R&D Briefing

December 5, 2013

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Trademarks

Agenda December 2013 R&D Briefing

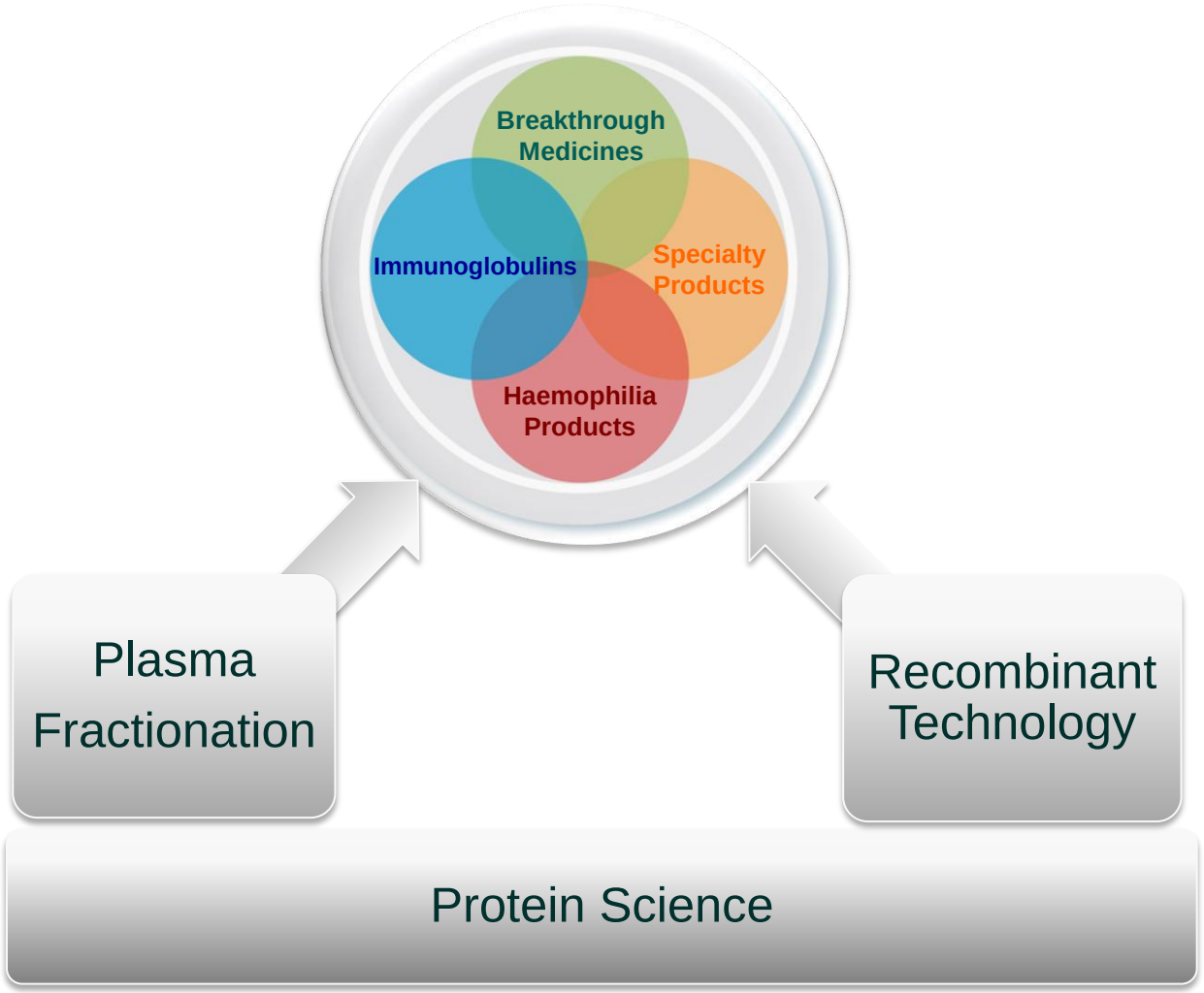
• Welcome	Mark Dehring
• Introduction & Highlights	Andrew Cuthbertson
• Protein Science	Andrew Nash
• Immunoglobulins & Specialty Products	
◦ Clinical Development	Russell Basser
◦ Commercial Opportunities	Lutz Bonacker
• Q&A	

Break

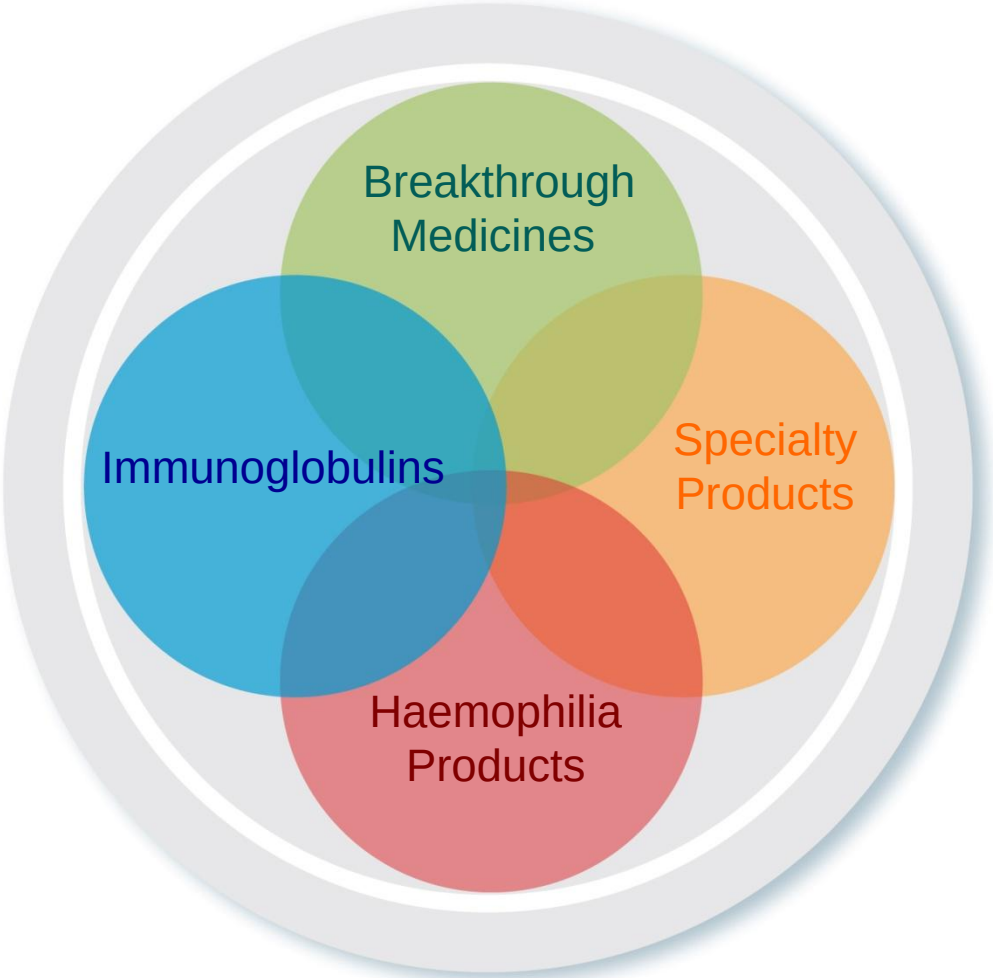
• Coagulation/Haemophilia	
◦ Clinical Development	Russell Basser
◦ Commercial Opportunities	Lutz Bonacker
• Breakthrough Medicines & Licensing	Andrew Cuthbertson
• Summary	Andrew Cuthbertson
• Q&A	

