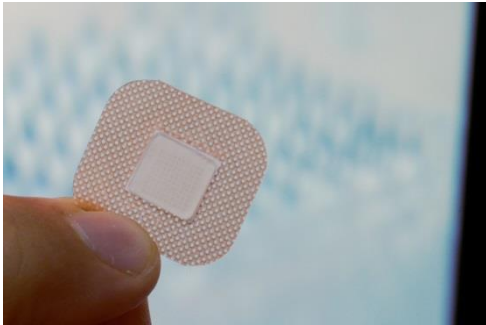


\* Pooled estimate from studies NHF-04-05, USF-10-69, USF-07-36

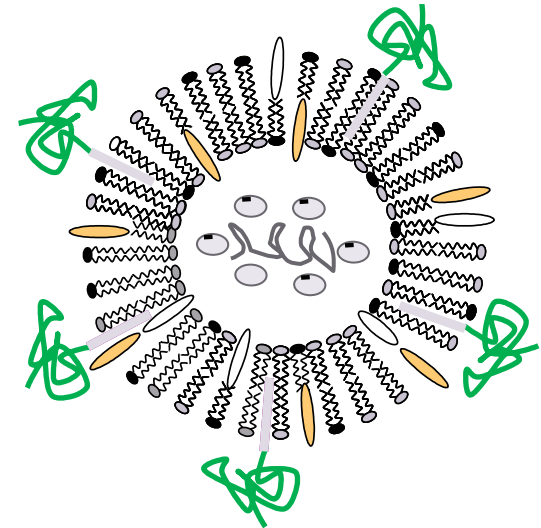
- In-depth scientific investigations → manufacturing changes
- Comprehensive clinical program → fever rates now equivalent to comparable marketed QIV

