



# R&D Investor Briefing

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December 5, 2017

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# Introduction and Highlights

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Professor Andrew Cuthbertson AO  
R&D Director and Chief Scientist

# Agenda

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

– *Break* –

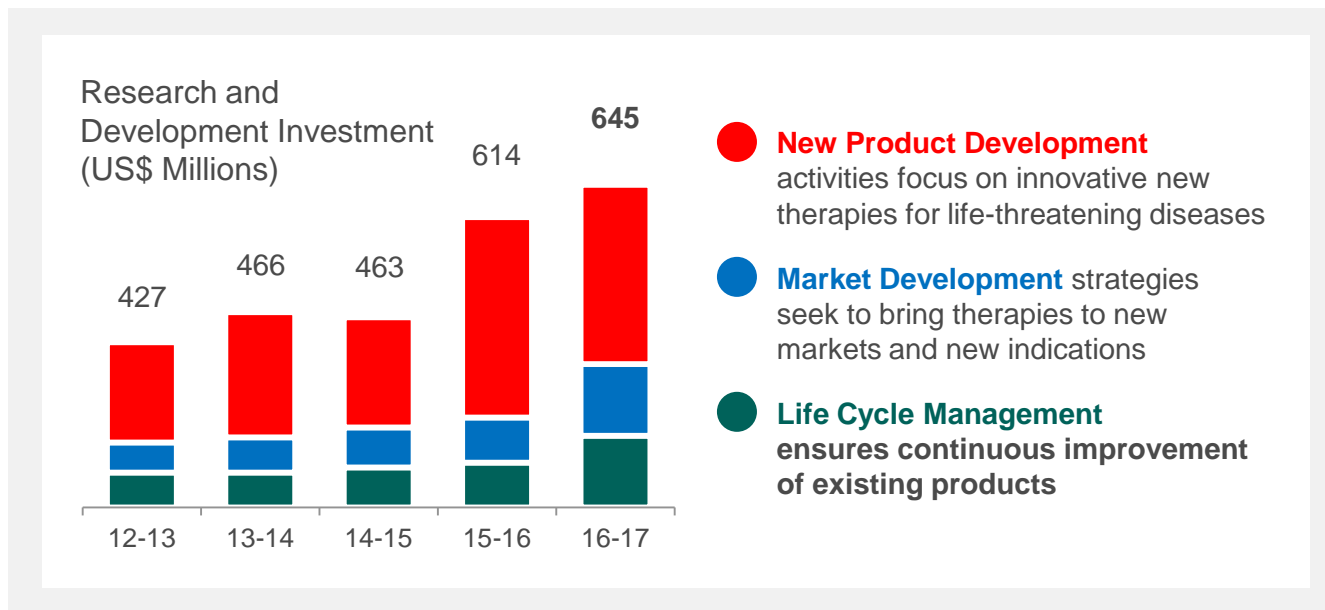
- Transplant and Breakthrough Medicines (CSL112)
  - Clinical Development
  - Commercial Opportunities
- Summary
- Q&A

Mark Dehring  
Andrew Cuthbertson  
Andrew Nash  
Charmaine Gittleson

Bill Mezzanotte  
Bill Campbell

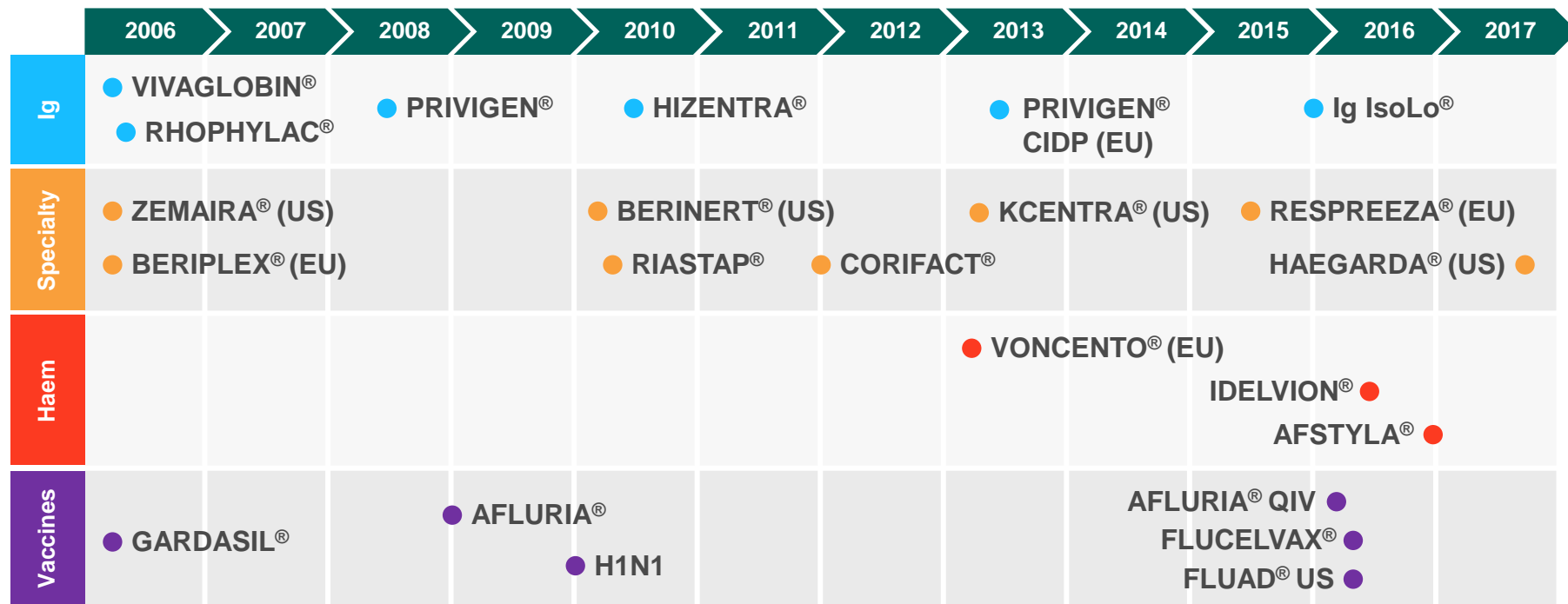
Bill Mezzanotte  
Bill Campbell  
Andrew Cuthbertson

# Commitment to Research and Development



- R&D investment ~10-11% global revenue

# Key Past Launches from R&D Portfolio



# Leveraging Global Capabilities



# R&D Portfolio – December 2016

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

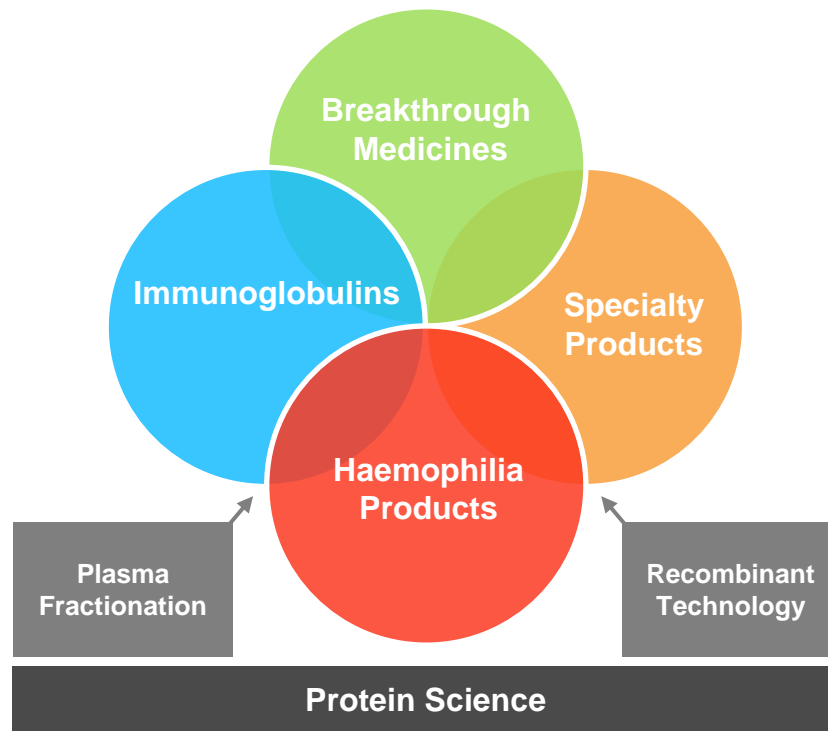
Core Capabilities: **Immunoglobulins** | **Haemophilia** | **Specialty Products** | **Breakthrough Medicines** | **Vaccines & IP**

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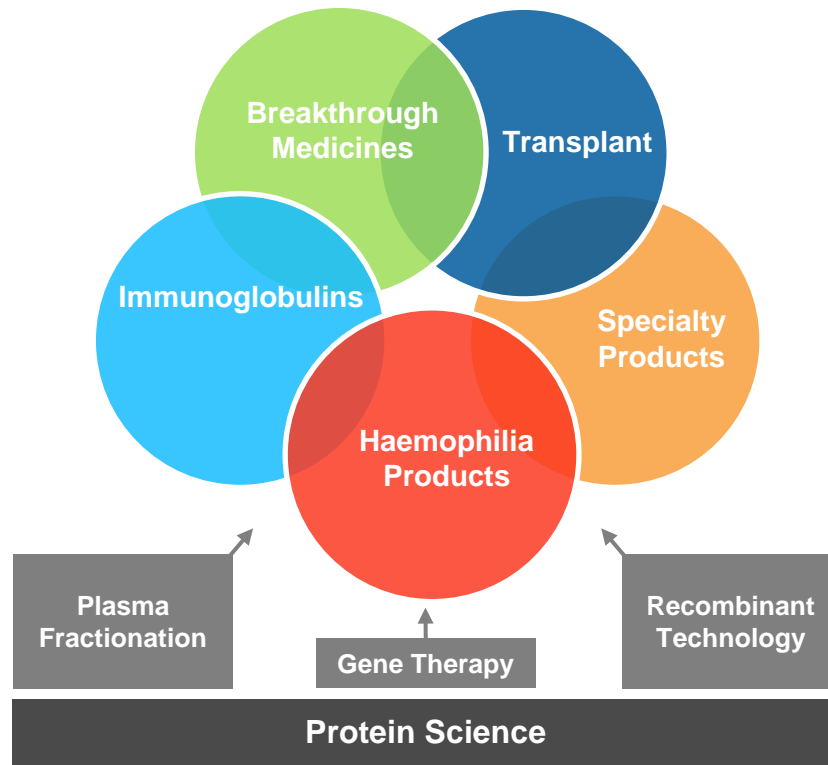
\*Partnered Projects  
<sup>#</sup>LCM includes direct post marketing commitments as well as pathogen safety, capacity expansions, yield improvements, new packages and sizes for all registered products



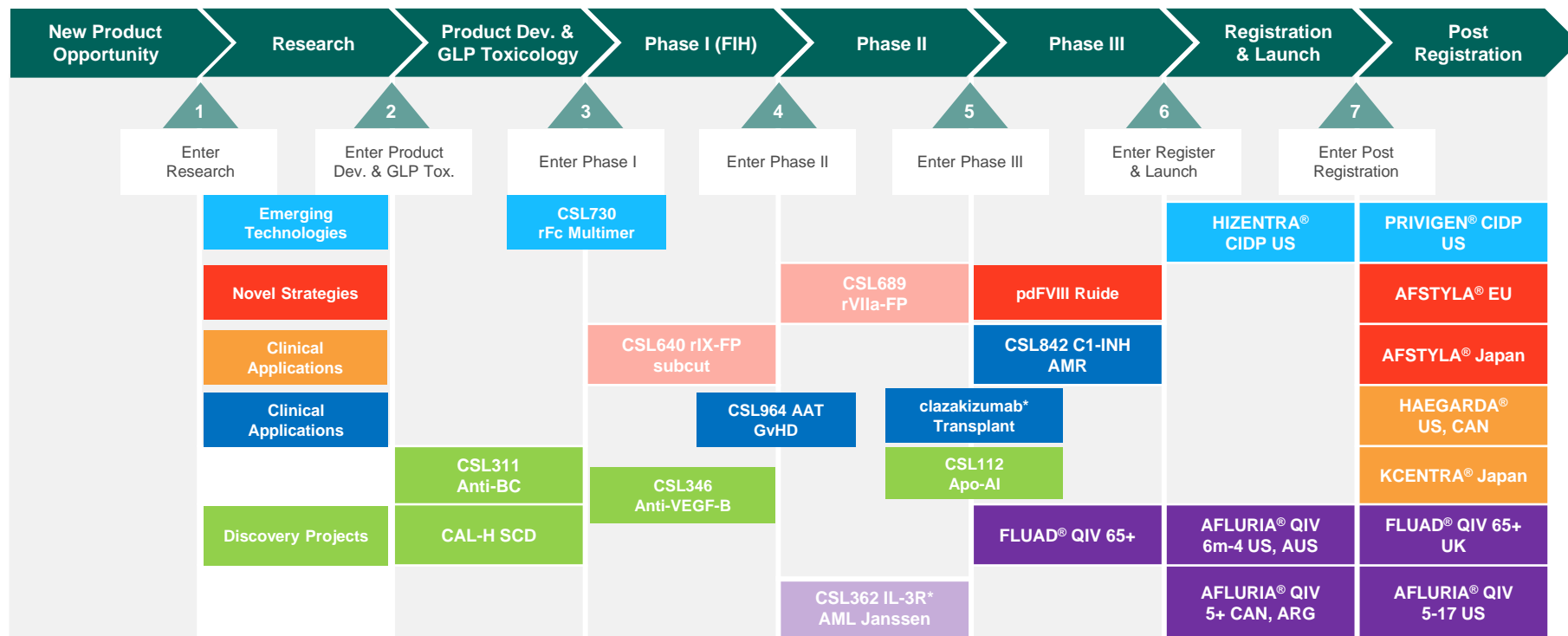
# CSL Behring Protein Therapeutics Platform



# Evolving Therapeutics Platform



# Progress Through Stage Gates in 2017



Core Capabilities: [Immunoglobulins](#) | [Haemophilia](#) | [Specialty Products](#) | [Breakthrough Medicines](#) | [Vaccines & IP](#) | [Transplant](#)

\*Partnered Projects

# R&D Portfolio – December 2017

	RESEARCH	PRE-CLINICAL	PHASE I	PHASE II	PHASE III	REGISTRATION	COMMERCIAL / PHASE IV
Life Cycle Management / Market Development	Clinical Applications	C1-INH New Indications			PRIVIGEN® Japan	HIZENTRA® CIDP	PRIVIGEN® CIDP US
		Fibrinogen New Formulations			HIZENTRA® IIM		KCENTRA® Japan
		Haptoglobin/Hemopexin		CSL964 AAT GvHD		HAEGARDA® EU	HAEGARDA® US
		CSL640 rIX-FP subct			PRIVIGEN® CIDP Japan	AFLURIA® QIV 5-17 AUS	FLUAD® TIV 65+ US, UK
					CSL842 C1-INH AMR		FLUCELAX® QIV 4+ US
							AFLURIA® QIV 5-17 US
New Product Development	Emerging Technologies	CSL730 rFc Multimer			clazakizumab* Transplant		IDELVION®
	Novel Strategies	CSL626 D'D3 LA rVIII	CSL312 Anti-FXIIa	Mavri GM-CSFR-AZ*	pdFVIII Ruide		AFSTYLA®
	Discovery Projects	CSL334 IL-13R* ASLAN	CSL324 Anti-G-CSFR				
	Clinical Applications	CSL311 Anti-BC	CSL346 Anti-VEGF-B		CSL112 apo-AI		
		P. gingivalis/POD* OH-CRC					

Core Capabilities: [Immunoglobulins](#) | [Haemophilia](#) | [Specialty Products](#) | [Breakthrough Medicines](#) | [Vaccines & IP](#) | [Transplant](#)

# Research Portfolio and Technologies

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Dr Andrew Nash  
Senior Vice President, Research

# Research Organisation & Portfolio

- Coordinated global project portfolio



- Hub (Bio21, Parkville) & spoke model
- Bio21 expansion to be completed Feb 2018
- Research capabilities: plasma & recombinant proteins, gene and cell-based therapies