Introduction and Highlights

CSL Protein Therapeutics Technical Platform



CSL R&D Strategy



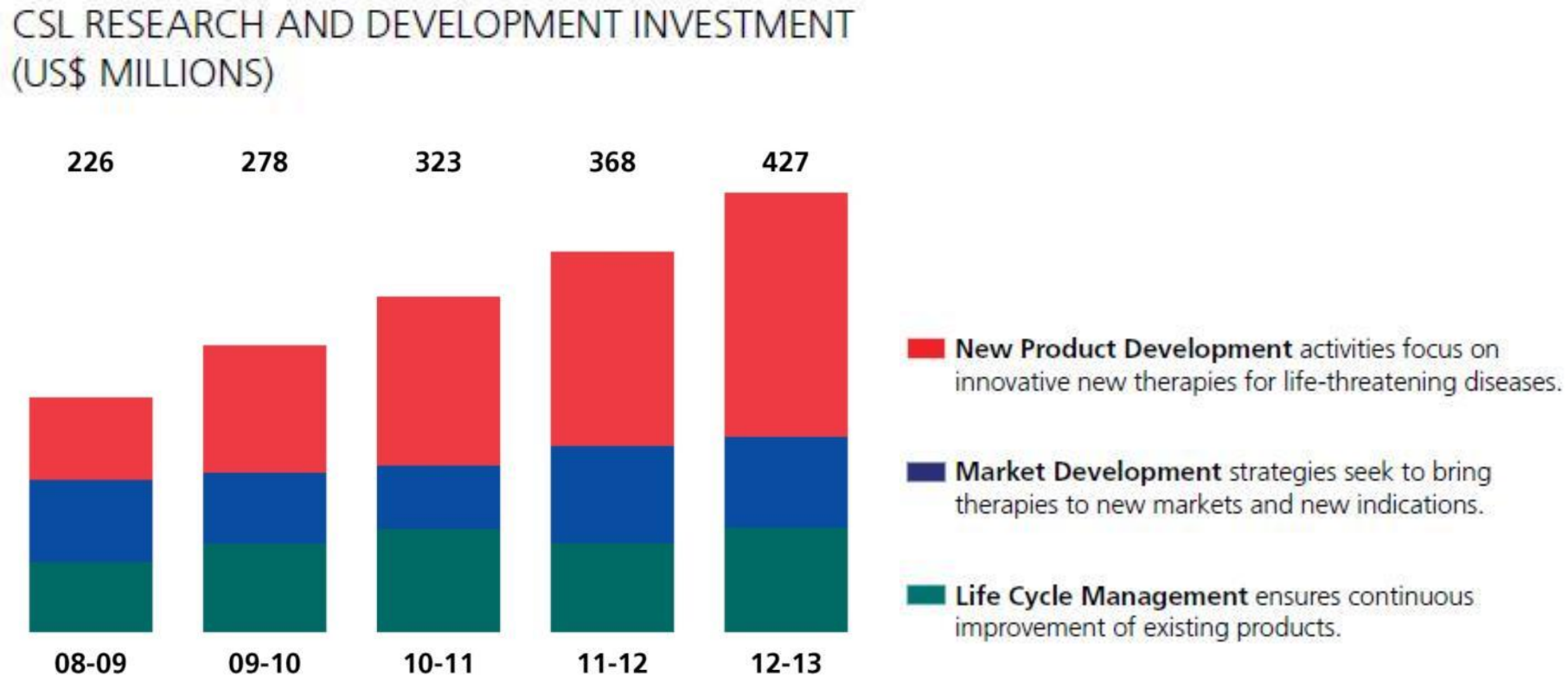
- Maintain commitment to extracting maximum value from existing assets and supporting and improving current products
- Develop new protein-based therapies for treating serious illnesses focusing on products that align with our technical and commercial capabilities

Leveraging Global Capabilities

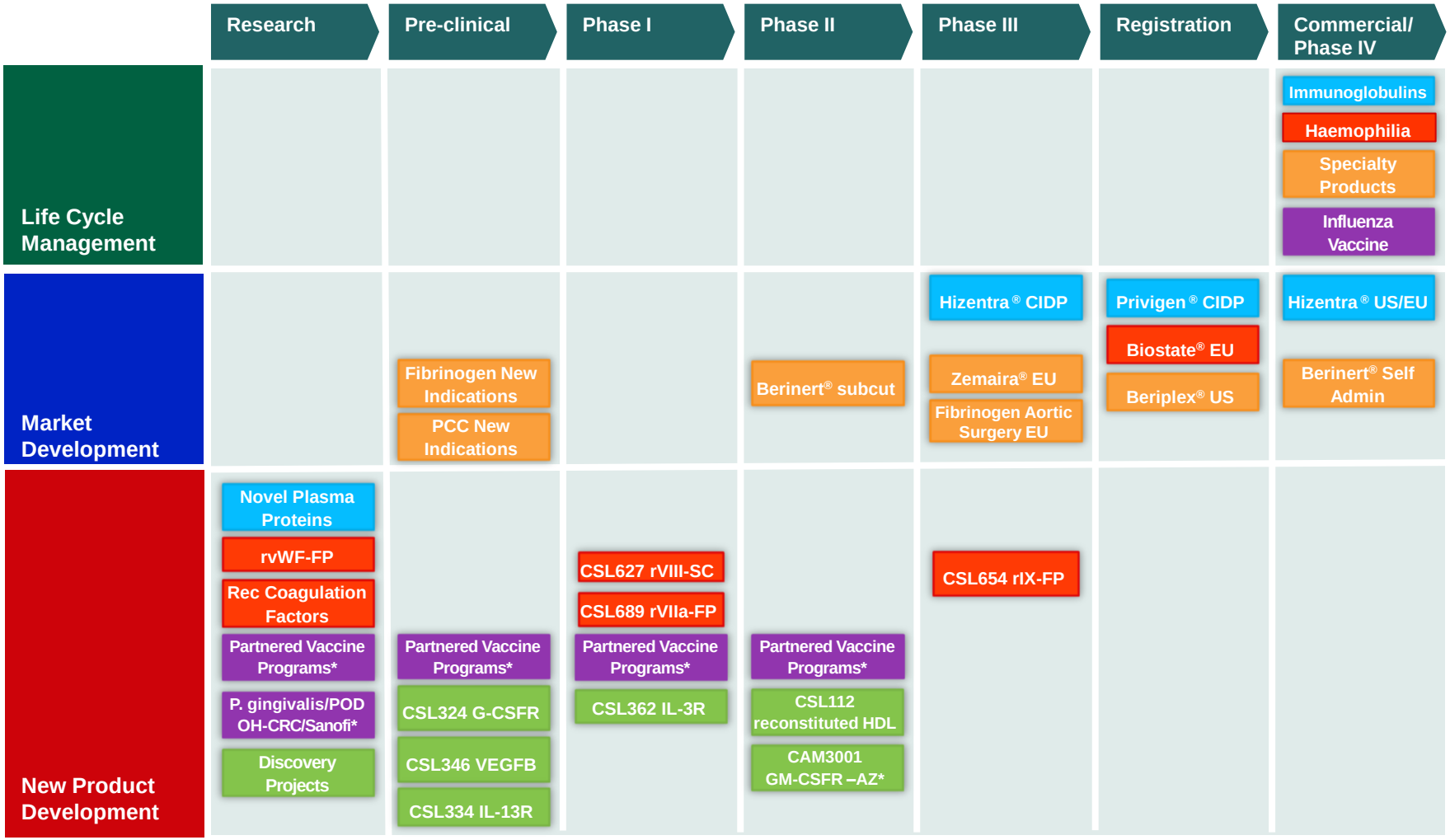
Bern	Broad-meadows	Kankakee	King of Prussia	Marburg	Parkville	Tokyo