# Longer Term Directions for Influenza Vaccine Innovation

## Alternate routes of delivery

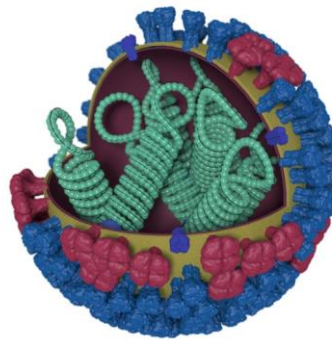


## Novel sources of antigens

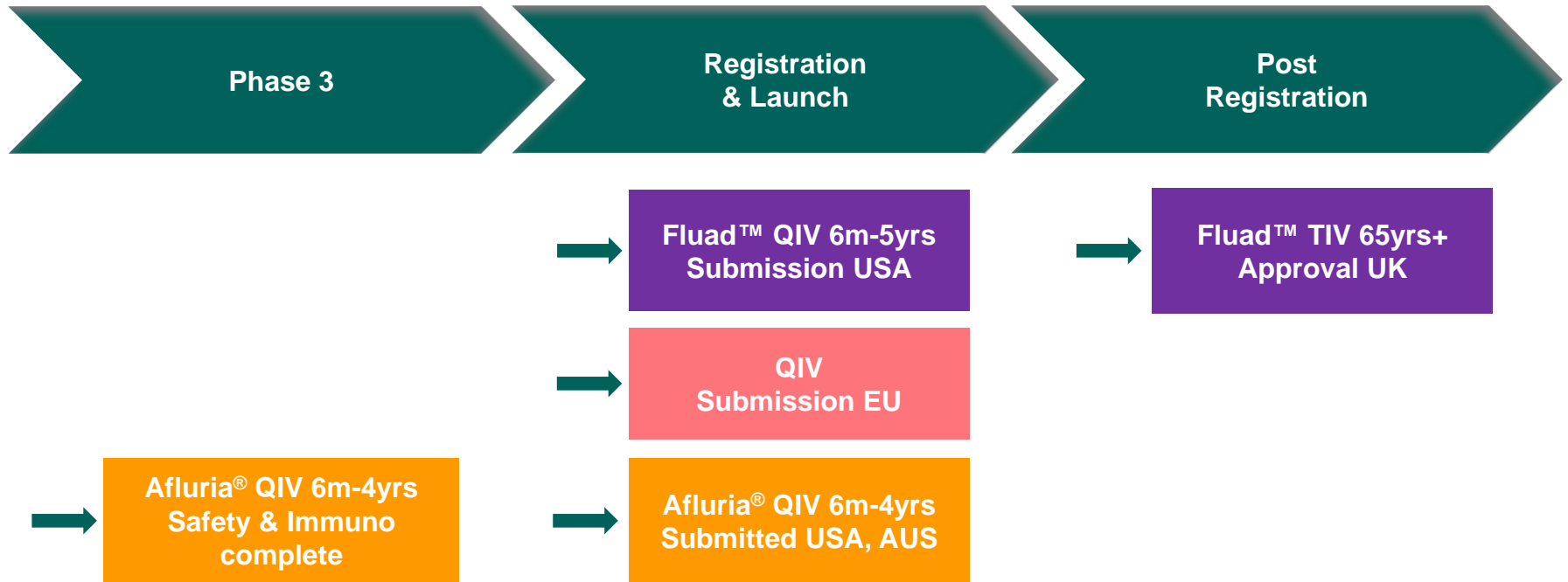


## Universal vaccine

AN INFLUENZA VIRUS



# Milestones Expected for 2017



A dark teal world map is centered in the background of the slide.

# Summary





	Research	Pre-clinical	Phase I	Phase II	Phase III	Registration	Commercial/ Phase IV
Life Cycle Management#							Immunoglobulins Haemophilia Specialty Products Influenza Vaccine
Market Development	PCC New Indications	C1-INH New Indications Fibrinogen New Formulations Haptoglobin/Hemopexin			HIZENTRA® CIDP PRIVIGEN® Japan Hizentra® IIM CSL842 C1-INH Transplant	PRIVIGEN® CIDP US KCENTRA® Japan CSL830 C1-INH subcut	VONCENTO® VWD EU RESPREEZA® EU/US
New Product Development	Next Gen Ig Formulations Rec Coagulation Factors P. gingivalis/POD OH-CRC Discovery Projects	CSL626 D'D3 LA rVIII CSL334 IL-13R* ASLAN CSL346 VEGFB	CSL689 rVIIa-FP Congen Def CSL640 rIX-FP subct CSL312 Anti-FXIIa CSL324 G-CSFR	CSL689 rVIIa-FP Inhibitors CAM3001 GM-CSFR – AZ* CSL362 IL-3R* AML Janssen CSL112 apo-AI		AFSTYLA® Europe AFLURIA® QIV 5-17 US, AUS	IDELVION® US, EU, Japan AFSTYLA® US AFLURIA® QIV 18+ US & AUS FLUAD® TIV 65+ US FLUCELVAX® QIV 4+ US

Core Capabilities:

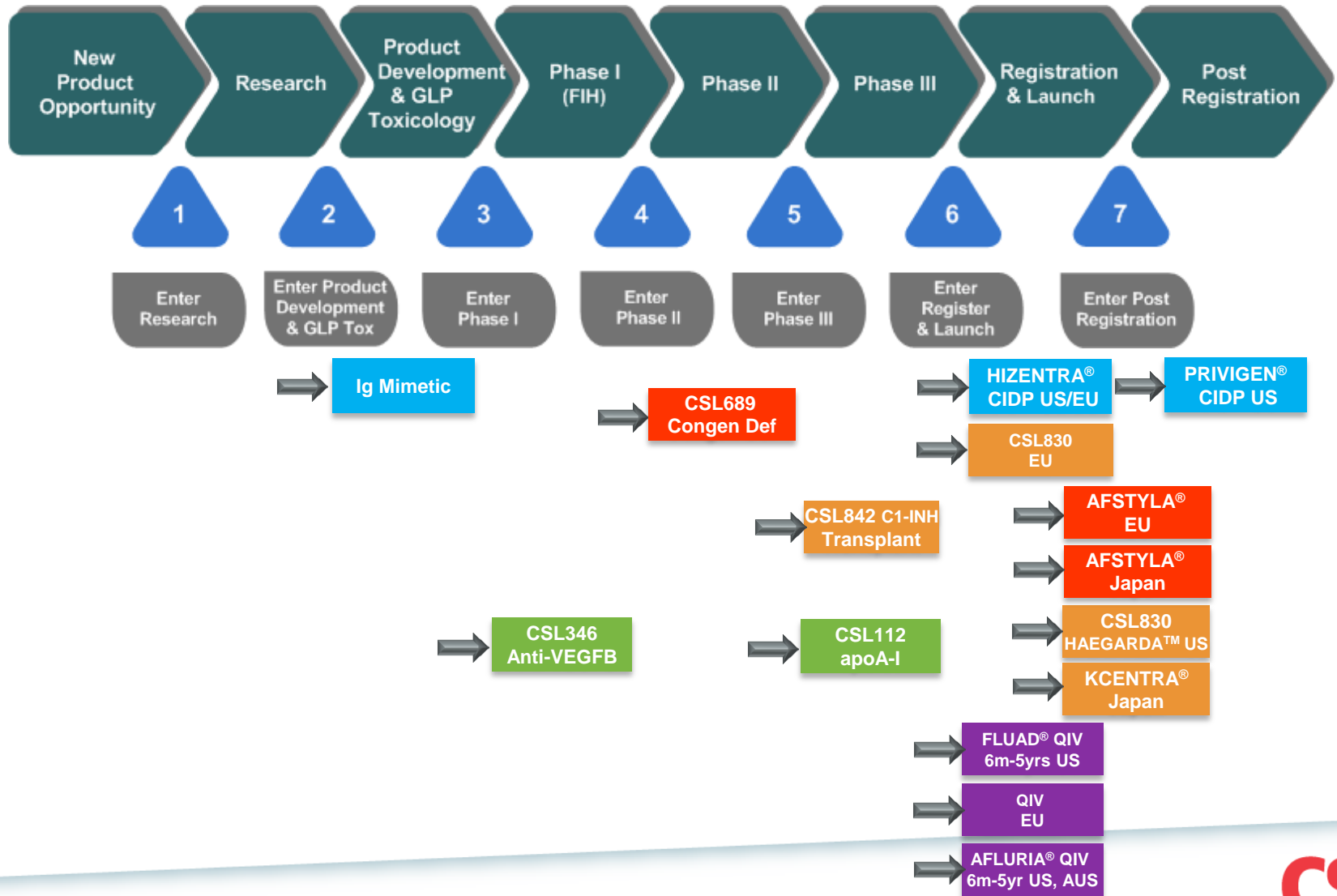
Immunoglobulins
Haemophilia
Specialty Products
Breakthrough Medicines
Vaccines & IP