Bio21 expansion

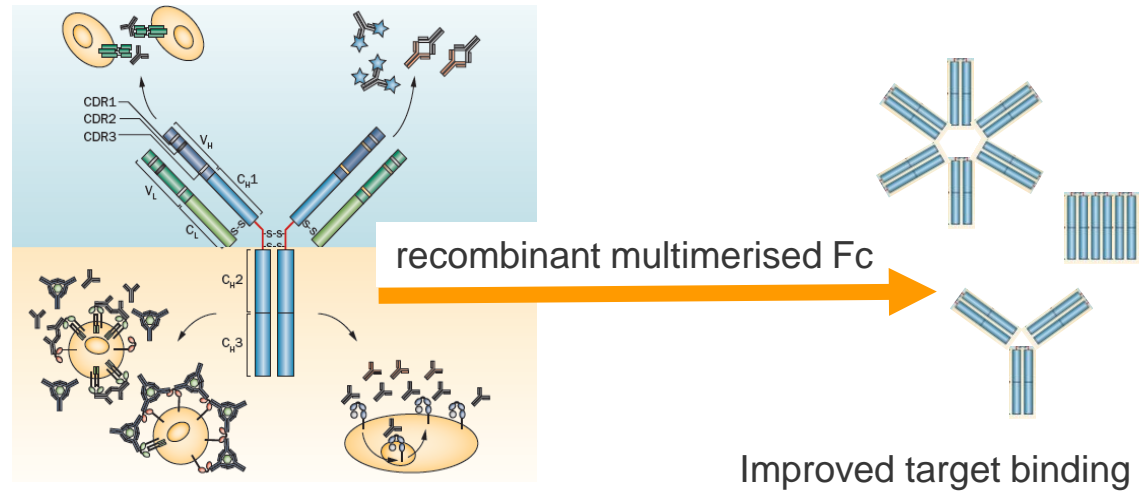
# Recombinant Fc Multimer – CSL730

## Fab region

- Immune deficiencies

## Fc region

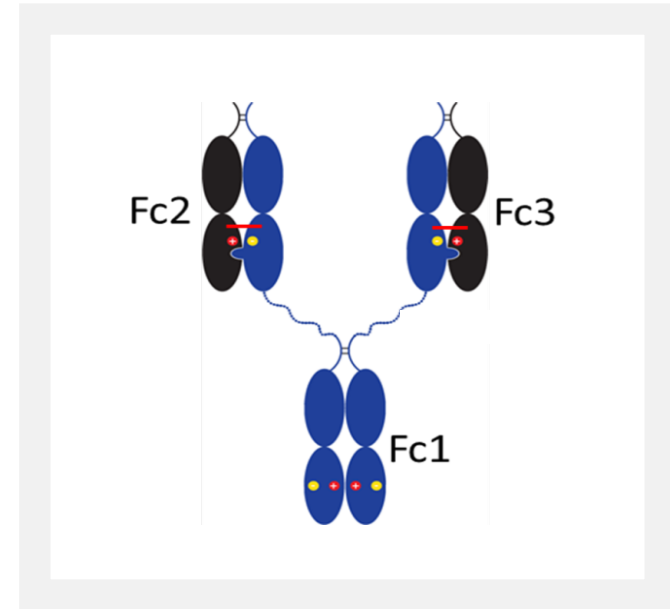
- Autoimmune conditions



# Recombinant Fc Multimer – CSL730

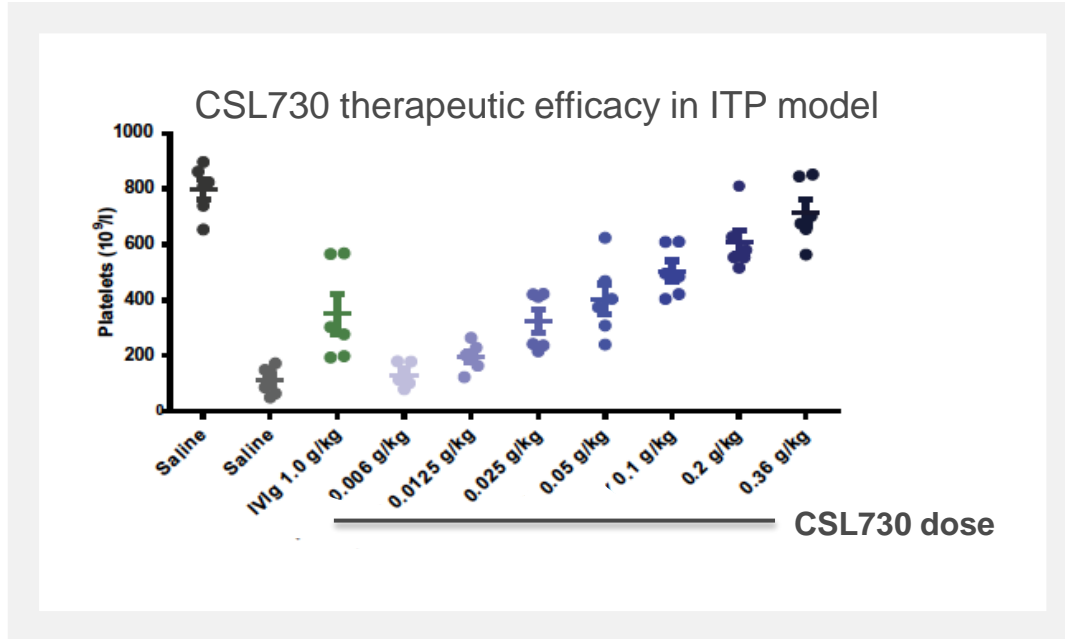
## CSL / Momenta Collaboration

- First-in-class recombinant Fc multimer targeting Fc $\gamma$  receptors
- Exclusive Research Collaboration and License Agreement
  - Development and commercialisation of the Fc multimer M230/CSL730
  - Research & development of additional Fc multimers
- Momenta has elected to co-fund development of CSL730





# Recombinant Fc Multimer – CSL730



- Non-clinical safety toxicity data supports commencement of FIH studies
- Phase I study (healthy volunteers) planned to commence Q1 2018
- Phase Ib proof of mechanism study anticipated for 2019

# Calimmune Technology

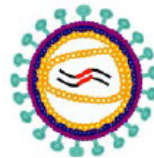
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- Acquisition of California based biotechnology company
  - Performance based milestones
- Gene / cell based therapy, rare genetic disorders
  - *ex vivo* Lenti virus transduction of hematopoietic stem cells (HSC's)
- Calimmune differentiating technology:



## **Cytegrity** Lentivirus Manufacturing

- stable & scalable GMP compliant system



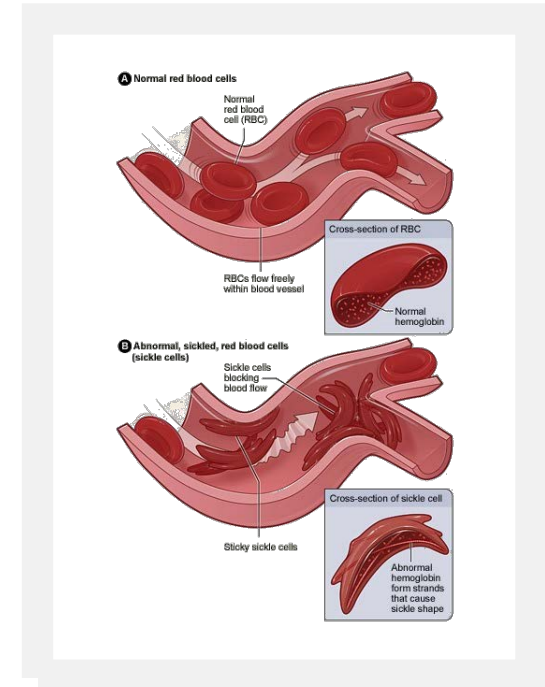
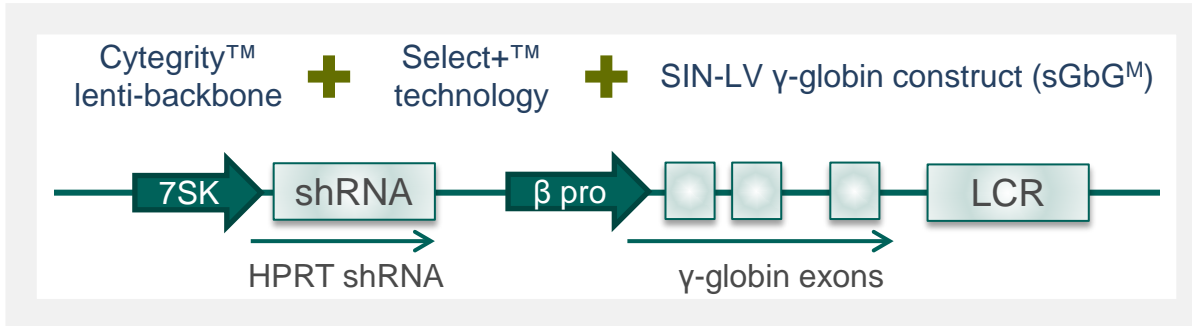
## **Select+** In Vivo Selection Tool

- drives engraftment with lower intensity conditioning
- significantly reduced burden on patient

# Calimmune – CAL-H Program

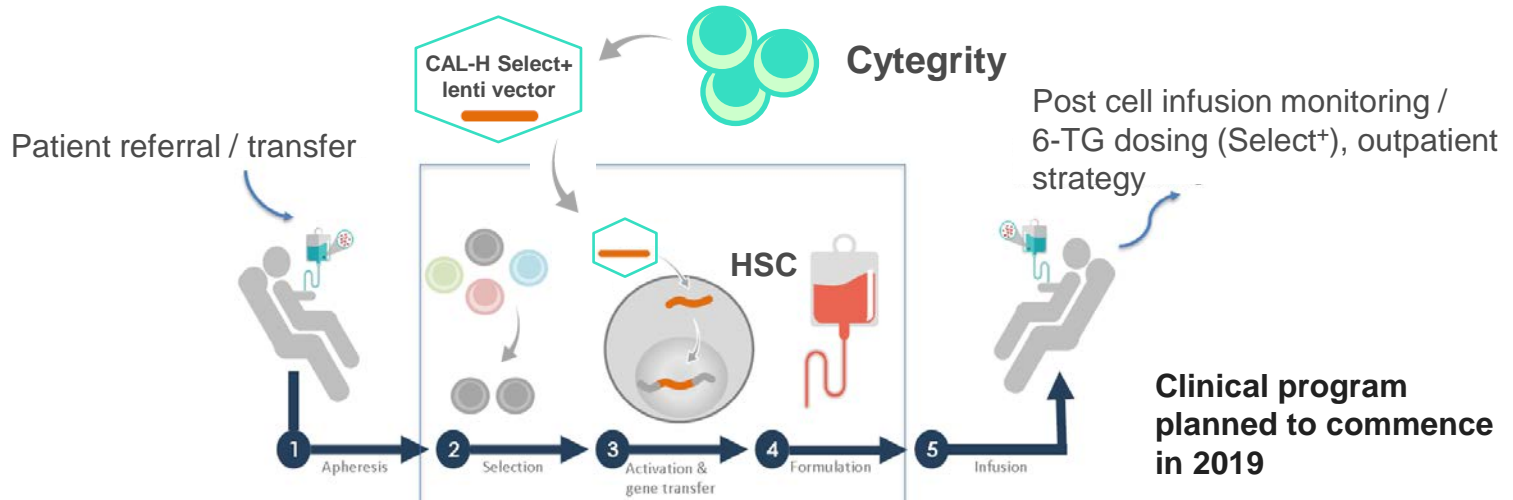
## Sickle Cell Disease

- Group of disorders caused by abnormal beta-globin gene resulting in sickled red cells
- Average life expectancy in the developed world is 40 – 60yrs
- High unmet need
- Total SCD patients: 155,000 (US + 5EU)



- CAL-H program aims to provide sufficient functional globin gene to prevent sickling

# Calimmune – CAL-H Program



- Range of further opportunities beyond SCD

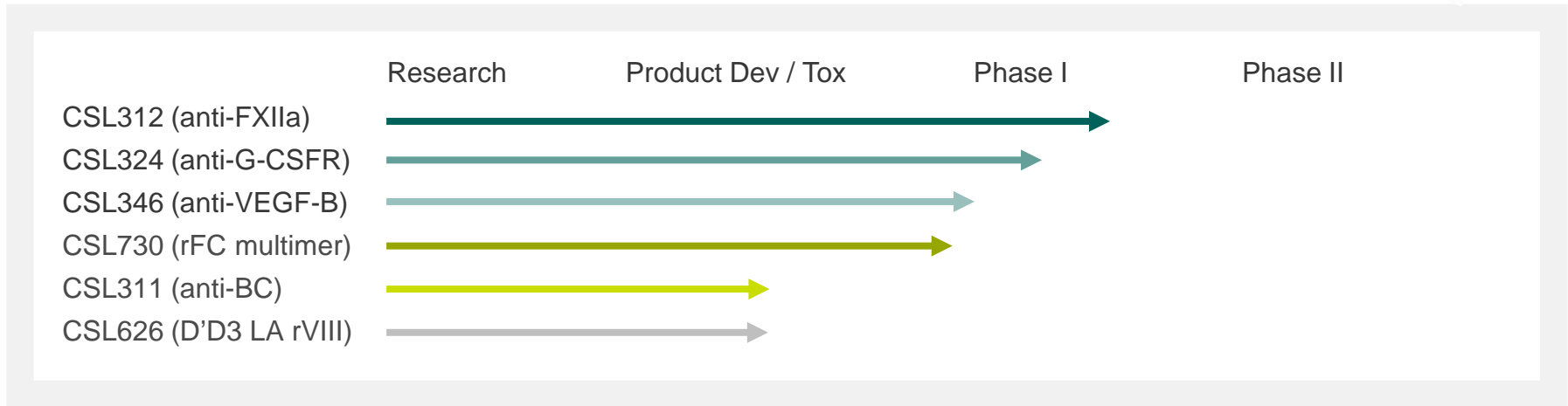
# Early Development Portfolio

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Dr Charmaine Gittleson  
Chief Medical Officer

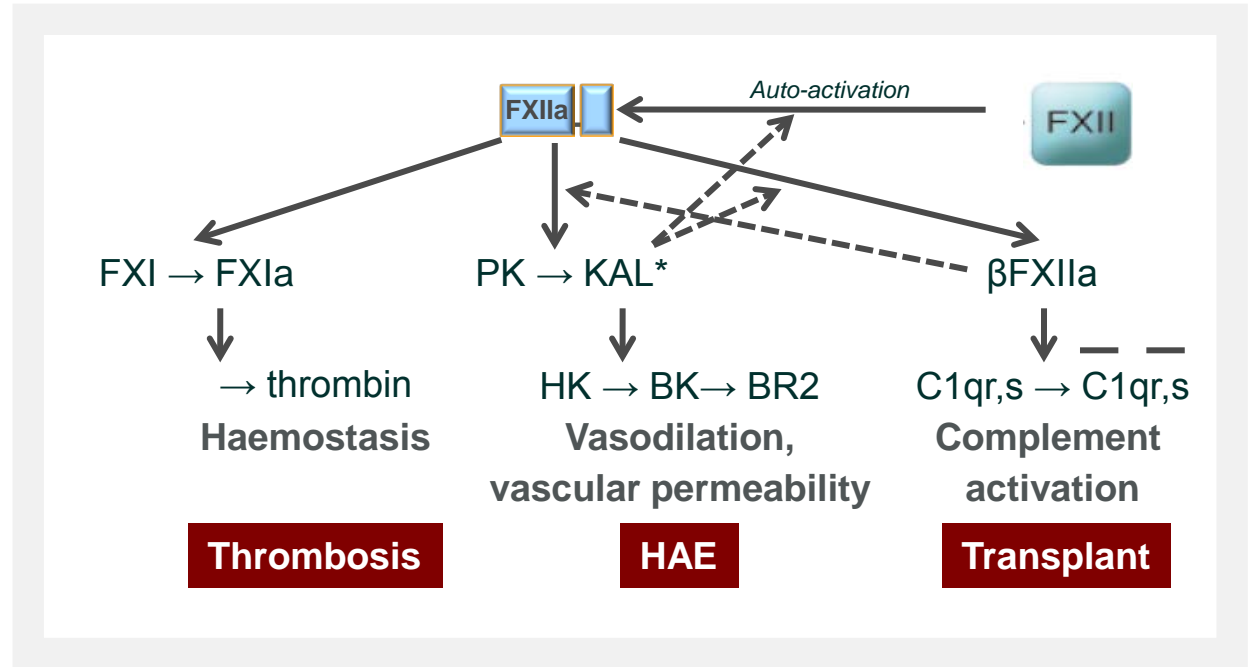
# Early Development Portfolio

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



# 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

## Phase I (dosing complete Nov 2017)

Normal Healthy Volunteers  
• Safety/PK/PD

Safe, well tolerated  
GO

## Phase II (2018/19)

Patients with HAE

## Phase Ib (~2019)

Proof of mechanism in thrombosis

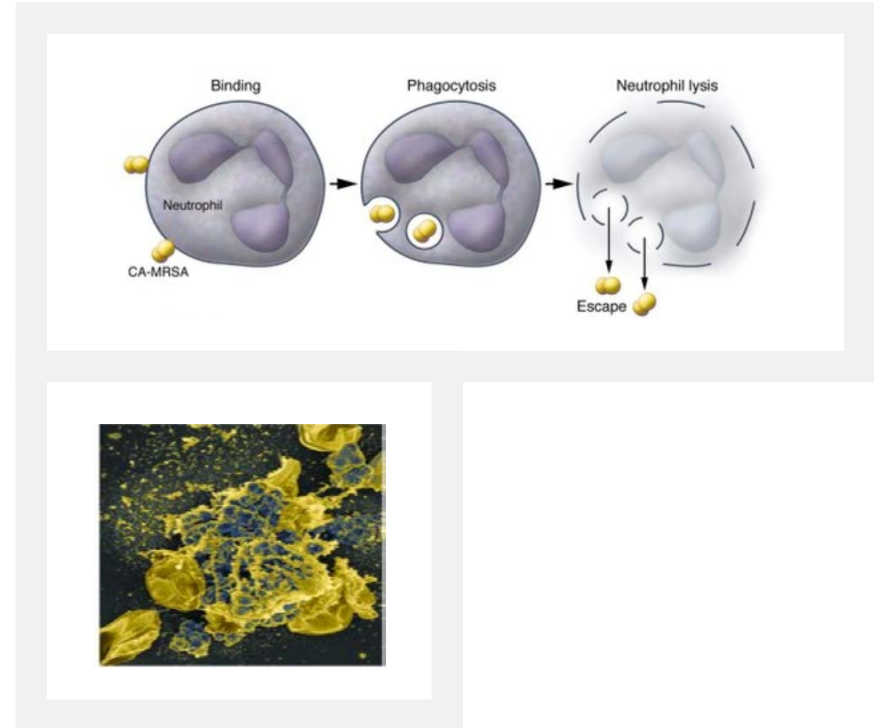
### First in Human Phase I study

- Single doses administered
- Confirmed CSL312 safe and well tolerated with good bioavailability



# CSL324 Anti-G-CSF Receptor Antibody

- White blood cells (neutrophils) – contribute to protective mechanism against infections
- Neutrophil numbers and activity under control of Granulocyte Colony Stimulating Factor (G-CSF)
- Excessive activated neutrophils, in absence of infection, cause chronic severe inflammatory diseases
- Blocking G-CSF could decrease unwanted effects of excessive neutrophils, possibly ameliorate chronic inflammatory diseases