Integration via project management processes

R&D Investment



Global R&D Portfolio December 2012

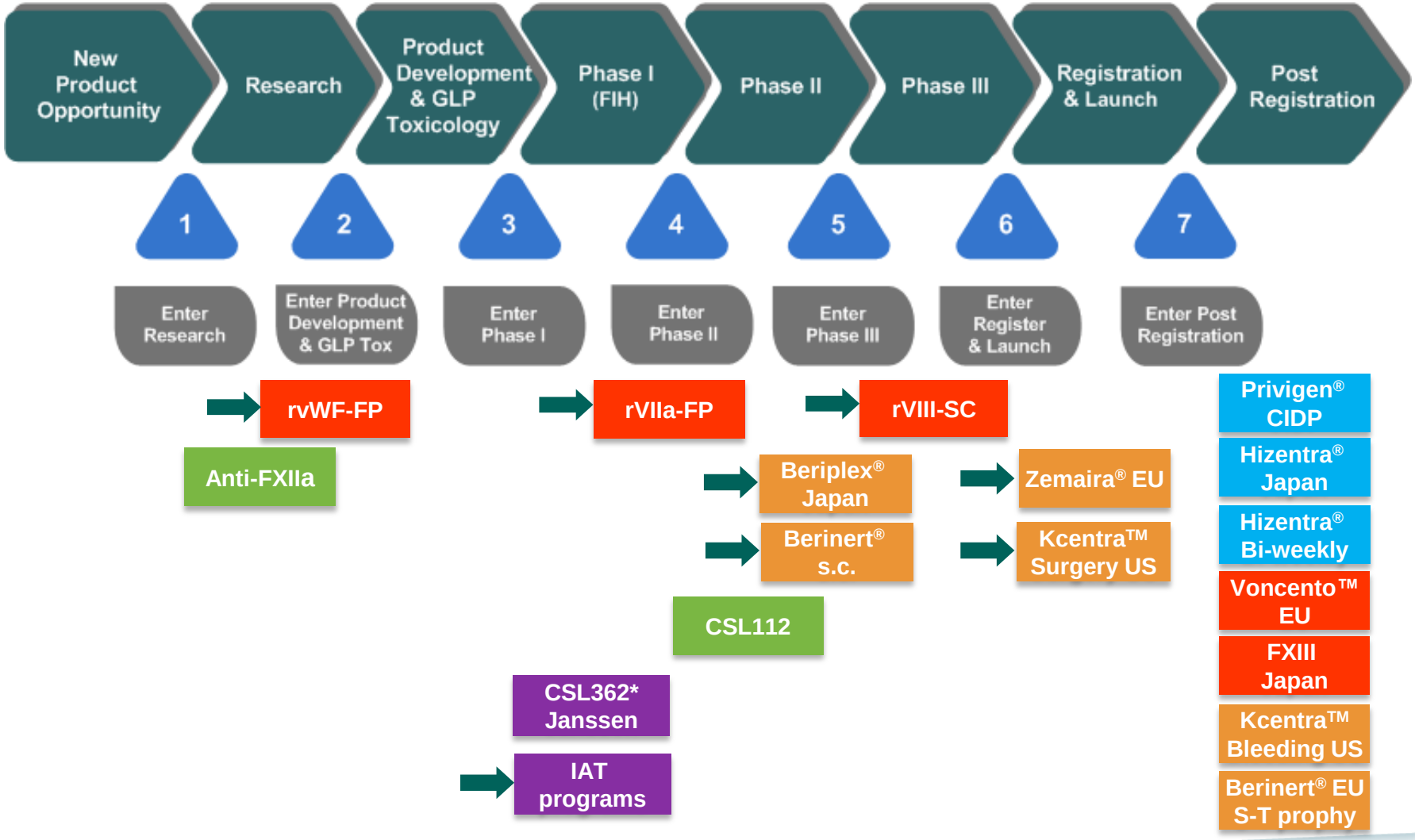


Core Capabilities: Immunoglobulins | Haemophilia | Specialty Products | Breakthrough Medicines | Vaccines & IP

***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

Progress through Stage Gates in 2013



Protein Science

CSL's Global Research Capability

- ~130 of 1000 scientists dedicated to research
- Hub & spoke model
- Single coordinated project portfolio
- Research excellence in therapeutic proteins
- Plasma and recombinant manufacturing platforms



Bio21 - Research Hub

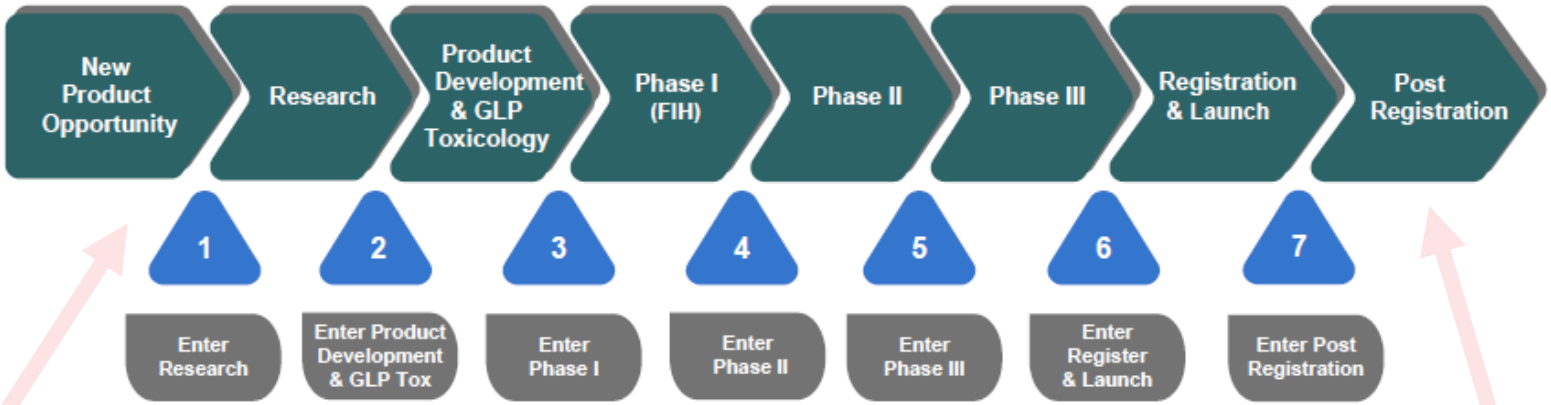
- Located within world class university, medical research and hospital precinct in Parkville
- Technical expertise
  - protein engineering, molecular biology, cell biology, models of disease, genomics / bioinformatics
- Improved access to
  - high quality staff
  - cutting edge technologies
  - ideas / innovations / collaborations
  - patients and patient samples
- Model for Biotech / Pharma Research
  - decentralisation into high quality academic research hubs

CSL Research Key Objectives

Deliver new development opportunities to SG2

Scientific support beyond SG2

Resolve critical scientific issues



Assess new product opportunities and emerging threats

Add value to the existing CSL product portfolio:
- yield improvements
- improved formulations
- new indications

Innovation in Key Areas of CSL's Business

Immunoglobulins

- PID - convenience
- Non-PID – efficacy / convenience

Haemophilia

- convenience / quality of life

Specialty Products

- product specific but.....
- efficacy / convenience

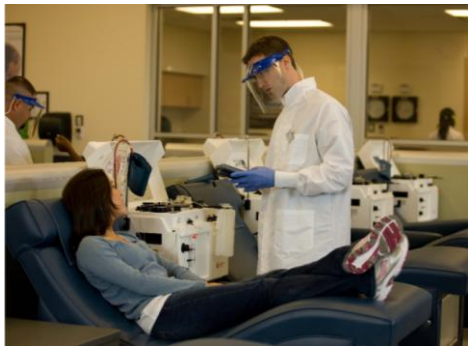
Breakthrough Medicines

- efficacy

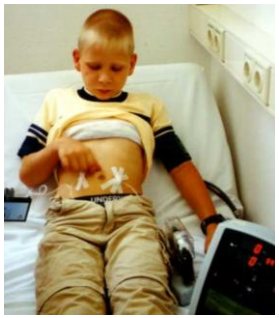
Plasma Proteins

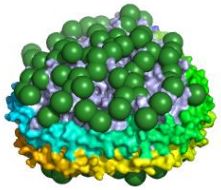
- Capabilities from discovery to market

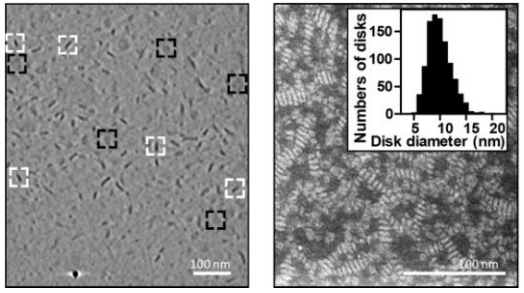
Plasma collection



Plasma fractionation

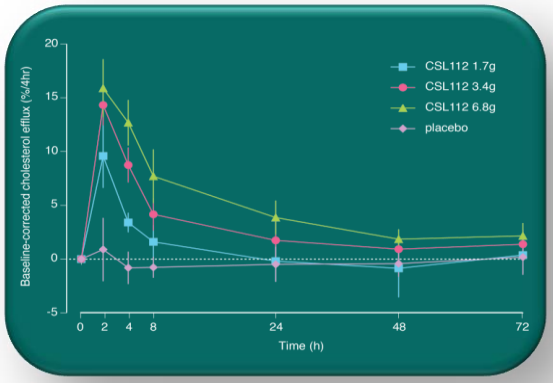






Electron microscopy of CSL112

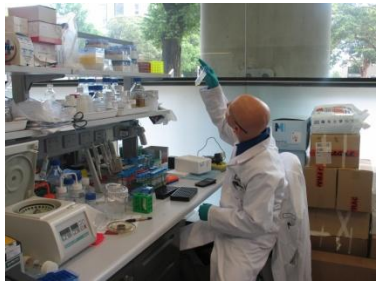
Completed Phase IIa - Strong increase in cholesterol efflux capacity