\*Partnered Projects

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



# Expected Progress in next 12 Months



## Significant Target Launch Dates

2016	2017	2018	2019	2020	2021
PRIVIGEN® IsoLo	PRIVIGEN® CIDP US	HIZENTRA® CIDP US/EU	HIZENTRA® CIDP Japan PRIVIGEN® Japan PID/SID		
IDELVION® US IDELVION® EU IDELVION® Japan AFSTYLA® US	AFSTYLA® EU/Japan				CSL689 rVIIa-FP Prophylaxis CSL689 rVIIa-FP On Demand
	CSL830 HAEGARDA™ US KCENTRA® Japan	CSL830 EU			
AFLURIA® QIV 18+ US & AUS FLUAD® TIV 65+ US FLUCELVAX® QIV 4+ US	AFLURIA® QIV 6-17yr US	AFLURIA® QIV 6m-5yr US AFLURIA® QIV 6-17yr AUS FLUAD® QIV 6m-5yrs US	AFLURIA® QIV 6m-5yr AUS QIV EU		

Core Capabilities:

Immunoglobulins

Haemophilia

Specialty Products

Vaccines & IP

\* Calendar Years

## Immunoglobulins

- PRIVIGEN® IsoLo® approved in major markets
- HIZENTRA® CIDP Phase III study (PATH) completed
- PATH supports efficacy of PRIVIGEN® in CIDP

## Specialty Products

- C1-INH subcut (CSL830) Phase III (COMPACT) completed
- COMPACT demonstrates efficacy of CSL830 in HAE prophylaxis
- CSL830 BLA accepted for review by US FDA

## Haemophilia

- IDELVION® registered in major markets
- IDELVION® is a new standard of care for haemophilia B
- AFSTYLA® registered in US; positive opinion in EU; submitted in JPN
- AFSTYLA® unique single chain design results in longer acting product

## Breakthrough Medicines

- CSL112 (Apo A-1) Phase IIb study (AEGIS-I) completed
- CSL112 safely and rapidly elevates cholesterol efflux capacity
- Anti-GCSFR and anti-FXIIa mAbs Phase I studies commenced

## Licensing & Vaccines

- AFLURIA® QIV registered in US & AUS in 18+ yrs
- FLUAD® TIV registered in US in 65+ yrs
- FLUCELVAX® QIV registered in US in 4+ yrs



# Q&A

## R&D Briefing



Just getting started

## **Presentation Playback**

A webcast of the presentation can be accessed in the investors section of the CSL website.  
Contact: [maria.pikos@csl.com.au](mailto:maria.pikos@csl.com.au)

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