# CSL324 Anti-G-CSF Receptor Antibody

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## Phase I (completing Jan 2018)

Normal Healthy Volunteers

- Safety/PK/PD

Safe, well tolerated  
GO

## Phase Ib (2018/19)

Patients with neutrophil driven disease

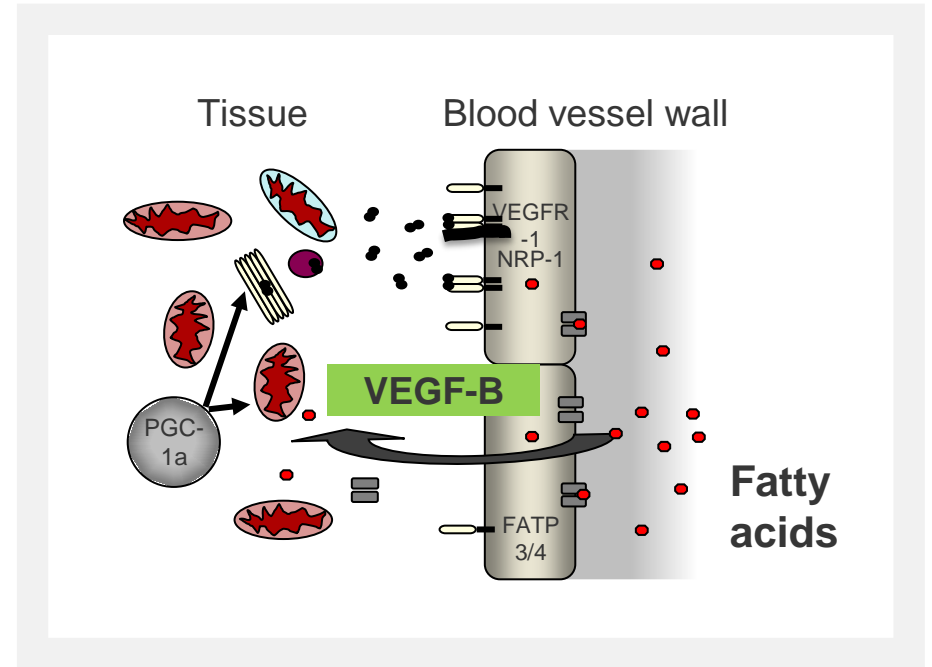
- Proof of mechanism

### First in Human Phase I study

- Single and multiple doses administered; dosing completed
- Confirmed CSL324 can block receptors and lower neutrophil counts

# CSL346 Anti-VEGF-B Antibody

- Free fatty acids (FFA) in diet support normal energy requirements in skeletal muscle, heart and kidney
- VEGF-B controls FFA movement into tissues
- Excess fatty acid uptake causes:
  - Reduced glucose utilisation, insulin resistance and diabetic complications
  - Toxic fat accumulation in vital organs (liver, kidney)
- Blocking VEGF-B action may help prevent or treat effects of excess FFA



# CSL346 Anti-VEGF-B Antibody

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## Phase I

Normal Healthy Volunteers

- Safety/PK/PD
- Started November 2017

**Safe, well tolerated  
GO**

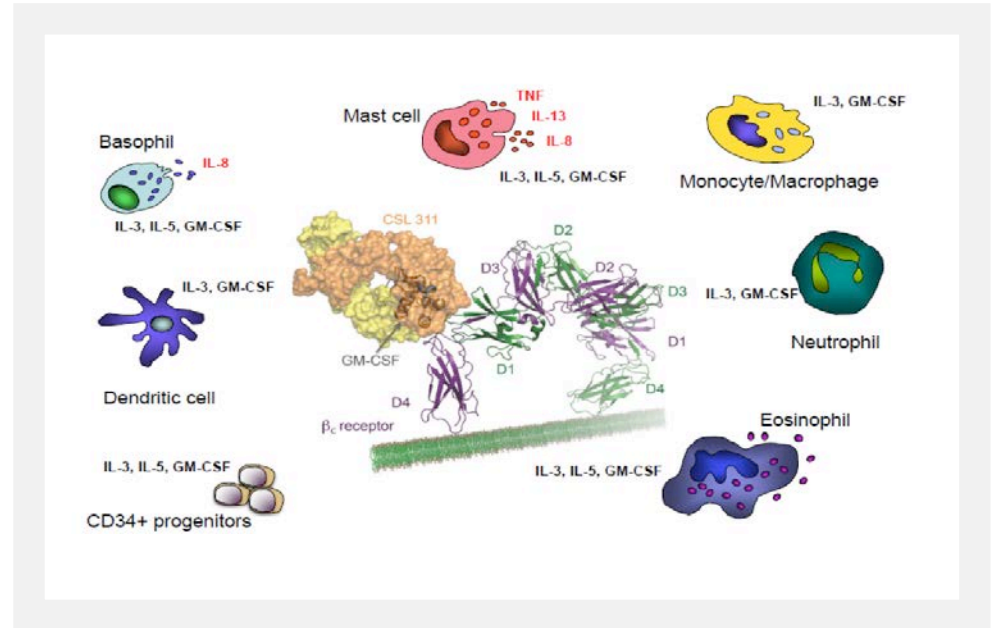
## Phase Ib

Patients with metabolic disorders

- Proof of mechanism
- Study anticipated for 2019

# CSL311 – Anti-Beta Common

- Central receptor (Beta Common) involved in stimulating immune modulating cells
- Increased activation in Auto-immunity, Allergy and Inflammation
- Blocking Beta Common (CSL311) and down regulating cells may ameliorate disease
- CSL311 blocks activity of GM-CSF, IL-3 and IL-5
- CSL311 inhibits activity of myeloid cells from normal and diseased tissue
  - FIH targeted for calendar year 2019

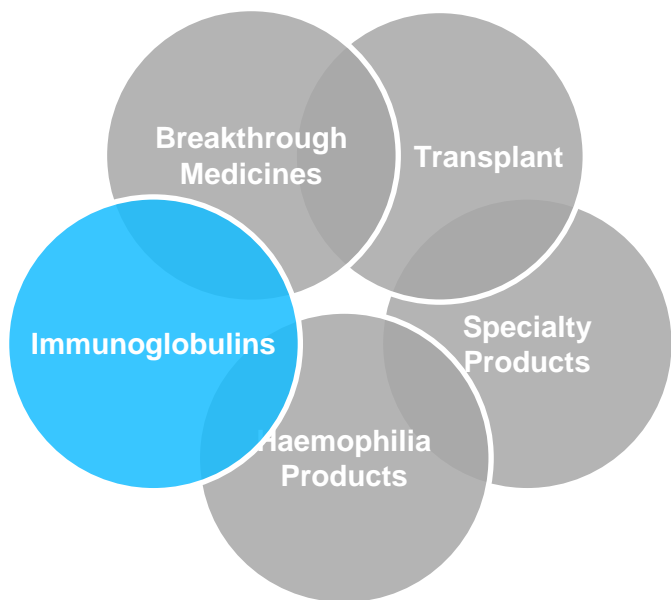


# Immunoglobulins, Haemophilia and Specialty Products

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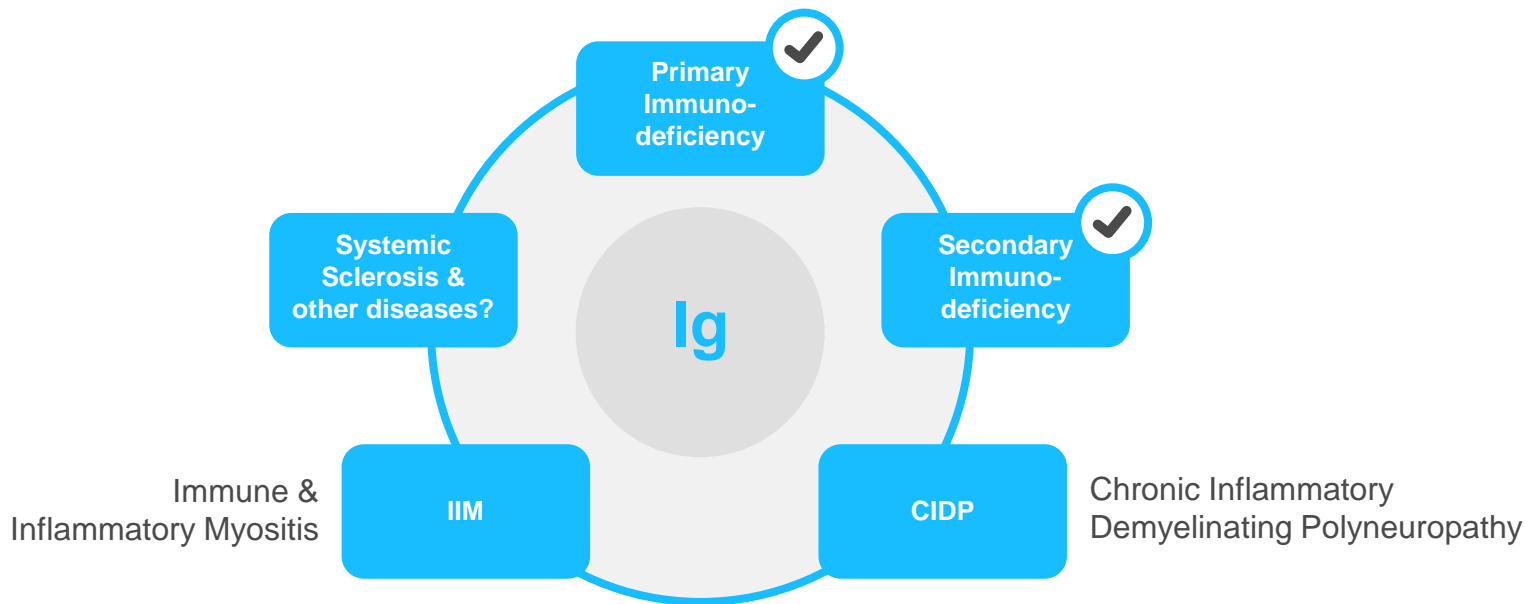
Dr Bill Mezzanotte  
Senior Vice President, Clinical Development

# Immunoglobulins



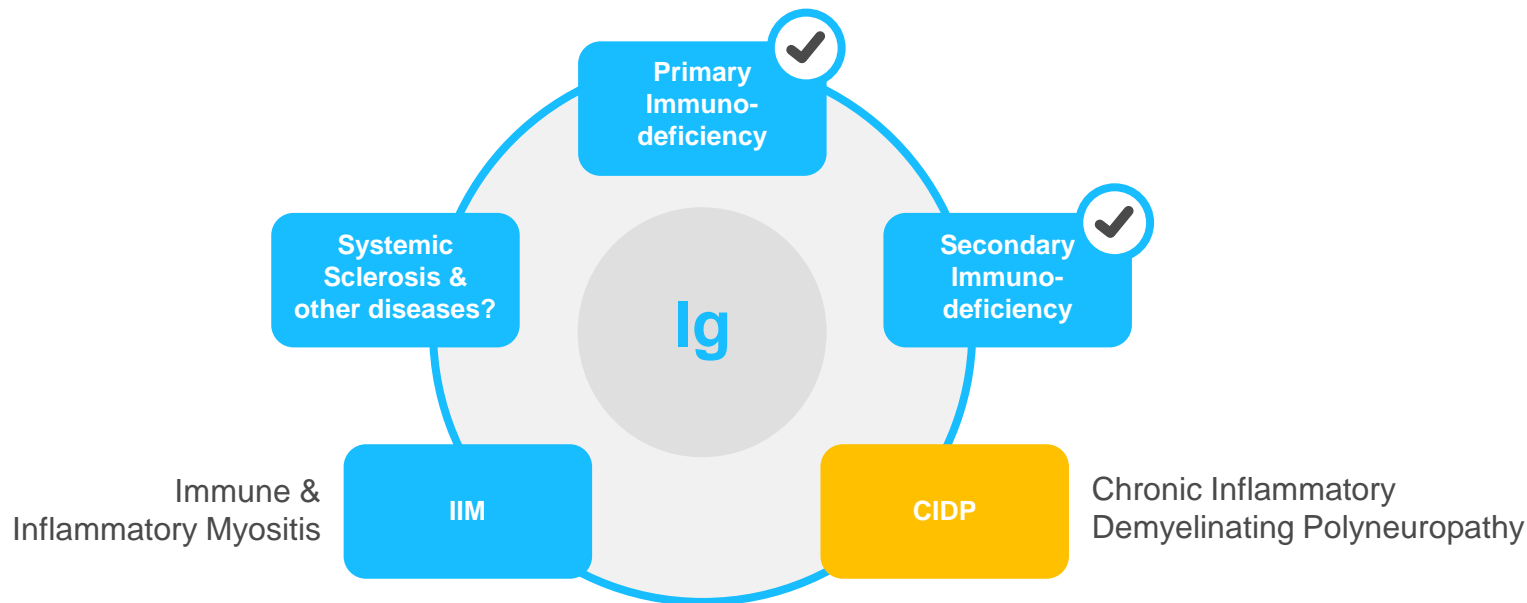
- **Maintaining leadership position through focus on:**
  - New Indications
  - Geographic expansion
  - Delivery options
- **Key Focus:**
  - HIZENTRA®
  - PRIVIGEN®

# Impact of Ig (IV & SC) in Rare Diseases

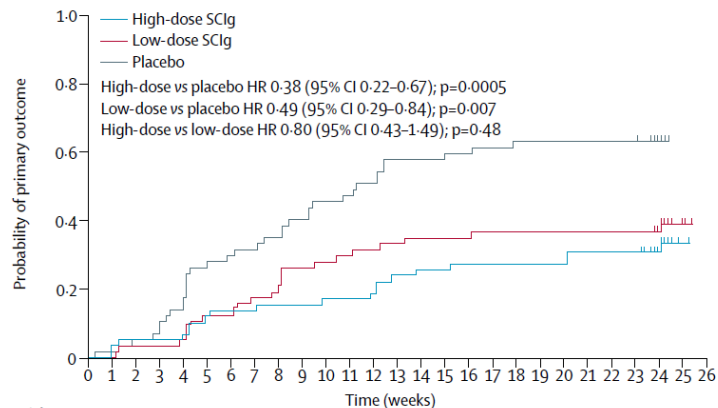




# Impact of Ig (IV & SC) in Rare Diseases



# PATH: SCIg (HIZENTRA®) Provides Effective Prophylaxis for CIDP Patients



Number at risk  
(number censored)

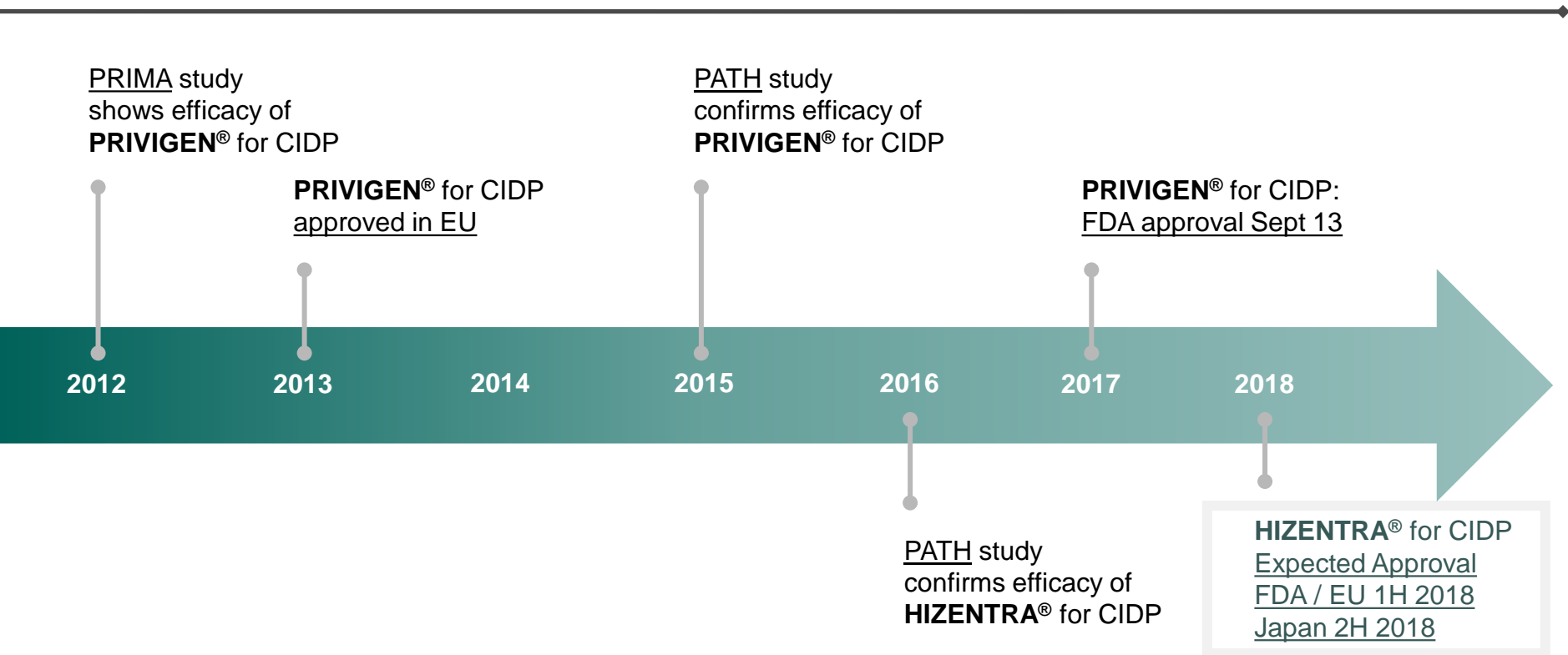
High-dose SCiG	58 (0)	51 (0)	48 (0)	43 (0)	42 (0)	0 (39)
Low-dose SCiG	57 (0)	50 (0)	41 (0)	37 (0)	36 (0)	0 (35)
Placebo	57 (0)	42 (0)	31 (0)	24 (0)	21 (0)	0 (21)