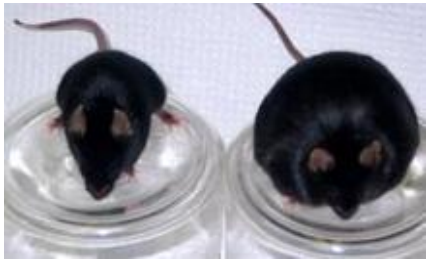
Recombinant Proteins

- Capabilities from discovery to market

Protein Engineering Lab



Animal models of disease



Manufacturing CLD Lab

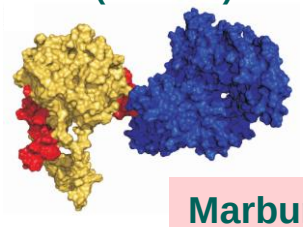
Phase I / II manufacturing

Phase III / launch manufacturing

Patient

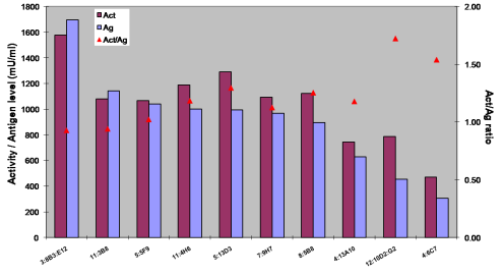
CSL654 (rIX-FP) – Discovery to Development

Factor IX fused to human albumin (CSL654)



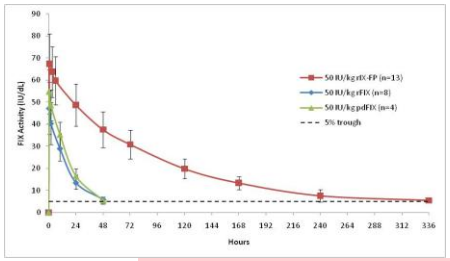
Marburg

CSL654 manufacturing CHO clones

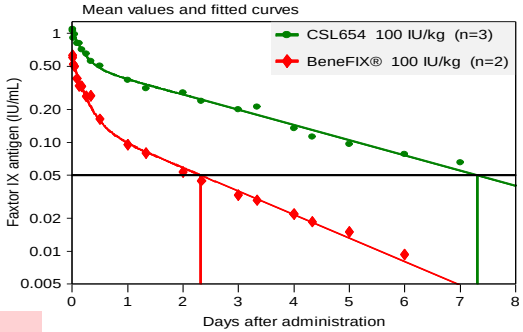


Bio21

CSL654 $T_{1/2}$ extension in Haem B patients compared to Benefix



King of Prussia



Marburg

CSL654 $T_{1/2}$ extension in Haem B dogs compared to Benefix

Parkville

500L fed batch fermentation

Research Publications

Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients

Elena Santagostino,[1] Claude Negrier,[2] Robert Klamroth,[3] Andreas Tiede,[4] Ingrid Pabinger-Fasching,[5] Christine Voigt,[6] Iris Jacobs,[6] and Massimo Morfini[7]

[1]Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda Foundation, Maggiore Hospital Policlinico, Milan, Italy; [2]Centre Régional de Traitement de l'Hémophilie, Hôpital Edouard Herriot, University Claude Bernard, Lyon, France; [3]Haemophilia Treatment Centre, Vivantes Klinikum im Friedrichshain, Vivantes Hospital, Berlin, Germany; [4]Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany; [5]Division of Haematology and Haemostaseology, Department of Internal Medicine I, Medical University of Vienna, Wien, Austria; [6]Clinical Research and Development, CSL Behring, King of Prussia, PA; and [7]Centro Emofilia, Azienda Ospedaliera Careggi, Florence, Italy

blood

Targeting VEGF-B as a novel treatment for insulin resistance and type 2 diabetes

Carolina E. Hagberg[1,2]*, Annika Mehlem[1]*, Annelie Falkevall[1,2], Lars Muhl[1,2], Barbara C. Fam[3], Henrik Ortsäter[4], Pierre Scotney[5], Daniel Nyqvist[1], Erik Samén[6,7], Li Lu[6], Sharon Stone-Elander[6,7], Joseph Proietto[3], Sofianos Andrikopoulos[3], Åke Sjöholm[4], Andrew Nash[5] & Ulf Eriksson[1]

nature

Scientific investigations into febrile reactions observed in the paediatric population following vaccination with a 2010 Southern Hemisphere Trivalent Influenza Vaccine

Eugene Maraskovsky[a,*,1], Steve Rockman[a], Allison Dyson[a], Sandra Koernig[a], Dorit Becher[a], Adriana Baz Morelli[a], Megan Barnden[a], Sarina Camuglia[a], Jesse Bodle[a], Kirsten Vandenberg[a], I-Ming Wang[b], Razvan Cristescu[b], Andrey Loboda[b], Mike Citron[b], Jane Fontenot[b], Derchieh Hung[a], Peter Schoofs[a], Martin Pearse[a]

Vaccine

Interleukin-11 Is the Dominant IL-6 Family Cytokine during Gastrointestinal Tumorigenesis and Can Be Targeted Therapeutically

Tracy L. Putoczki,[1,6,10,11,*] Stefan Thiem,[1,10,11] Andrea Loving,[1] Rita A. Busuttil,[3,4,5] Nicholas J. Wilson,[2] Paul K. Ziegler,[7] Paul M. Nguyen,[1,10,11] Adele Preaudet,[1,10,11] Ryan Farid,[1,10,11] Kirsten M. Edwards,[2] Yeliz Boglev,[1] Rodney B. Luwor,[6] Andrew Jarnicki,[1,12] David Horst,[8] Alex Boussioutas,[3,4,5] Joan K. Heath,[1,10,11] Oliver M. Sieber,[1,10,11] Irina Pleines,[9] Benjamin T. Kile,[9] Andrew Nash,[2] Florian R. Greten,[7] Brent S. McKenzie,[2] and Matthias Ernst[1,6,10,11,*]

Cancer Cell

Intravenous Immunglobulin Binds Beta Amyloid and Modifies Its Aggregation, Neurotoxicity and Microglial Phagocytosis *In Vitro*

Susann Cattepoel[1]*, Alexander Schaub[1], Miriam Ender[1], Annette Gaida[1], Alain Kropf[1], Ursula Guggisberg[1], Marc W. Nolte[2], Louis Fabri[3], Paul A. Adlard[4], David I. Finkelstein[4], Reinhard Bolli[1], Sylvia M. Miescher[1]

1 CSL Behring AG, Bern, Switzerland, **2** CSL Behring GmbH, Marburg, Germany, **3** CSL Limited, Melbourne, Australia, **4** Mental Health Research Institute, Parkville, Australia

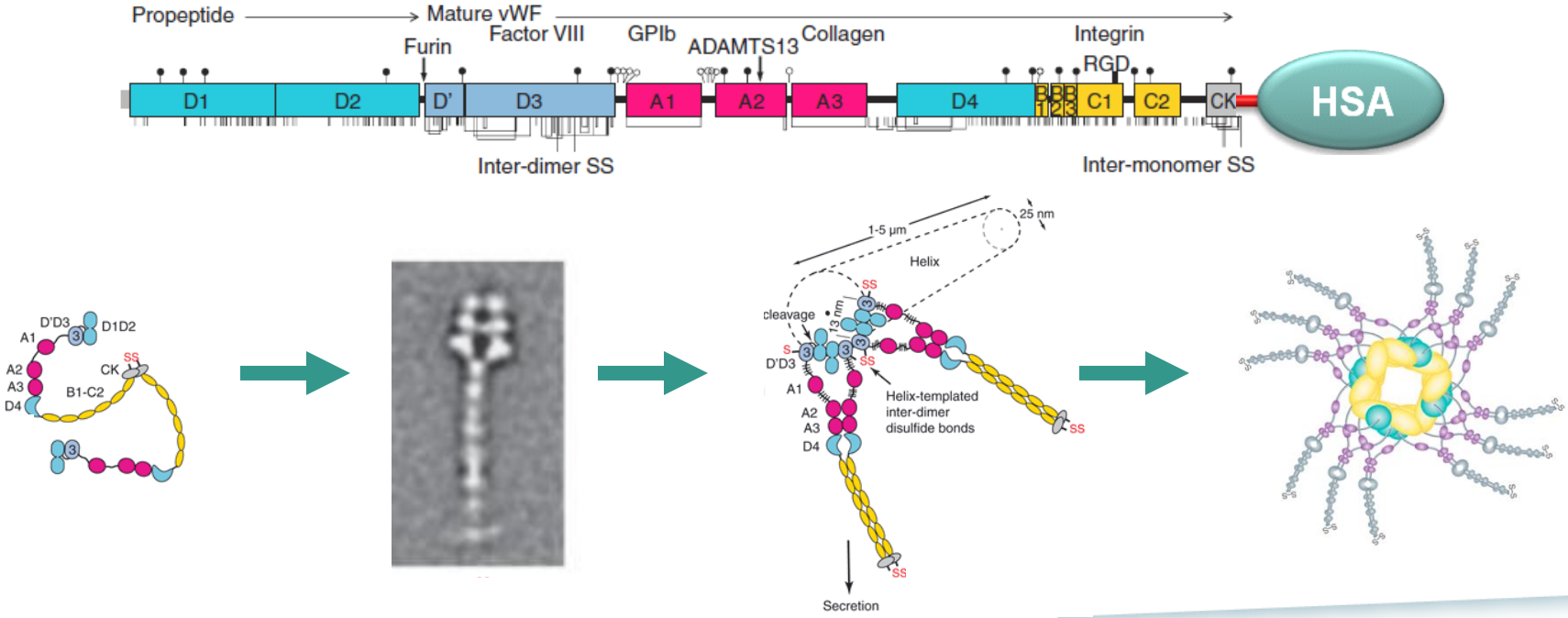
PLOS | ONE

CSL™

Plasma and Recombinant Synergies

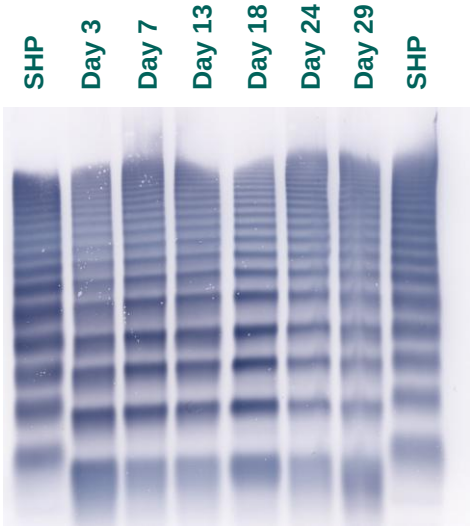
Plasma therapeutics expertise / new recombinant therapies

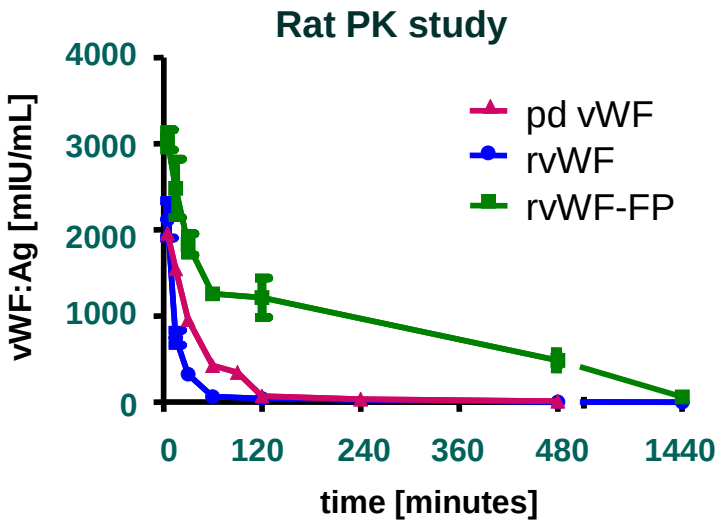
- Recombinant coagulation factors
  - CSL654 / rIX-FP, CSL689 / rVIIa-FP, CSL627 / rVIII-SingleChain
  - CSL650 / rvWF-FP



CSL650 (rvWF-FP)

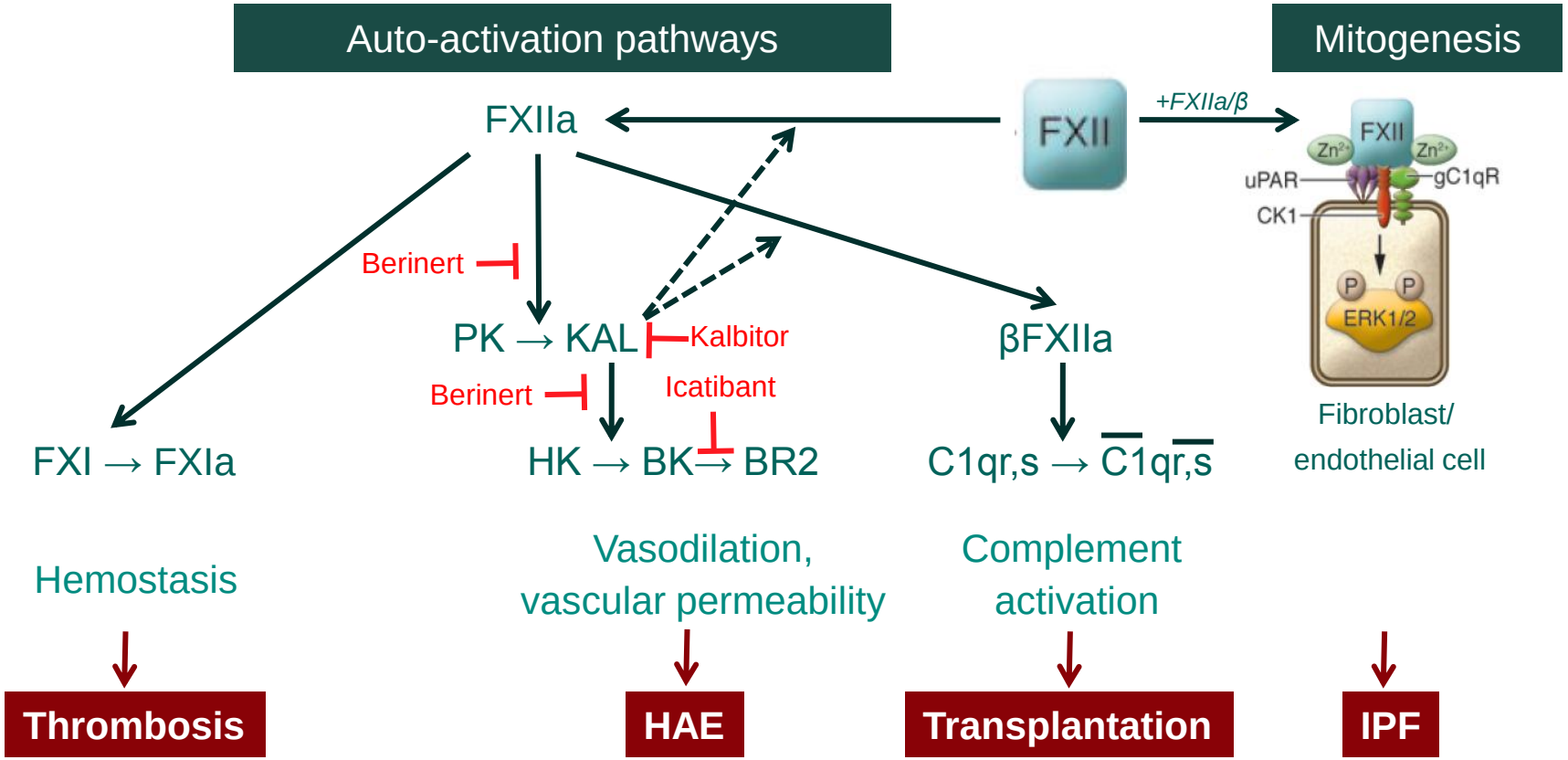
- vWF-FP expressed in CHO cells forms multimers and demonstrates an extended half-life