- PATH study the largest controlled CIDP study ever performed
- Investigated multiple doses
- Disease control demonstrated in patients previously treated with IVIG

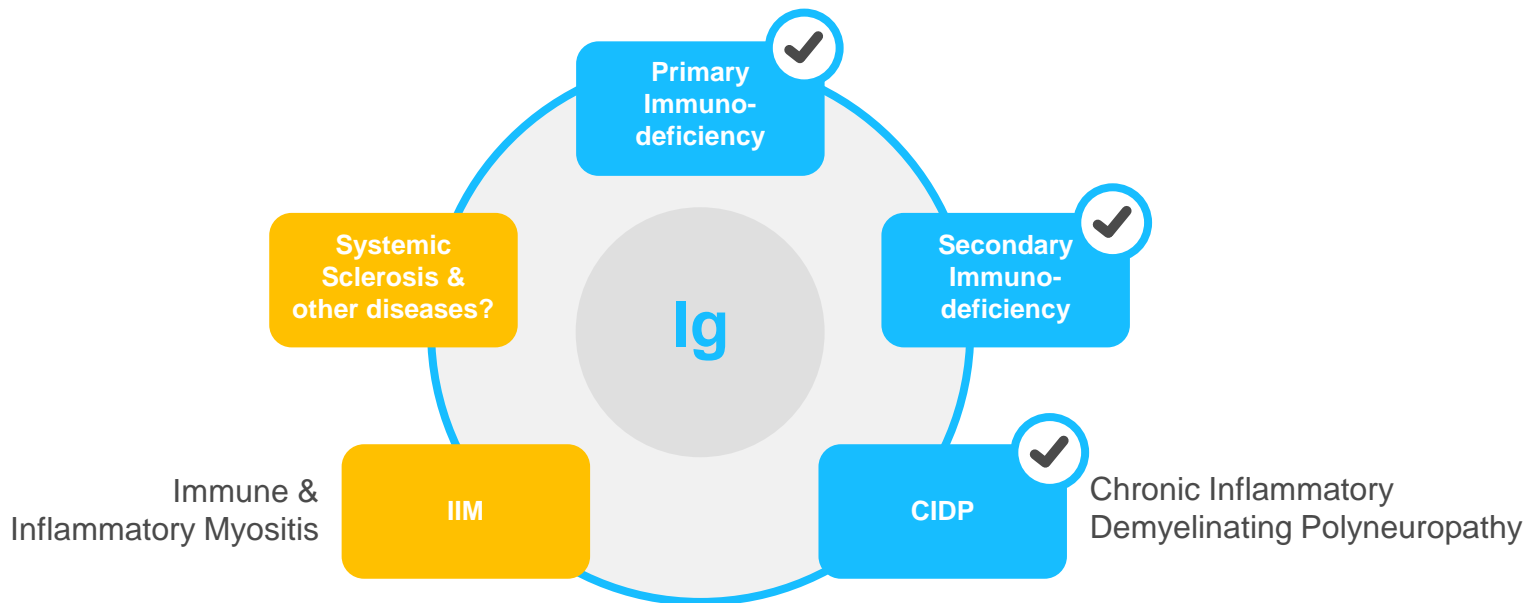
# IV and SC Ig are Effective Treatments for CIDP

- In the **PRIMA trial**
  - 61% of patients responded to PRIVIGEN®; 50% after the first dose
  - Almost 50% of IVIG-naïve patients responded to PRIVIGEN®
- In the **PATH study**
  - 81% patients on high dose and 67% on low dose of HIZENTRA® remained relapse free (after initial PRIVIGEN® stabilisation)
  - All efficacy outcomes showed clinically relevant improvements
- **PRIVIGEN® & HIZENTRA®:**
  - Improve multiple measures of CIDP disease activity
  - Are well tolerated by patients with CIDP

# Milestones in Ig Development for CIDP

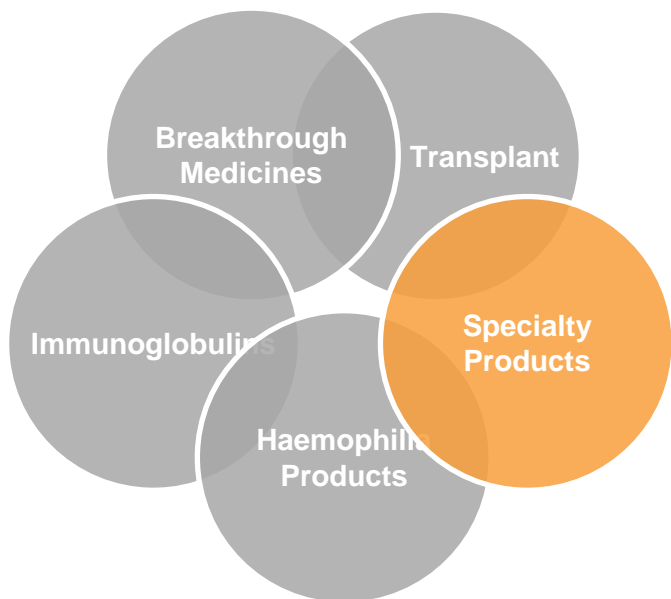


# Impact of Ig (IV & SC) in Rare Diseases



- Proposed Ig IIM with Unique Study Design to start 2018
- Health Authority (FDA, EMEA, PMDA) interactions 1Q 2018

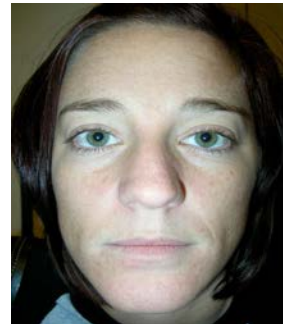
# Specialty Products



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

# Hereditary Angioedema (HAE)

- Hereditary angioedema (HAE) is a disorder that results in recurrent attacks of severe swelling
- All body sites are associated with impairment and patients are impacted during and between attacks
- Most severe are laryngeal attacks which can require emergency interventions to protect the airway



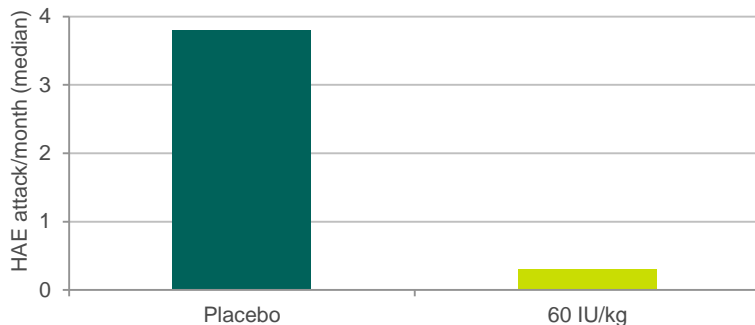
# Demonstrating the Unique Benefit of HAEGARDA®

The NEW ENGLAND JOURNAL of MEDICINE

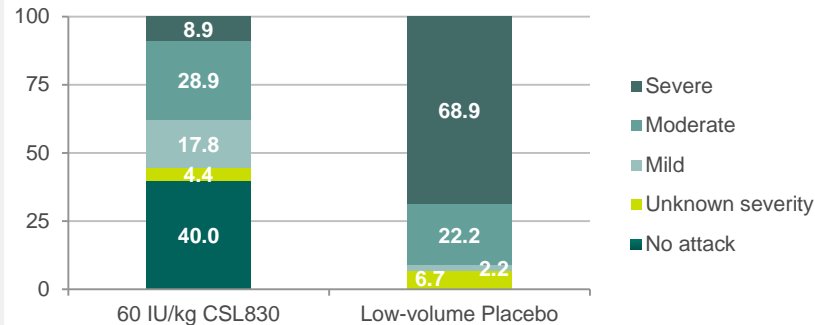
ORIGINAL ARTICLE

Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor

Median Attack Rate Reduction: 95%



CSL830 Reduces Severity of Attacks



- Approval in US & Canada; approval pending EU



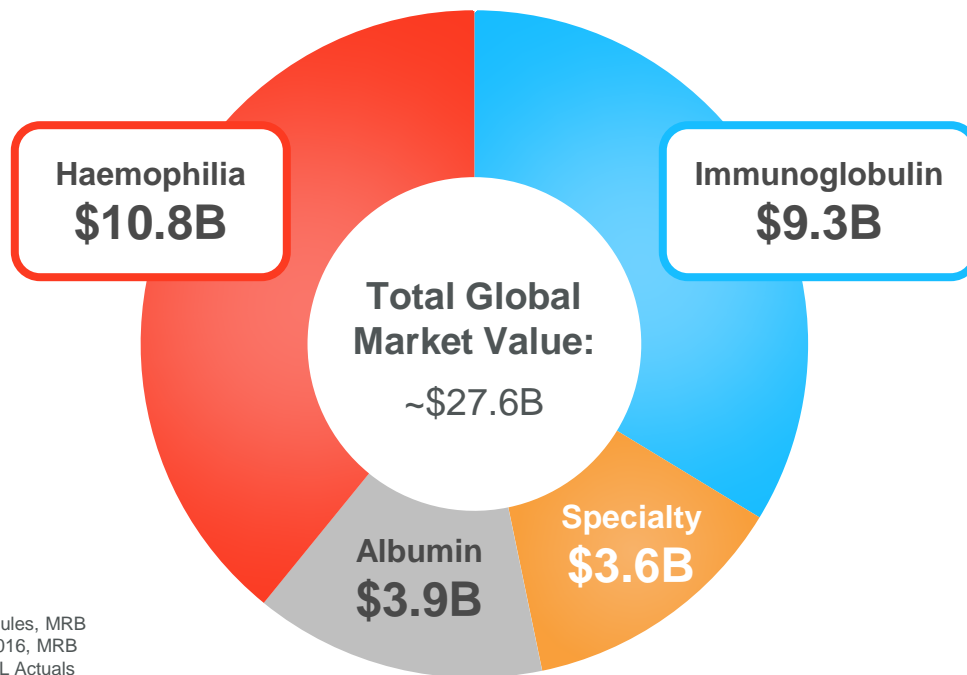
# Commercial Market Overview

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Mr Bill Campbell

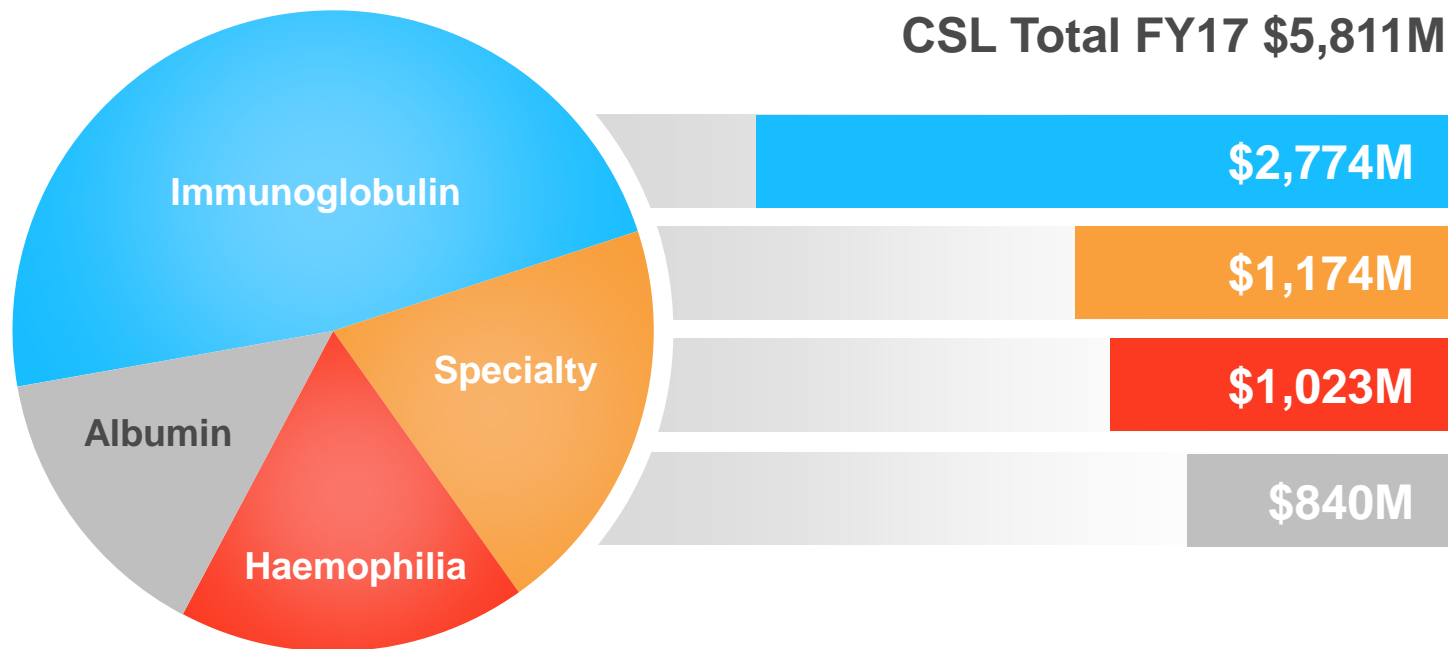
Executive Vice President & Chief Commercial Officer

# Targeted Protein Therapeutic Market



**Sources:** Company annual reports/financial schedules, MRB global Coagulation Factors Concentrate Market 2016, MRB WW Plasma Fractionation Market 2015 report, CSL Actuals FY17.

# CSL Portfolio



# Commercial / R&D Partnership

- Integrated strategy teams
- Coordinated New Product Development / Market preparation
- Disciplined launch preparation & execution



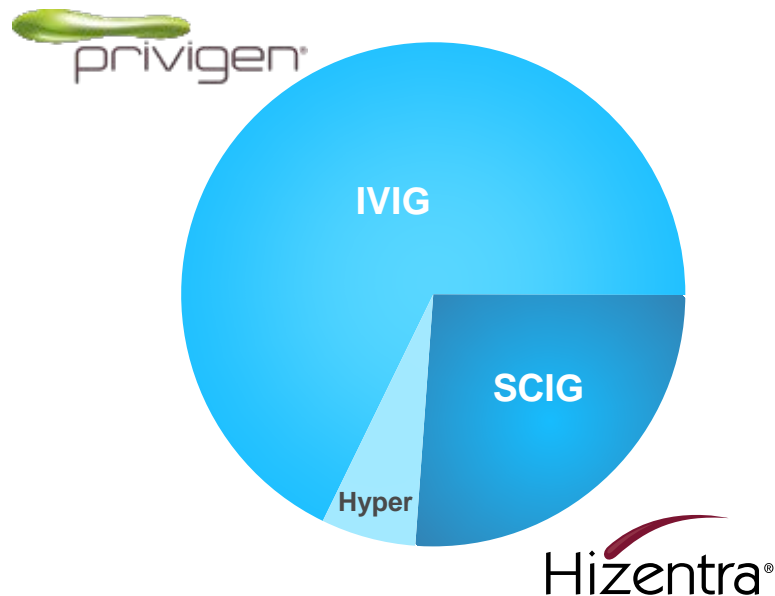
Multiple high value product launches:

- 2013 KCENTRA®
- 2016 IDELVION® & AFSTYLA®
- 2017 HAEGARDA®
- 2018 HIZENTRA® CIDP  
(pending approval)

**Foundational products plus new launches will continue to fuel significant growth**

# CSL's Global Performance

- CSL FY17 Sales \$2,774 M
- Significant growth opportunity
  - Per capita use varies widely
  - Core areas PID / SID
  - Neurology
  - New indications
- Continued acceptance, growth & patient benefits of SCIG



# Immunoglobulins: Category Leadership



## GROW

the current business

- Maximise PID / SID opportunity
- Leverage broad portfolio
- Enhance product offerings



## EXPAND

our presence in neurology

- Replicate our approach to build market leading segments
- Build on PRIVIGEN® experience in CIDP
- Launch HIZENTRA® in CIDP



## INNOVATE

and protect the franchise

- Novel delivery devices
- New indications eg IIM, SSc
- rFc multimer

# HIZENTRA®: Innovator, Market Leader



**7 years and  
51 countries**

**90,000 patient-years,  
4.8M exposures  
worldwide**

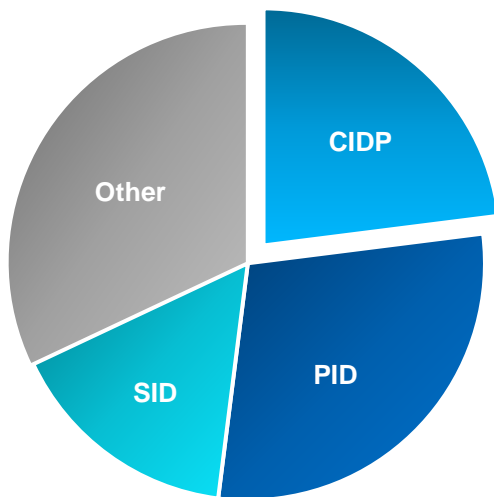
**Convenient  
self-administration**

**Individualised  
therapy**

**Most prescribed  
SCIG worldwide**

# CIDP – Growing Area of Focus

## Global IG volume by indication



- ~23% of all IG usage globally
- Growing market segment
- Many unmet needs remain



# HIZENTRA® addresses unmet needs in CIDP therapy

## Unmet Needs



IVIG improves CIDP symptoms but many patients experience “wear off” with IVIG therapy



**Steady state IG levels for continuous control**



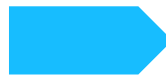
IVIG therapy difficult for patients with poor venous access



**Hizentra therapy does not require venous access**



Many patients on IVIG suffer from systemic effects like nausea and headache



**4 fold lower systemic AE rates than IVIG**



Majority of patients receive IVIG at infusion centers

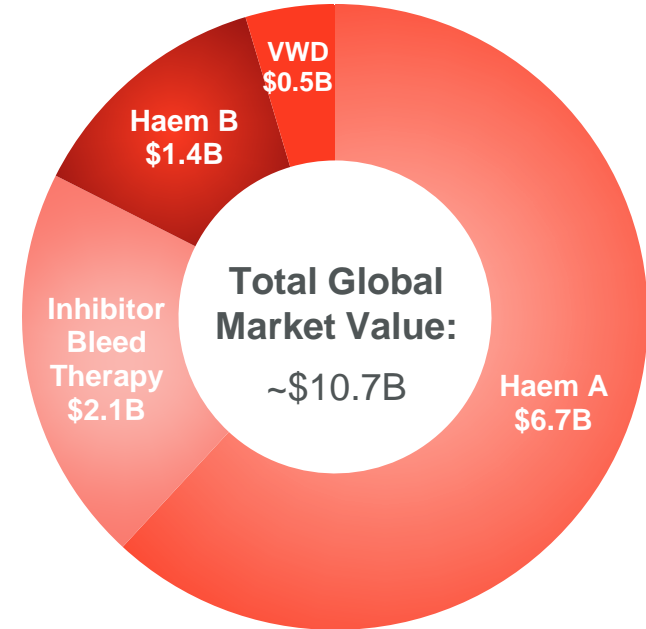


**Increased independence and flexibility (time/site/frequency)**

**HIZENTRA® was preferred by 3X as many patients as IVIG**

# Global Market

- Highly competitive Haem A market space
- Rapid transition of Haem B category
- Major advancements in patient care
- 75% of patients with bleeding disorders are under/untreated



**Sources:** Company annual reports/financial schedules, based on 2017 data, MRB Global Coagulation Factors Concentrate Market 2016, CSL Actuals FY17.