Animal	Half-life extension
VWF k.o. mouse	4x
rat	5x
rabbit	4x

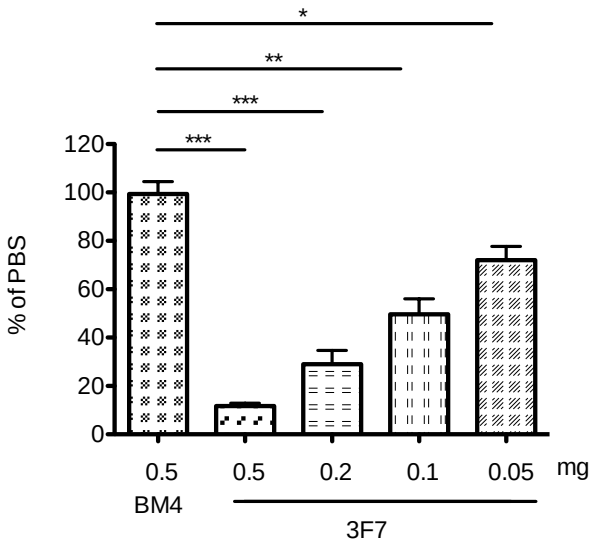
FXIIa Antagonists



FXIIa Antagonist mAb - HAE

Percutaneous anaphylaxis, a mouse model of HAE

- anti-FXIIa mAb 3F7 inhibits edema



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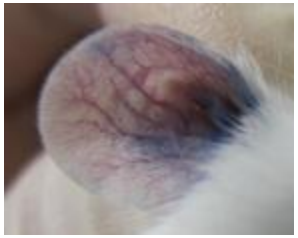
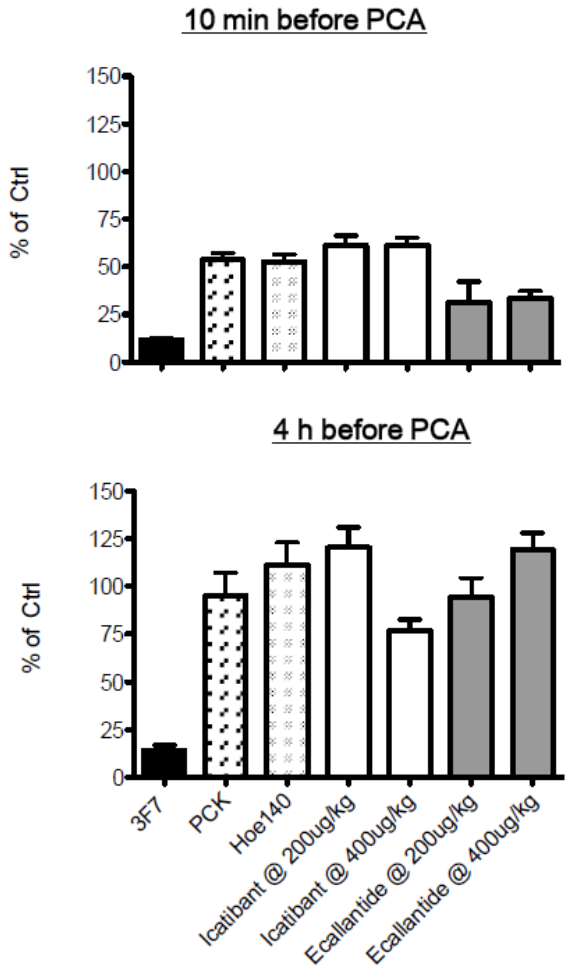
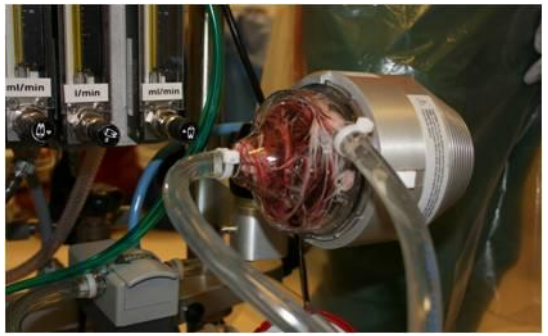


3F7



FXIIa Antagonist mAb - Thrombosis

- Extracorporeal membrane oxygenation (ECMO)
- Heparin coated circuits and heparin infusion are required to prevent thrombosis
- Bleeding is the most frequent complication
  - intracerebral hemorrhage (particularly new borns)
  - pulmonary hemorrhage
  - bleeding into chest cavity following cardiac surgery etc.



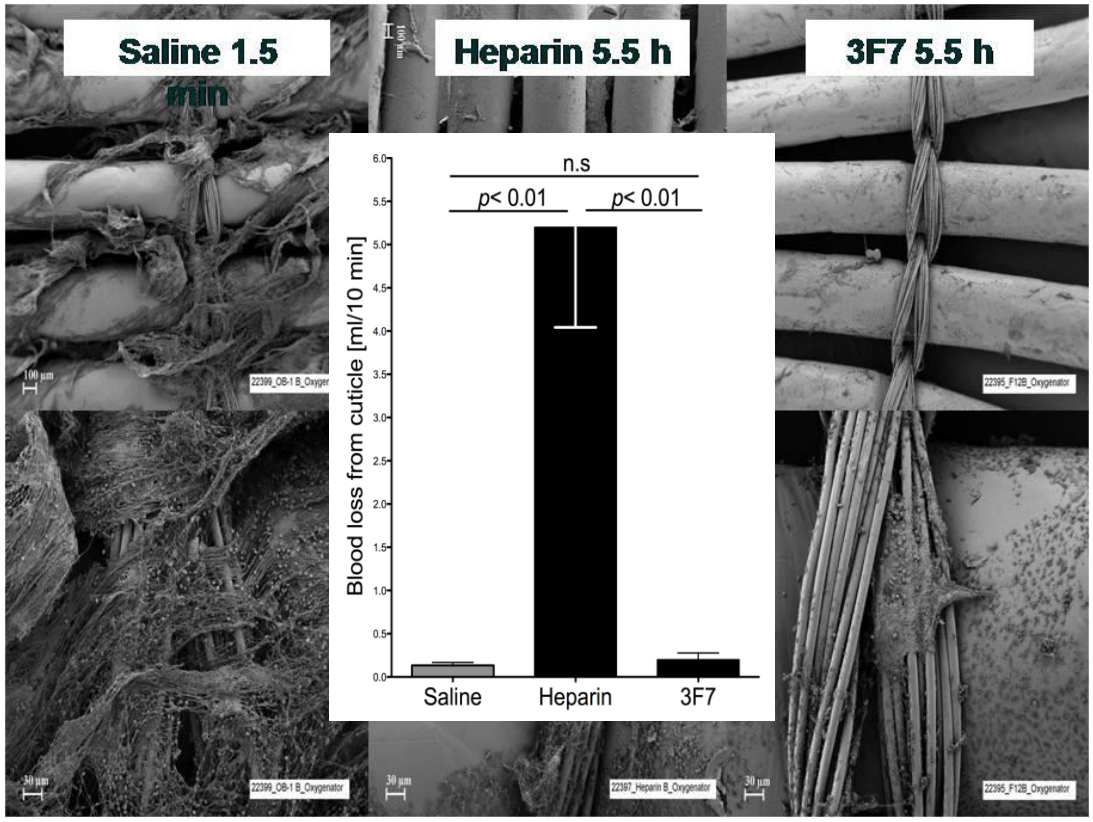
need for thromboprotection without increasing bleeding risk

- In certain circumstances inhibition of FXIIa prevents thrombosis without increased bleeding risk