# Coagulation Portfolio

## Haemophilia A

**AFSTYLA**<sup>®</sup>  
Antihemophilic Factor  
(Recombinant), Single Chain

**Helixate**<sup>®</sup>**ES**  
Antihemophilic Factor (Recombinant)

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

**Beriate**<sup>®</sup> P

## Haemophilia B

**IDELVION**<sup>®</sup>  
albutrepenonacog alfa  
(Recombinant Coagulation Factor IX, Albumin Fusion Protein)

**Mononine**<sup>®</sup>  
MONOCLONAL ANTIBODY PURIFIED  
Coagulation Factor IX (Human)

## VWD

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

**VONCENTO**<sup>®</sup>  
(Human Coagulation Factor VIII/  
Von Willebrand Factor Complex)

## Other

**RiaSTAP**<sup>®</sup>  
Fibrinogen Concentrate (Human)

**Corifact**<sup>®</sup>  
Factor XIII Concentrate (Human)

**STIN**  
(desmopressin acetate) Nas

# Transforming Care of Haemophilia B Patients



#1 “Switch to” brand providing highest factor levels for the longest period of time

<b>1<sup>st</sup> Haemophilia therapy with up to 14-day dosing</b>	<b>Long-lasting protection with high trough levels</b>	<b>Excellent efficacy</b>
UP TO <b>14-DAY</b> DOSING	14 DAYS <b>ABOVE 13%</b> WITH 75 IU/KG	<b>ZERO</b> BLEEDS MEDIAN AsBR
Greater freedom from infusions	Ability to live a more normal life	Protection from bleeds

”

## Product of Choice for Physicians

“All my IDELVION® patients were on prophylaxis previously with BeneFIX... **they were very interested in having less frequent infusions.**”

– Hematologist, HTC

“This is not something I would associate with another FIX. It’s higher than Alprolix, and, from a physician’s perspective **the most important thing is that a patient not bleed.**”

– Hematologist, MD

“I mean, it’s very impressive. Once we get to 21%, you know the patient is very well-protected. **Seven-day dosing – there’s nothing not to like about this.**”

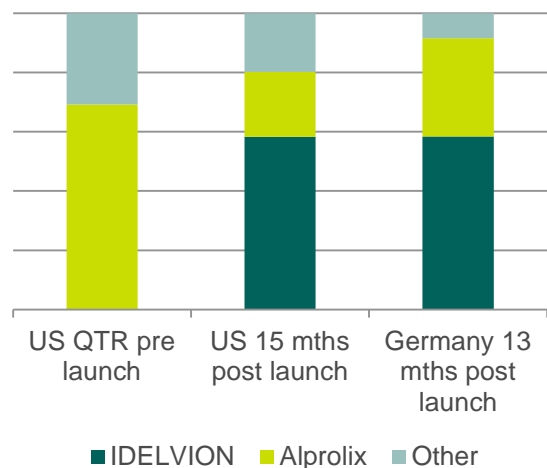
– HTC MD

“**About half of my Alprolix patients have switched to IDELVION® now.** I expect more will do the same.”

– Hematologist, MD

# Transition to New Products in Haemophilia B

Patient switches %



- Demand exceptionally strong
  - Capturing ~2/3 of patient switches
- Ongoing launch
  - Launched in 12 countries
  - First hemophilia product in Japan
  - France, Spain, Greece, Poland, Portugal, Israel, Canada, Australia, New Zealand and others still to come
- Extension Study
  - Clinically meaningful efficacy using 21 day regimen

# Accelerating AFSTYLA® Adoption



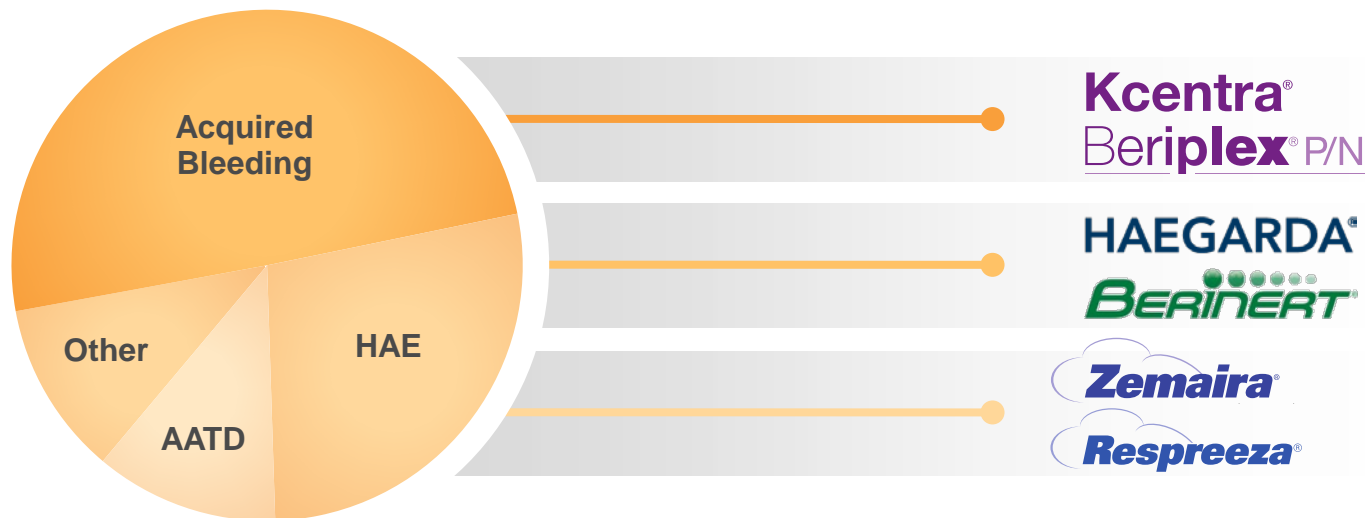
Proven long-lasting bleed protection with a unique single-chain design

Higher binding affinity to vWF	Long-lasting protection with high trough levels	Excellent efficacy	Individualised dosing
<b>3X HIGHER</b> COMPARED TO OCTOCOG ALFA	<b>ABOVE 1.9%</b> WITH 2X/WEEK DOSING	<b>ZERO</b> BLEEDS MEDIAN AsBR	<b>2X WEEKLY</b> AVAILABLE
Extended time in circulation	Ability to live a more normal life	Protection from bleeds	Flexible dosing – 2x or 3x weekly

# CSL's Global Performance

- Specialty portfolio growth FY17 +20%
  - KCENTRA®/ BERIPLEX® +35%; BERINERT® +31%
- HAEGARDA® US launch & rapid acceptance
- Often under or misdiagnosed

CSL FY17  
Sales \$1,174 M

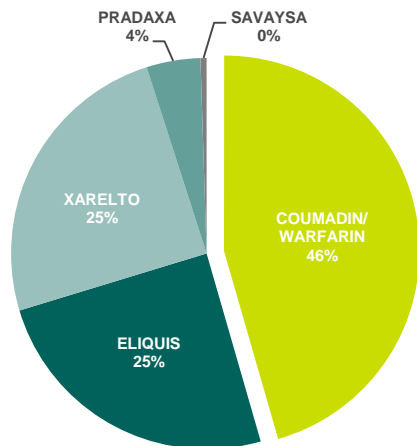




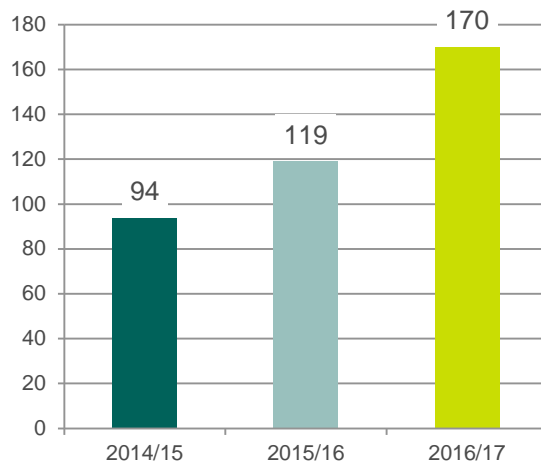
# Continued Growth Opportunities for Kcentra®

Kcentra®

## US Anti-Coagulation Market



## US Demand (IU)



## Japan

- Launch Sep 2017
- Fast formulary acceptance
  - Over 300 hospitals

Sources: IMS Health NPA data, Sept 2017; Decision Resource Group Claims data, Mar 2017; Internal data (Japan)

# Specialty Products – HAEGARDA®

HAEGARDA®

- Product launched July 2017
- 7 year orphan exclusivity
- 95% reduction in HAE attacks
- >99% reduction in the need for rescue medication
- First and only subcutaneous formulation
- Strong patient, physician and provider engagement



”

“I haven’t had a **single attack** since starting the HAEGARDA® study in 2015!”

“This is the **longest period in my life having gone without a single attack** since my very first one at age 13.”

“I **choose not to suffer**, and HAEGARDA® gives me that choice.”

“I feel like I am finally a **participant in my own life!**”

“The patient is just giddy.”

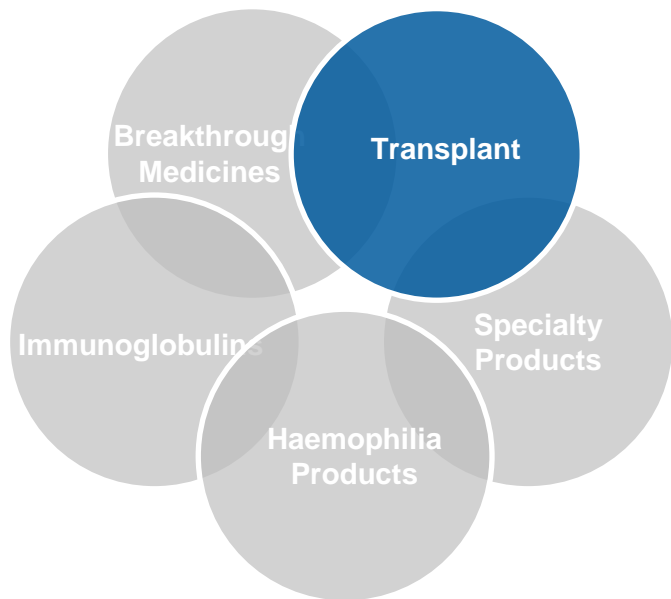
“It is, hands down, the easiest medication I’ve had to administer that **ACTUALLY works.**”

# Transplant and Breakthrough Medicines (CSL112)

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Dr Bill Mezzanotte  
Senior Vice President, Clinical Development

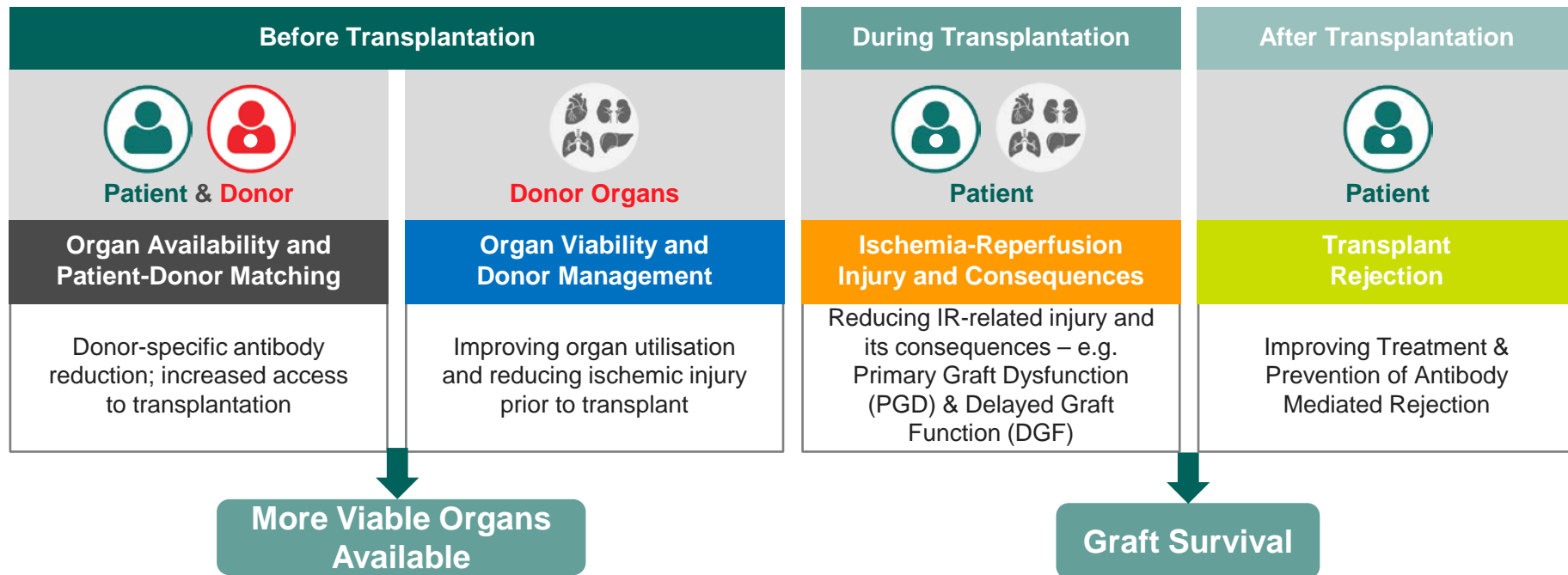
# Transplant



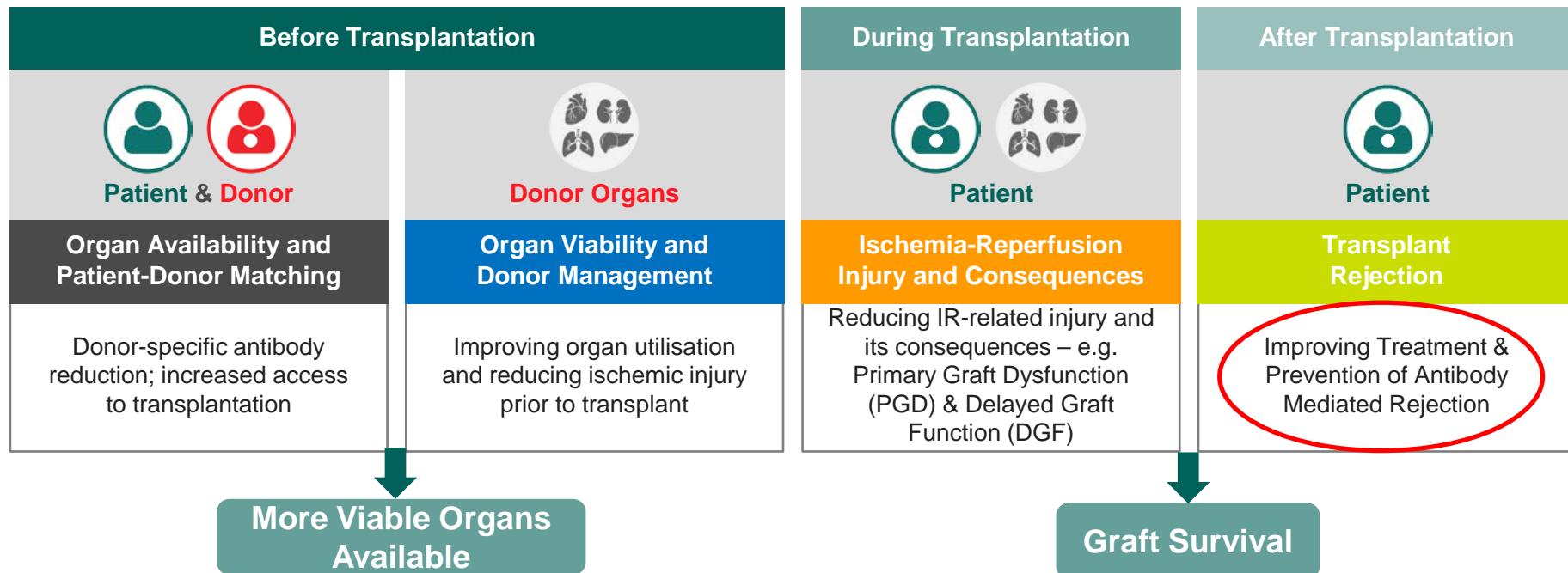
- **Developing CSL and other novel therapies with potential to improve transplant outcomes:**
  - Significant unmet need
- **Key Focus:**
  - C1 inhibitor (C1-INH) / BERINERT®
  - Alpha1 anti-trypsin (AAT) / ZEMAIRA®
  - Anti-IL-6 / clazakizumab\*
  - CSL312 (anti-FXIIa mAb)
  - CSL324 (anti-G-CSFR mAb)

\*Partnered project

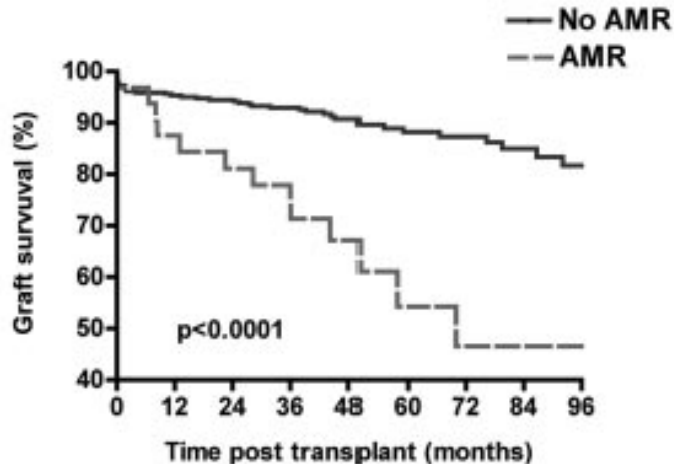
# Solid Organ Transplant (SOT): Unmet Medical Need



# Solid Organ Transplant (SOT): Unmet Medical Need



# Antibody Mediated Rejection (AMR) in Kidney Transplantation



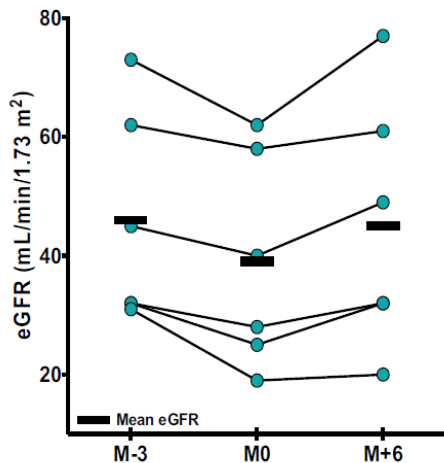
J Am Soc Nephrol 2010 Aug; 21(8): 1398–1406

The kidney is the most commonly transplanted solid organ

- AMR occurs in up to 5-10% of transplants acutely and up to 30% chronically
- AMR is marked by declining renal function and is associated with lower graft survival
- Patients with donor-specific antibodies are denied transplant due to the risk for AMR



# Long Term C1 INH Administration Stabilises Graft Function in AMR Patients Unresponsive to Standard of Care



↑  
Renal  
Function  
at the  
time of  
initial  
AMR Dx.

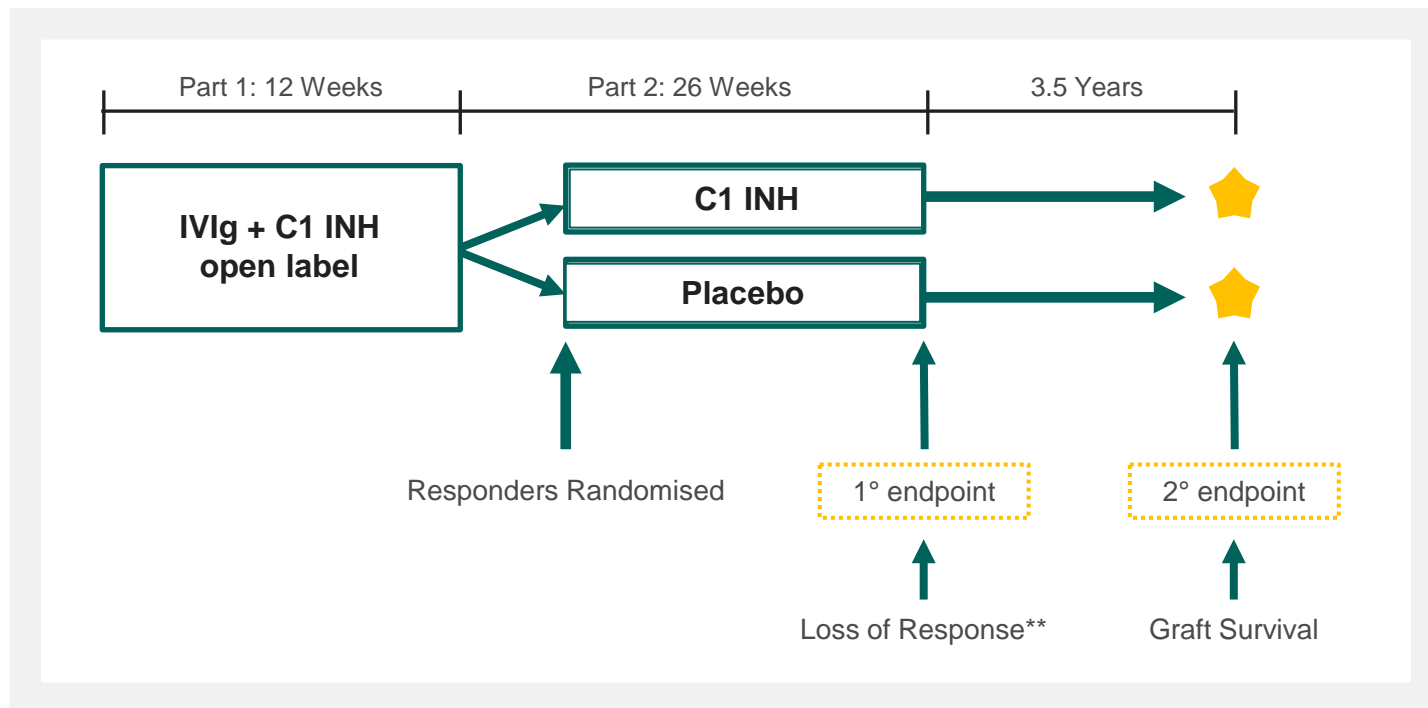
↑  
Renal  
Function  
at the  
end of  
first-line  
AMR  
SOC

↑  
Renal  
Function  
at the  
end of 6  
mos.  
C1inh  
Tx.

In a pilot study 6 patients with AMR, unresponsive to standard of care, were treated with C1 INH and had improved renal function (estimated Glomerular Filtration Rate, eGFR) at 6 months

*Viglietti et al., Am J of Transplantation 2016*

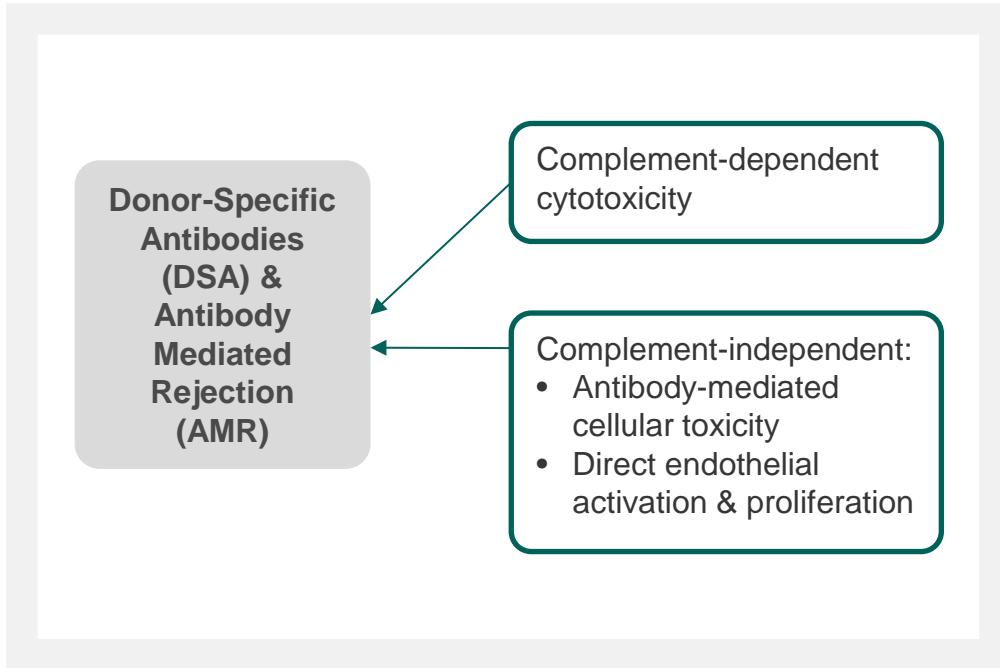
# CSL842 C1-INH to prevent recurrent AMR: Randomised, Placebo-controlled Withdrawal



\*\*occurrence of any of the following

- Decline in renal function (eGFR)
- Allograft failure
- Subject death

# Complement Dependent & Independent Pathways Involved in AMR



## Potential Benefits of Anti-IL6 therapy in AMR:

- Reducing DSA production
- Reducing DSA mediated injury to allograft
- Pilot study demonstrated blocking IL-6 stabilises renal function and prolongs graft survival\*

\*Choi et al Am J Transplantation 2017

# Vitaeris and CSL Strategic Collaboration

- Vitaeris Inc.
  - clazakizumab (anti-IL6 mAb) in clinical development
  - Successful FDA Type C Meeting
- Anticipated dosing in AMR patients in 2018
- CSL – Vitaeris Strategic Collaboration
  - Collaboration and purchase option agreement to expedite the development of clazakizumab
  - Exclusive Option to acquire company at later date with data readout
  - CSL with Board Observer & Director seats, Member of Scientific Advisory Board



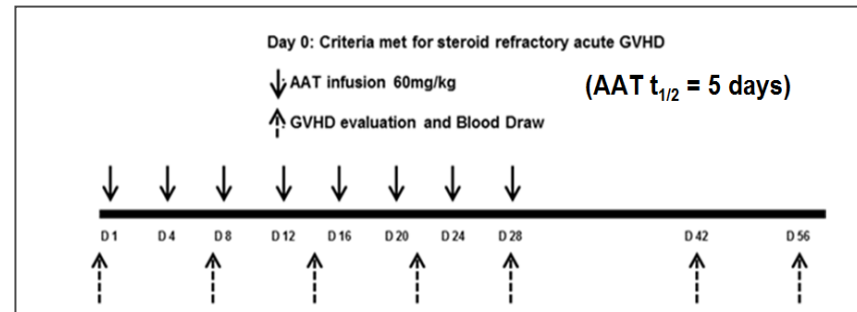
# Unmet Medical Need in Graft versus Host Disease (GvHD)

- Incidence and mortality
  - Hematopoietic Stem Cell Transplant (HSCT) is a common effective therapy for many life-threatening malignant and non-malignant diseases
    - Autologous – Patient's own cells
    - Allogenic – Donor cells
  - ~50-60% of Allogeneic HSCT develop acute Graft versus Host Disease (GvHD) despite prophylaxis
  - GvHD is a common cause of morbidity & mortality in HSCT
    - Therapies are often ineffective or cause severe immunosuppression
    - Survival is 30% for Grade III and 10% for Grade IV
  - Pathophysiology of GvHD in HSCT may be addressed by immunomodulatory effects of Alpha 1 Anti Trypsin (AAT)

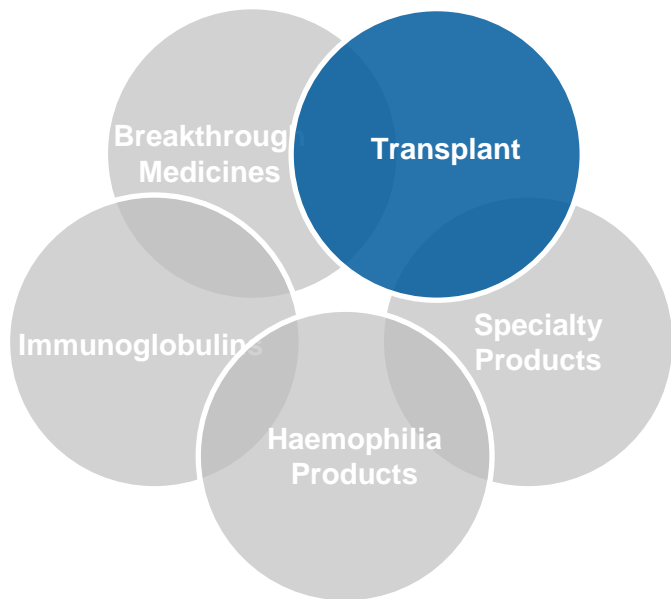
## Clinical Data:

# Treatment of Steroid-Refractory GvHD with AAT

- ZEMAIRA® (AAT) - *Mangenau, ASBMT 2016*
  - 40 Patients with Steroid refractory aGVHD
  - Open label AAT - **60mg/kg** twice weekly x 4 weeks
  - Overall response rate (ORR) - 65%
    - 35% Complete Response
  - Sustained responses - 73% at Day 60
  - Well tolerated with low rates of infection
- Proposed AAT GvHD Study
  - Anticipated study start in 2018
  - Final design pending ongoing regulatory discussions



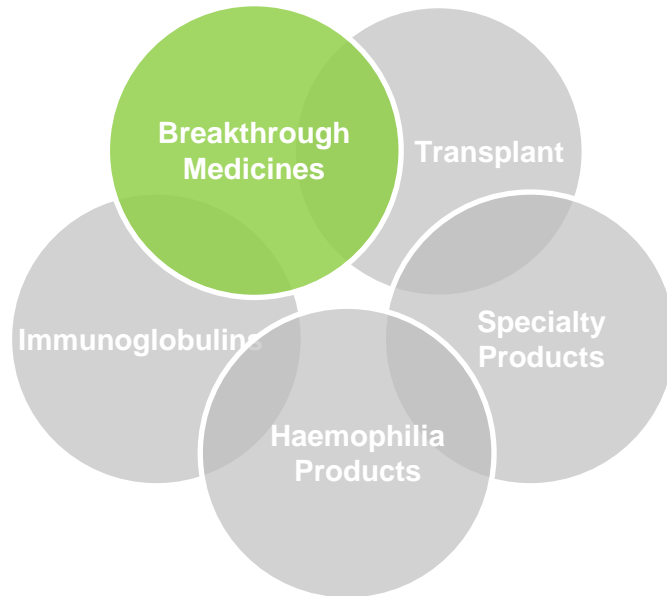
# Transplant



- **Developing CSL and other novel therapies with potential to improve transplant outcomes:**
  - Significant unmet need
- **Key Focus:**
  - C1 inhibitor (C1-INH) / BERINERT®
  - Alpha1 anti-trypsin (AAT) / ZEMAIRA®
  - Anti-IL-6 / clazakizumab\*
  - CSL312 (anti-FXIIa mAb)
  - CSL324 (anti-G-CSFR mAb)

\*Partnered project

# Breakthrough Medicines

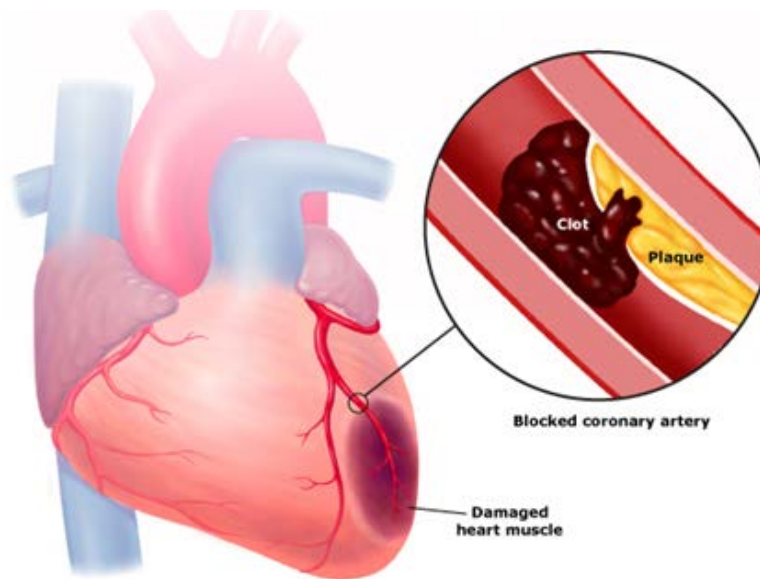


- **Leveraging clinical and technical insight in developing novel protein-based therapies:**
  - Significant unmet need
  - Multiple indications
- **Key Focus:**
  - **CSL112 (ApoA-I)**
  - CSL312 (anti-FXIIa mAb)
  - CSL324 (anti-G-CSFR mAb)
  - CSL346 (anti-VEGF-B mAb)
  - CSL311 (anti-BC mAb)



# Cardiovascular Disease (CVD) - High Unmet Medical Need

- CVD remains leading cause of death globally
- In the US alone, 800,000 acute MIs occur each year
- Survivors remain at high risk for early recurrent CV events
- Among high-risk populations:
  - 14% recurrence in year one
  - of these ~70% within first 90 days
- Reducing the risk of early recurrent events represents a significant unmet need