FXIIa Antagonist mAb - Thrombosis

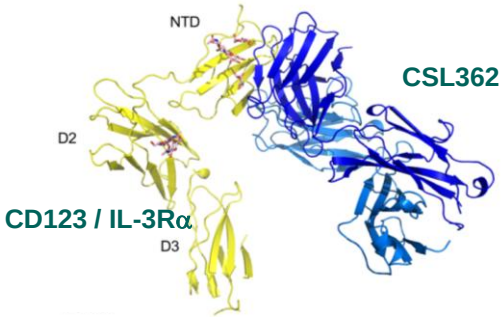
ECMO-rabbit model

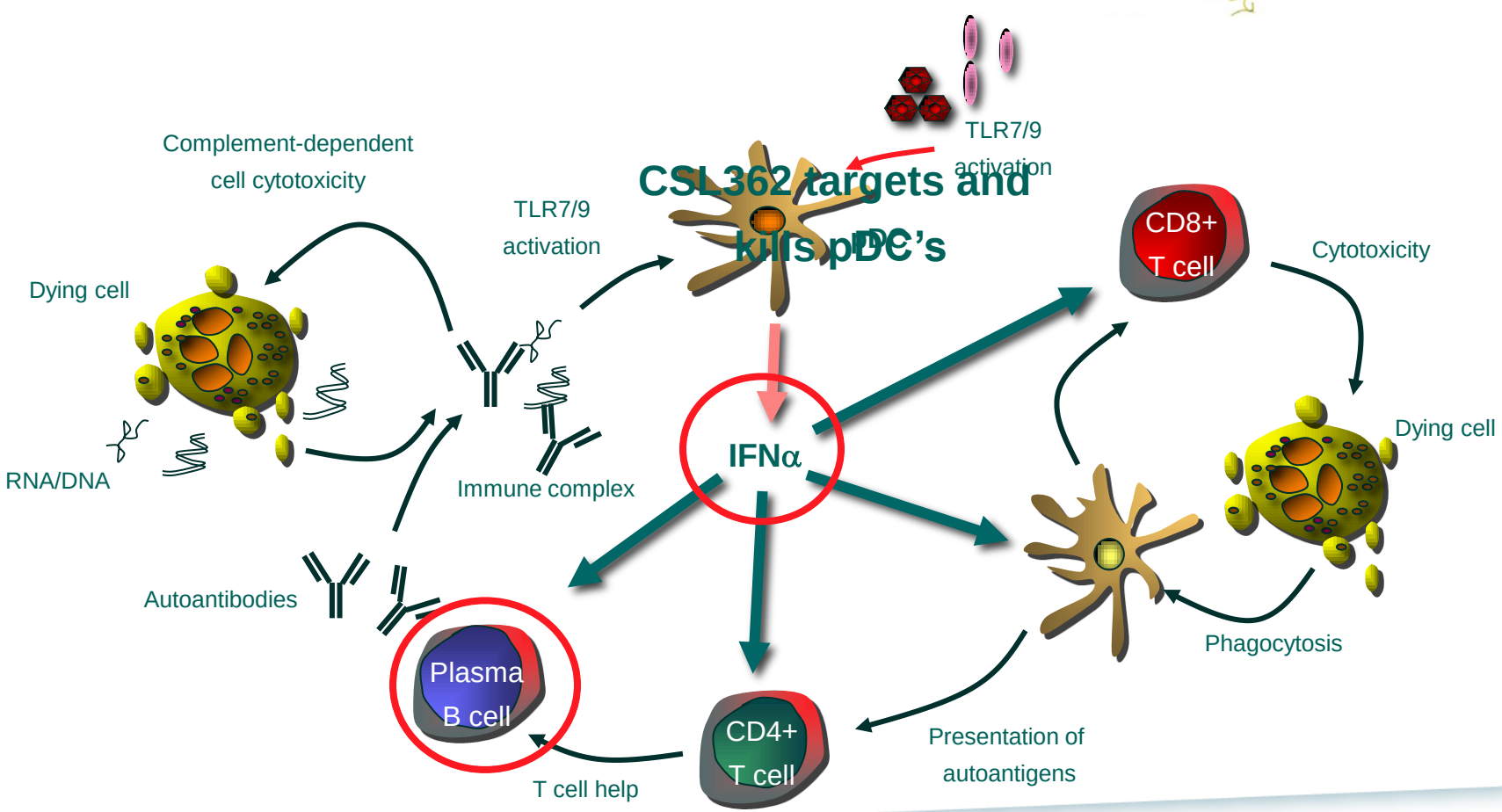
- anti-FXIIa mAb 3F7 prevents fibrin deposition with no increased risk of bleeding



CSL362 for the Treatment of SLE

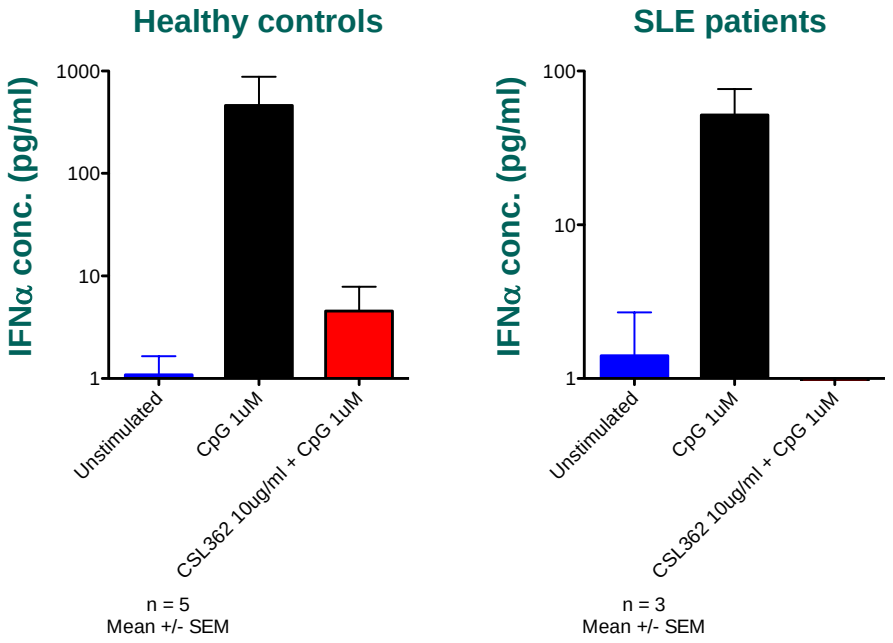
- Proposed role for pDC's in SLE

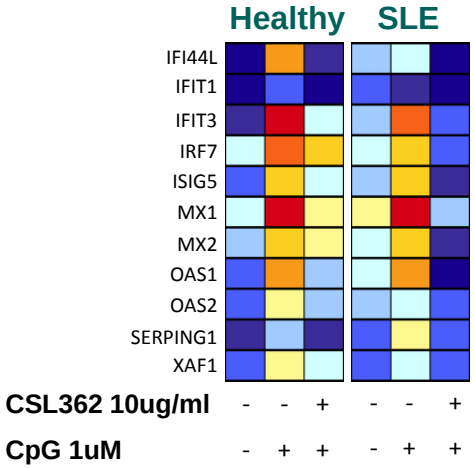




CSL362 for the Treatment of SLE (Lupus)

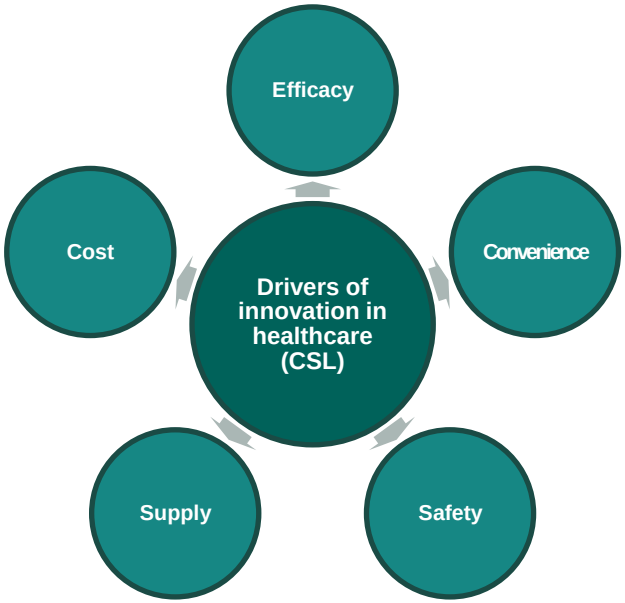
- CSL362 prevents IFNα production in blood from normal donors and SLE patients





CSL Research and Protein Science

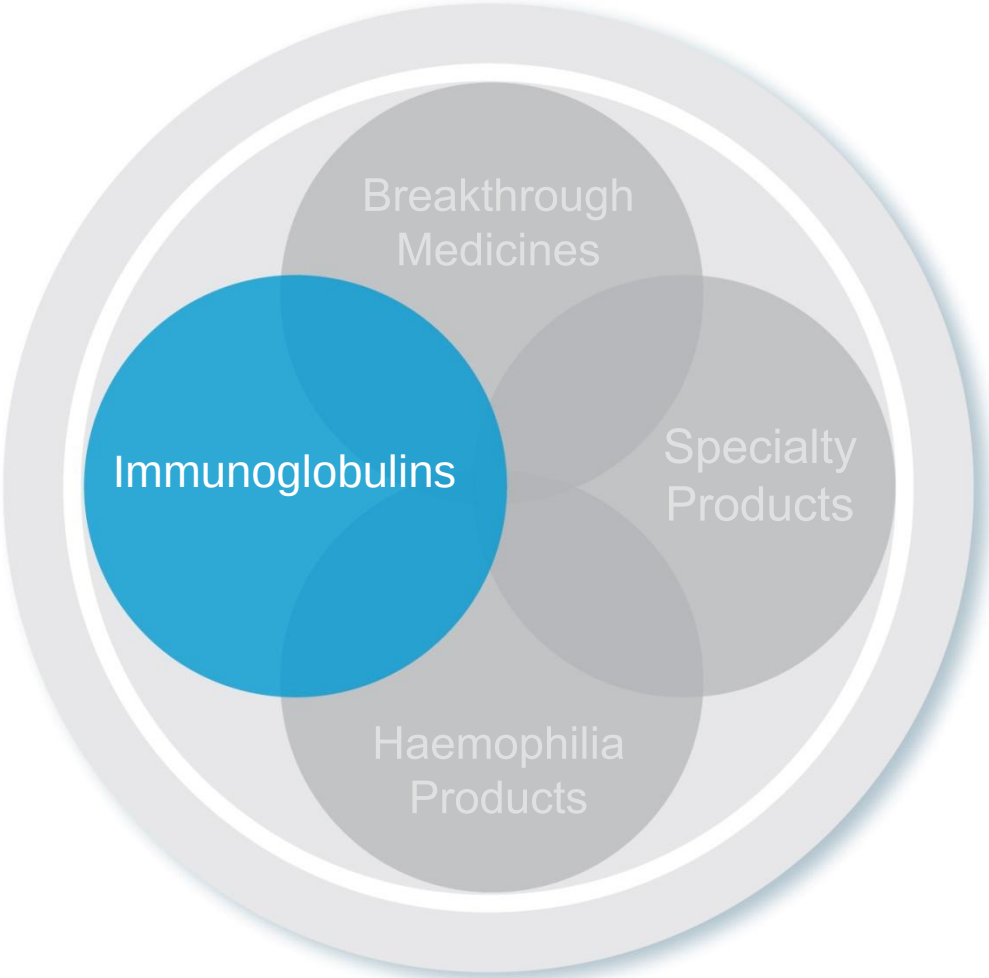
- High quality research capability to generate new development opportunities and address key scientific issues
- Expertise to identify and progress opportunities using both plasma and recombinant protein platforms