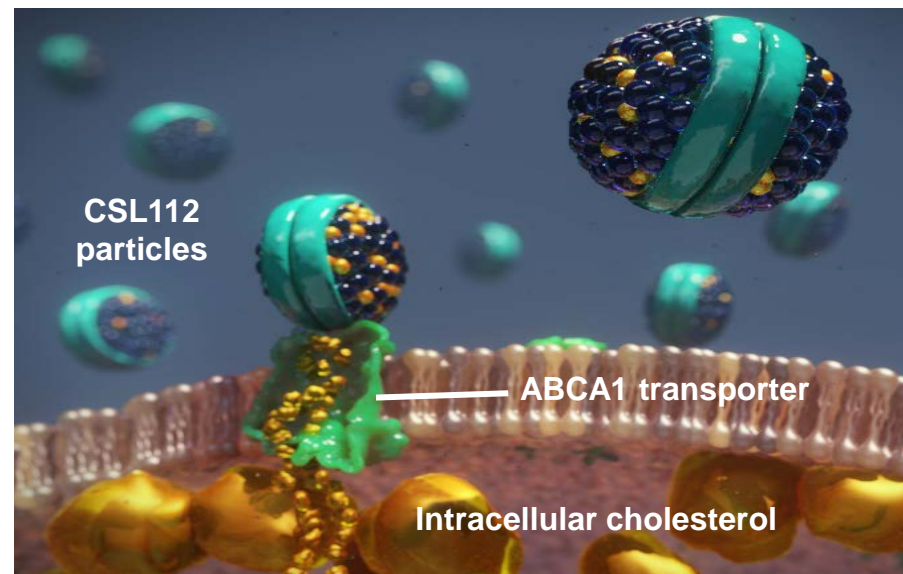
# Cholesterol Efflux With CSL112 (apolipoprotein A-I)

Apolipoprotein A-I (ApoA-I) is the primary component of HDL (“good cholesterol”) and responsible for cholesterol efflux capacity (CEC)

- HDL levels & CEC are inversely correlated with atherosclerotic heart disease

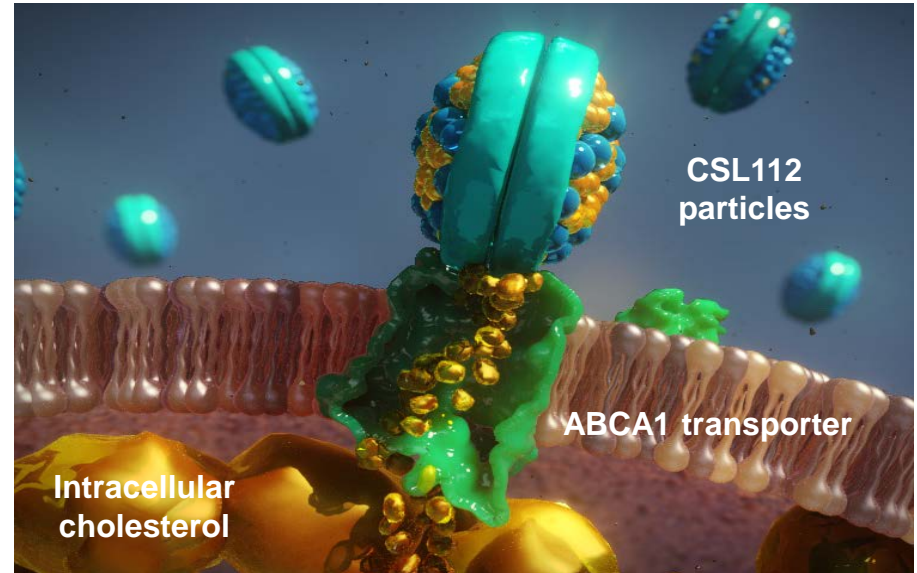
CSL112:

- purified ApoA-I from human plasma
- increases CEC, particularly ABCA1-dependent CEC
- unique compound

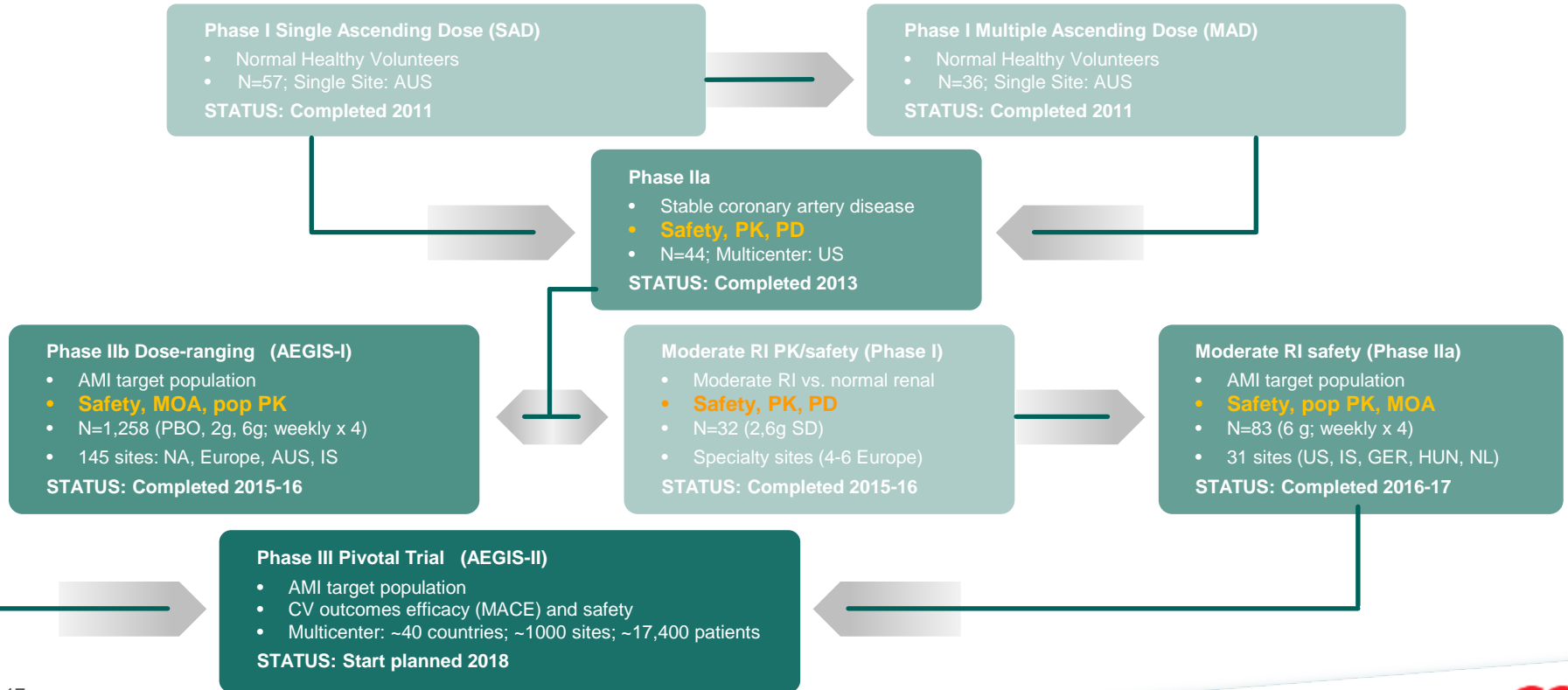


# CSL112 Hypothesis

- CSL112 will be safe and well tolerated
- CSL112 will enhance cholesterol efflux capacity (CEC)
- CSL112 will acutely stabilise atherosclerotic plaques and prevent subsequent major adverse cardiovascular events (MACE) in the early, highest risk period (unique treatment period)



# CSL112: Clinical Path to Phase III – Safety & Mechanism of Action



# No Safety Concerns in Patients with Moderate Renal Impairment

	Number of subjects with data	Number of subjects with events, n (%) n'
<b>Renal SAEs</b>		
CSL112 6g (N=52)	52	1 (1.9%) 1
Placebo (N=28)	28	4 (14.3%) 5
<b>Acute Kidney Injury (AKI) Events</b>		
CSL112 6g (N=52)	50	2 ( 4.0%) 2
Placebo (N=28)	28	4 (14.3%) 4

Low incidence of renal events across CSL112 and placebo

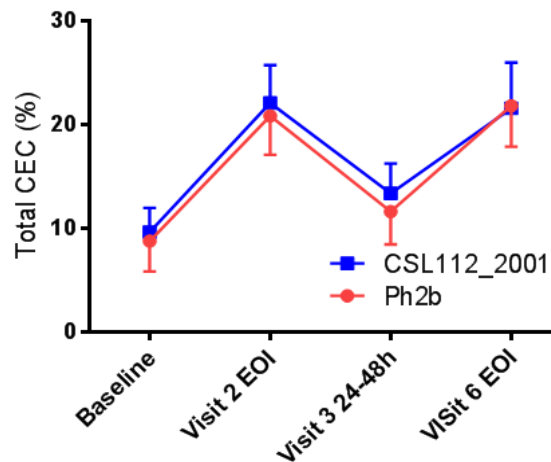
Safety data are consistent across:

- Degree of renal impairment: (eGFR 30- <45 ml/min) versus (eGFR 45 - <60ml/min)
- Presence or absence of antidiabetic therapy

Results support including patients with moderate renal impairment into Phase III (AEGIS II)

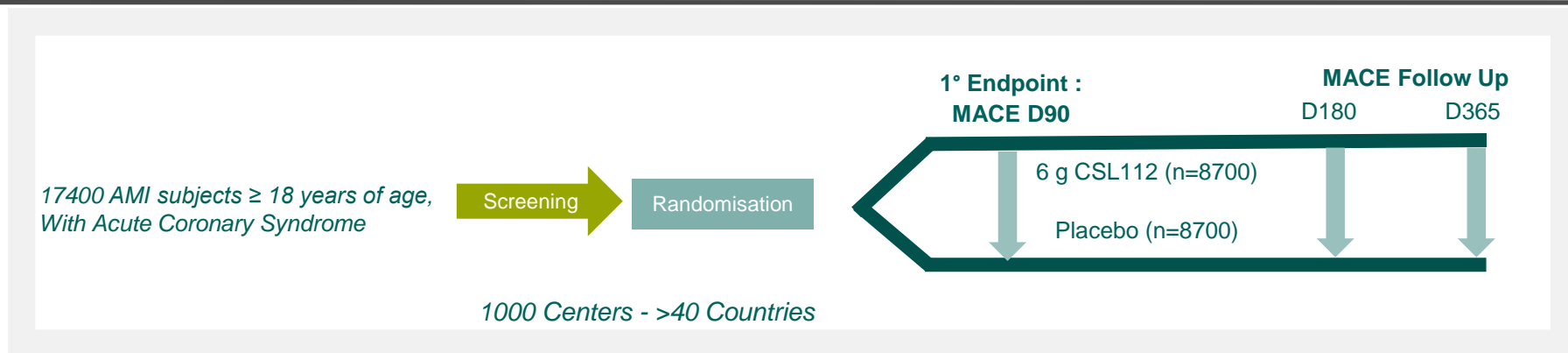
# CSL112 raises Cholesterol Efflux to a similar extent in Patients with and without Moderate Renal Impairment

## Total Cholesterol Efflux Capacity



- At the end of infusion time points, the relative increases in CEC and ABCA1 dependent CEC were similar in both studies
- These efflux results are encouraging as patients with moderate renal impairment tend to experience a greater number of MACE events

# Phase III (AEGIS-II): Study Design



- Enriched Study Population: Multi-vessel coronary artery disease and at least one of the following:
  - Age >65
  - History of MI
  - Diabetes mellitus
  - Peripheral artery disease (PAD)
- Registry data confirms enriched AEGIS-II population is associated with high early recurrent event rate and supports our trial assumptions

# Phase III (AEGIS-II)

## Designed with Health Authority Input

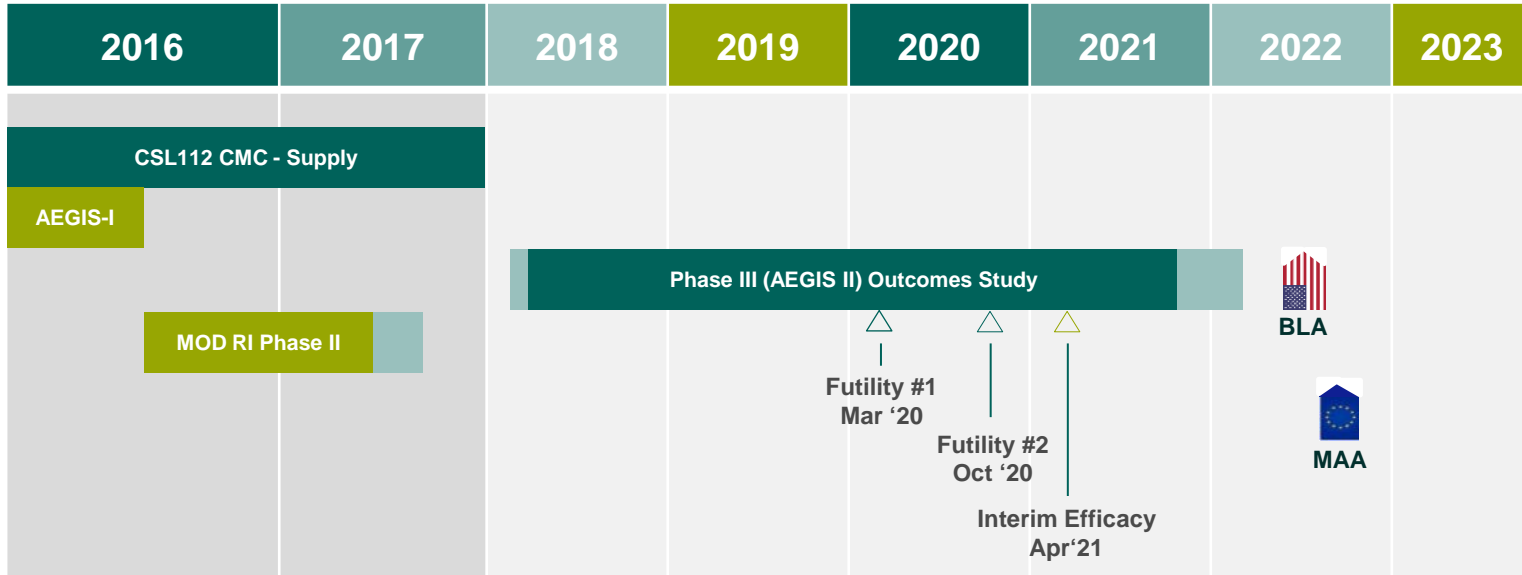


## Designed with International Trialists





# CSL112 Program Timeline



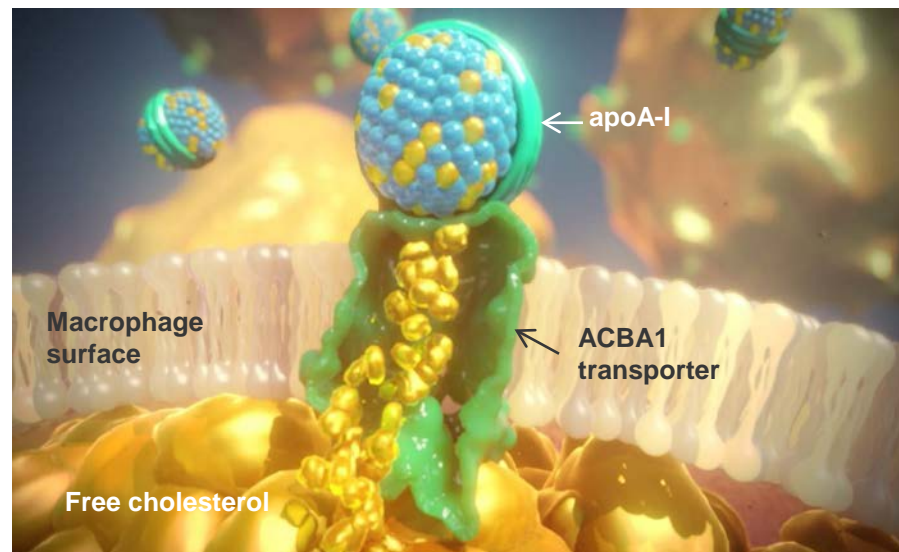
# Breakthrough Medicines Commercial Opportunities

Mr Bill Campbell

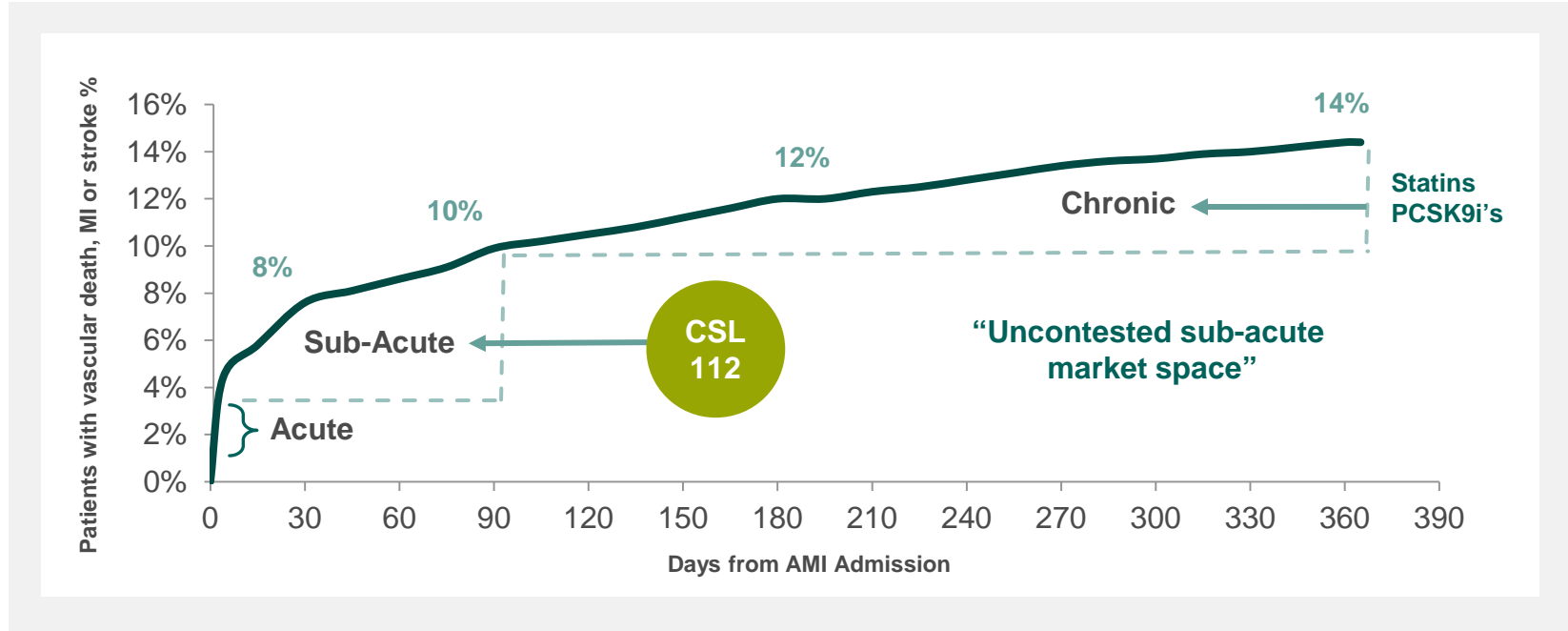
Executive Vice President & Chief Commercial Officer

# CSL112 to Address High Unmet Medical Need

- CVD remains leading cause of death globally
- In the US alone, 800,000 acute MIs occur each year
- Survivors remain at high risk for early recurrent CV events:
- Among high-risk populations:
  - 14% in year one
  - of these ~70% within first 90 days
- Reducing the risk of early recurrent events represents a significant unmet need

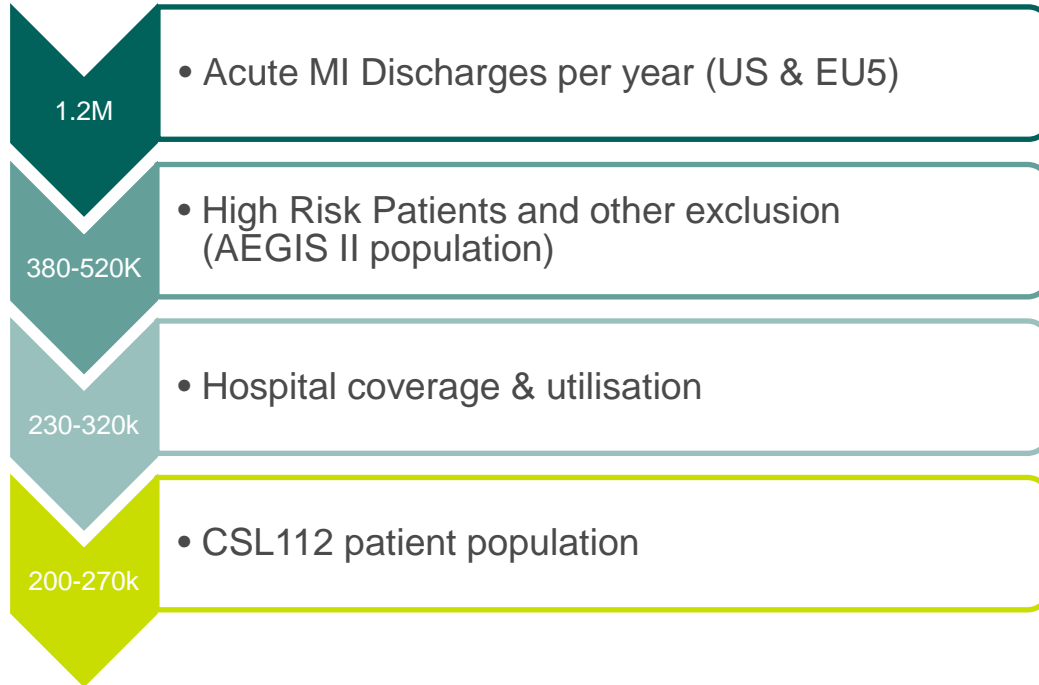


# AEGIS-II Population – High Early Recurrent Event Rate

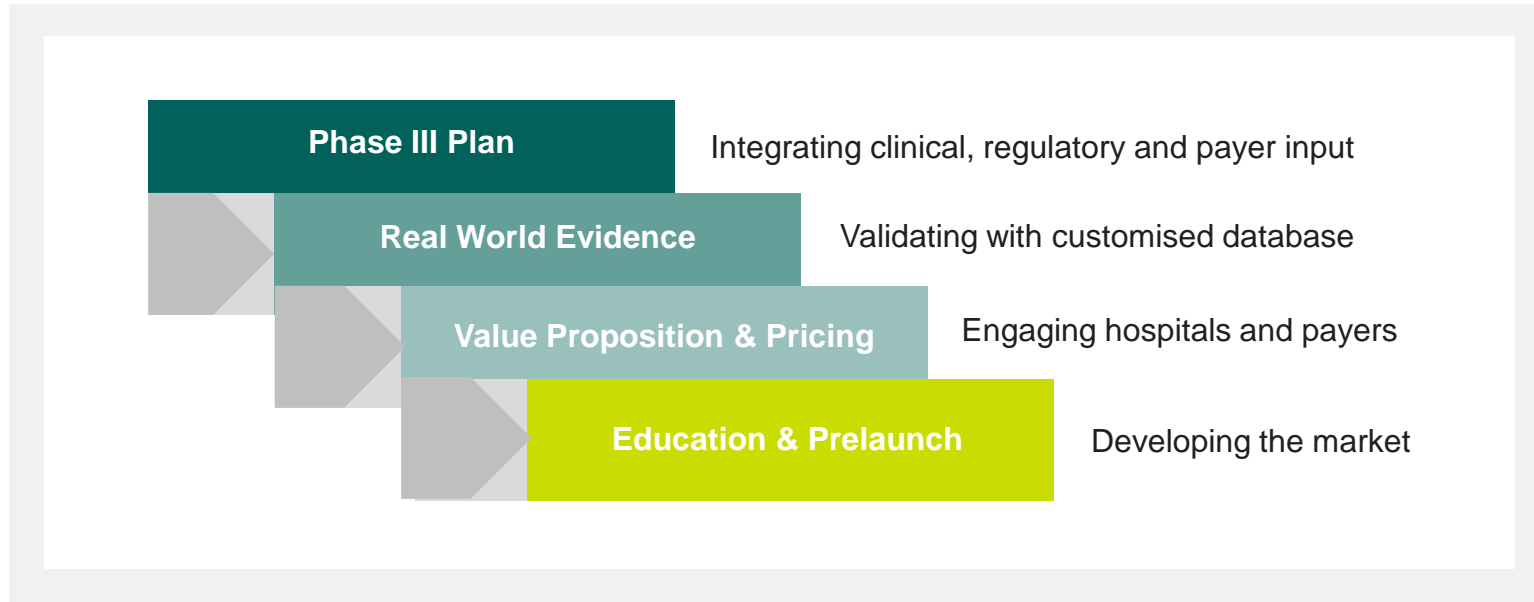


US AMI Registry/Symphony Health Claims Database  
N=75,758 (AEGIS-II eligible);2012-2015

# Significant Opportunity in Sub Acute Space



# CSL112 Strategic Commercial Activities



# Seqirus R&D

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Professor Andrew Cuthbertson AO  
R&D Director and Chief Scientist

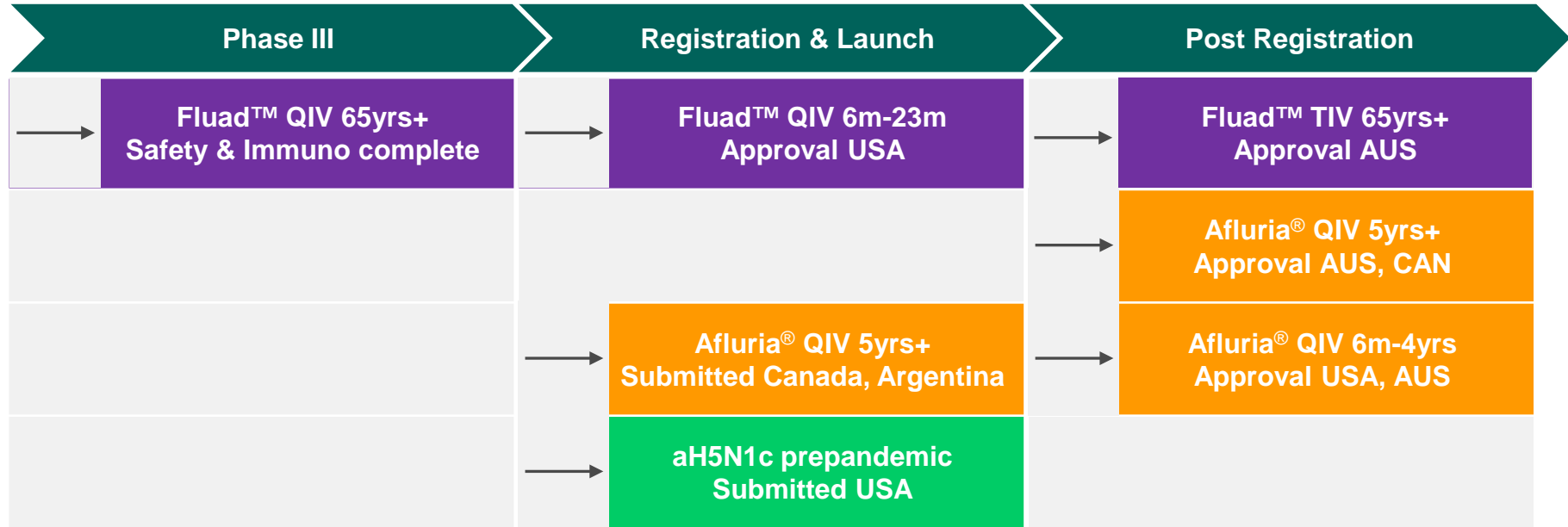


# Highlights of 2017

- **FLUAD™**
  - Approved in UK, strong recommendation for people 65yr and older
  - Holly Springs approved by FDA as a MF59 manufacturing and FLUAD fill-finish site
- **aQIV**
  - Submission for paediatric indication USA (end December)
- **AFLURIA® QIV**
  - 5 years+
    - Approved USA
    - Submitted Australia, Canada, Argentina, Sth Korea
  - 6 months to 4 years
    - Pivotal trial completed – confirms improved safety profile of product
    - Submitted USA, AUS
- **FLUCELVAX® QIV**
  - FDA approval and first commercial manufacture of H3N2 using cell-based seed
  - Manufactured volumes more than quadrupled to 21m doses



# Planned Milestones During 2018



NB: plan to increase QIVc volumes by further 20%

# Summary

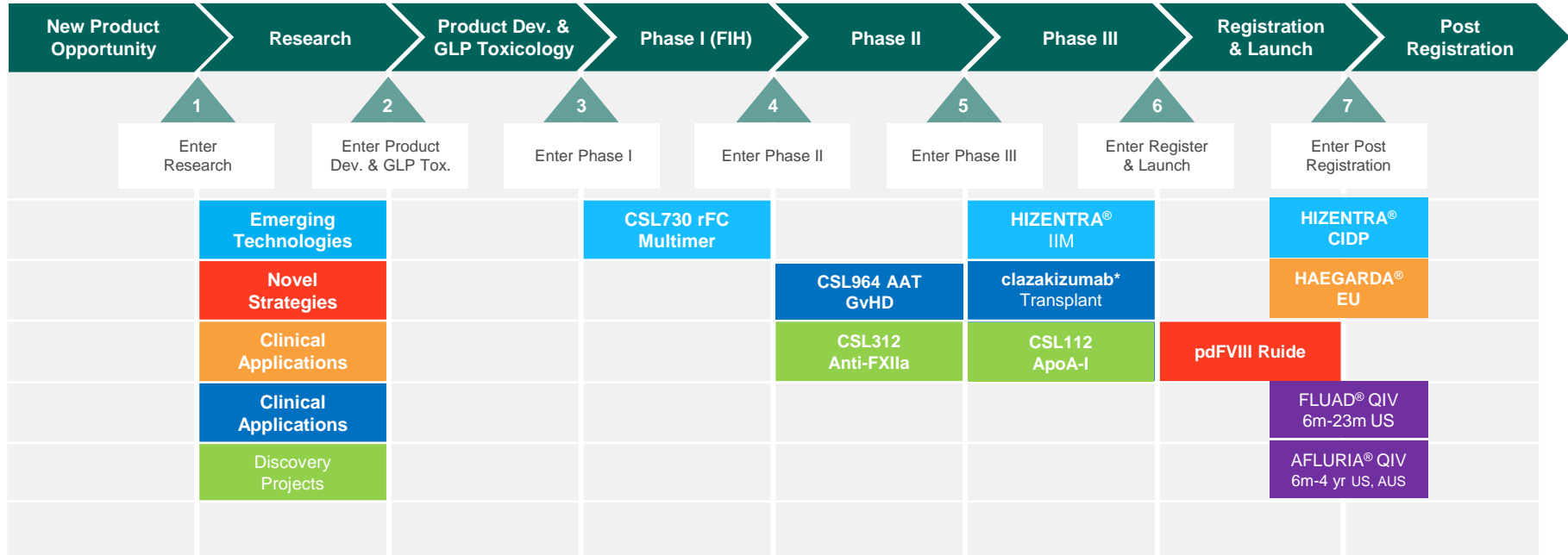
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# R&D Portfolio – December 2017

	RESEARCH	PRE-CLINICAL	PHASE I	PHASE II	PHASE III	REGISTRATION	COMMERCIAL / PHASE IV
Life Cycle Management / Market Development	Clinical Applications	C1-INH New Indications			PRIVIGEN® Japan	HIZENTRA® CIDP	PRIVIGEN® CIDP US
		Fibrinogen New Formulations			HIZENTRA® IIM		KCENTRA® Japan
		Haptoglobin/Hemopexin		CSL964 AAT GvHD		HAEGARDA® EU	HAEGARDA® US
		CSL640 rIX-FP subct			PRIVIGEN® CIDP Japan	AFLURIA® QIV 5-17 AUS	FLUAD® TIV 65+ US, UK
					CSL842 C1-INH AMR		FLUCELAX® QIV 4+ US
							AFLURIA® QIV 5-17 US
New Product Development	Emerging Technologies	CSL730 rFc Multimer			clazakizumab* Transplant		IDELVION®
	Novel Strategies	CSL626 D'D3 LA rVIII	CSL312 Anti-FXIIa	Mavri GM-CSFR-AZ*	pdFVIII Ruide		AFSTYLA®
	Discovery Projects	CSL334 IL-13R* ASLAN	CSL324 Anti-G-CSFR				
	Clinical Applications	CSL311 Anti-BC	CSL346 Anti-VEGF-B		CSL112 ApoA-I		
		P. gingivalis/POD* OH-CRC					

Core Capabilities: [Immunoglobulins](#) | [Haemophilia](#) | [Specialty Products](#) | [Breakthrough Medicines](#) | [Vaccines & IP](#) | [Transplant](#)

# Expected Progress in Next 12 Months



Core Capabilities: [Immunoglobulins](#) | [Haemophilia](#) | [Specialty Products](#) | [Breakthrough Medicines](#) | [Vaccines & IP](#) | [Transplant](#)

# Significant Target Launch Dates

2017	2018	2019	2020-2023
PRIVIGEN® CIDP US	HIZENTRA® CIDP US/EU	PRIVIGEN® CIDP Japan	Hizentra® IIM
		PRIVIGEN® PID/SID Japan	
		HIZENTRA® CIDP Japan	
AFSTYLA® EU/Japan		pdFVIII Ruide	
CSL830 HAEGARDA® US	CSL830 EU		
KCENTRA® Japan			
			CSL112 ApoA-I
AFLURIA® QIV 5-17yr US	AFLURIA® QIV 6m-4yr US	AFLURIA® QIV 6m-5yr AUS	
	AFLURIA® QIV 5-17yr AUS	QIV EU	
	FLUAD® QIV 6m-23m US		
			CSL842 C1-INH AMR
			clazakizumab* Transplant

Core Capabilities: [Immunoglobulins](#) | [Haemophilia](#) | [Specialty Products](#) | [Breakthrough Medicines](#) | [Vaccines & IP](#) | [Transplant](#)

# 2017 Highlights

## Immunoglobulins

- PRIVIGEN® CIDP approved in US
- HIZENTRA® CIDP accepted for review by US FDA and EMA
- Momenta collaboration to develop CSL730 (rFC Multimer)

## Specialty Products

- HAEGARDA® results in 95% reduction in HAE attacks and >99% reduction in rescue medication and new standard of care for HAE
- HAEGARDA® registered and launched in the US

## Haemophilia

- IDELVION® dosage extension study supports 21 day regimen
- AFSTYLA® registered in EU, Japan and Australia

## Transplant

- CSL842 (C1INH) Phase III study in kidney AMR commenced
- Strategic collaboration and option agreement with Vitaeris to develop clazakizumab (anti-IL6 MAb) as a therapeutic option for AMR

## Breakthrough Medicines

- Data supports decision to proceed to CSL112 (Apo A-1) Phase III study (AEGIS-II)
- CSL346 (anti-VEGF-B) Phase I study commenced
- Completion of CSL312 (anti-FXIIa) HAE Phase I study
- Acquisition of Calimmune platform gene therapy technology and CAL-H SCD program

## Licensing & Vaccines

- AFLURIA® QIV registered in US in 5+ yrs; 6mnths-4yrs trial completed
- FLUAD® registered in UK, strong recommendation for people 65yr and older

# Q&A

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# Further Information

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## **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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