- Global coordination of research capability to target highest priority projects
- Portfolio of early stage projects to progress through CSL Stage Gate 2 and beyond

Immunoglobulins

Immunoglobulins



Maintaining leadership position through focus on:

- Patient convenience
- Yield
- Label
- Formulation science
- Specialty Igs

Key Focus

- Privigen®
- Hizentra®

Privigen®

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

Strengthening Presence in Neurology Market

- Phase III study showed treatment with Privigen® improved function in patients with CIDP
- EMA approval for treatment of patients with CIDP in April 2013

Building Capacity to Address Patient Needs Globally

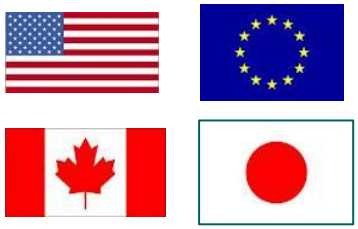
- New Ig manufacturing facility in Broadmeadows

Hizentra®

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

Global Rollout

- Launched in US since 2010
- Broad approvals in EU and Canada
- Approval in Japan for PID and SID in Sept 2013
  - First SCIg therapy approved for use in Japan



The PATH Trial: Hizentra® in CIDP

- 2 doses vs placebo
- Ongoing in US, EU & Japan
- Recruitment estimated to be completed by end 2014

Hizentra® Schedules

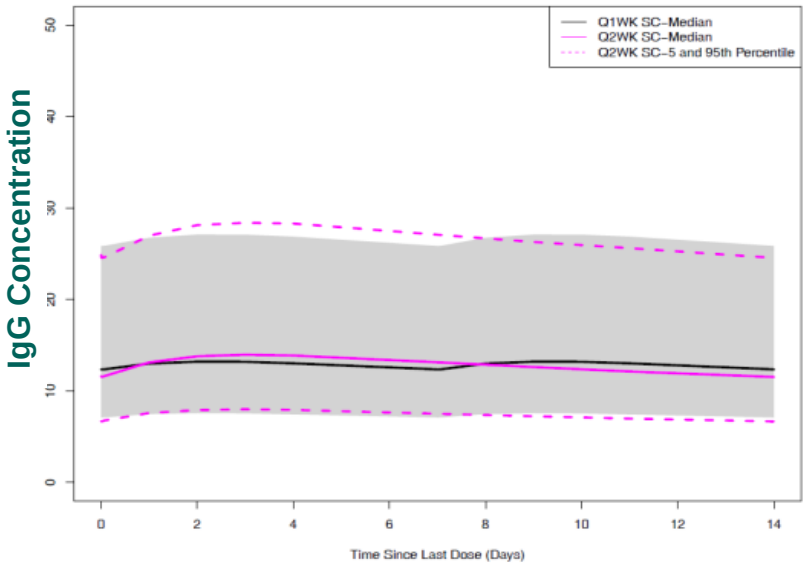
US administration options expanded to include dosing once every two weeks (biweekly) in Sept 2013

- FDA and EU approval of biweekly dosing based on principles of pharmacometrics and pharmacokinetic modelling of clinical trial data from registration program

Pharmacometrics

Clinical Pharmacology | **Biostatistics**

Simulation of SCIG q1W & q2W PK



From *Landersdorfer et al, Postgrad Med 2013*

Commercial Opportunities and Activities

Global Immunoglobulin Market

2012/13 Sales

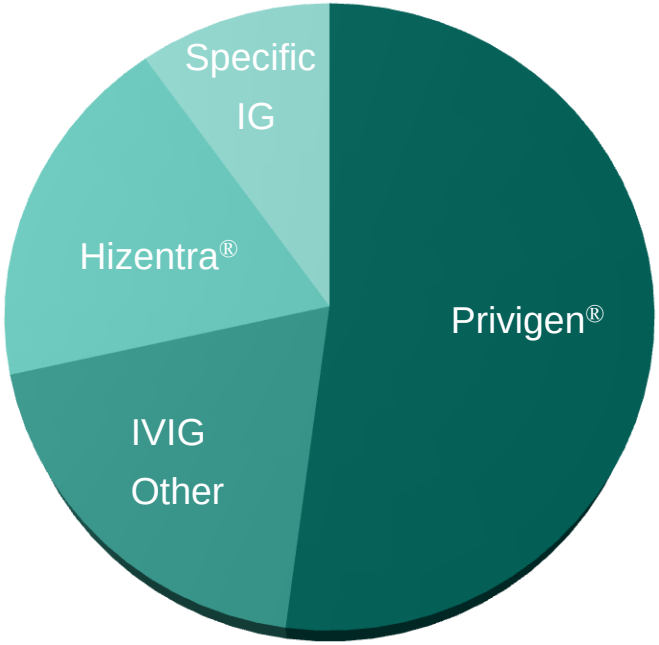
$US 7+ B

- Market includes IVIG, SCIG and Hyperimmunes
- Growing, but competitive, market
- CSL is well positioned:
  - privigen® Human Normal Immunoglobulin IVIG therapy made simple
  - Hizentra® Immune Globulin Subcutaneous (Human) 20%Liquid
  - Sandoglobulin® / CARIMUNE® NF

CSL's Immunoglobulin Portfolio

- Globalise portfolio
- Expand into neurology
- Increase convenience

2012/13 Sales

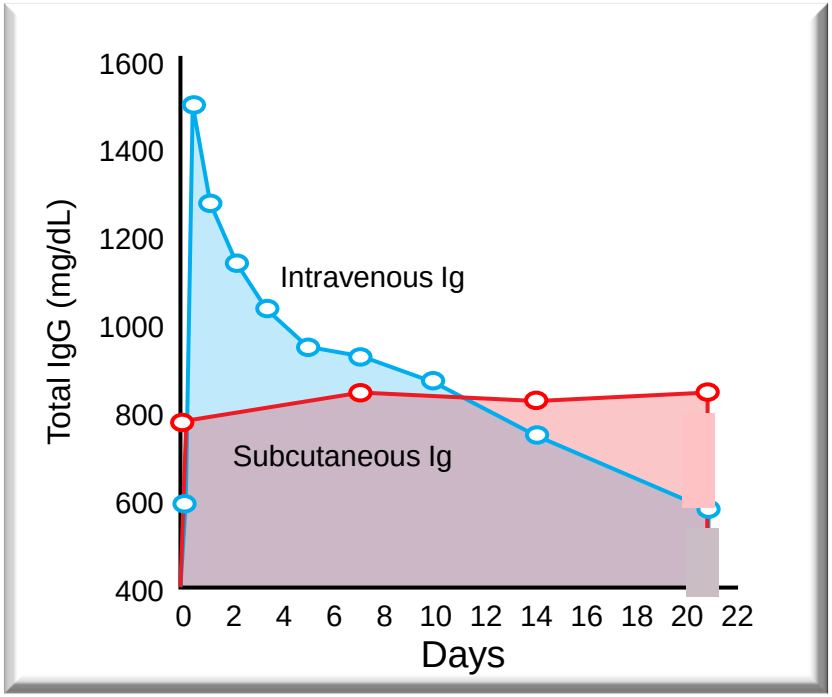


$US 2,081 M

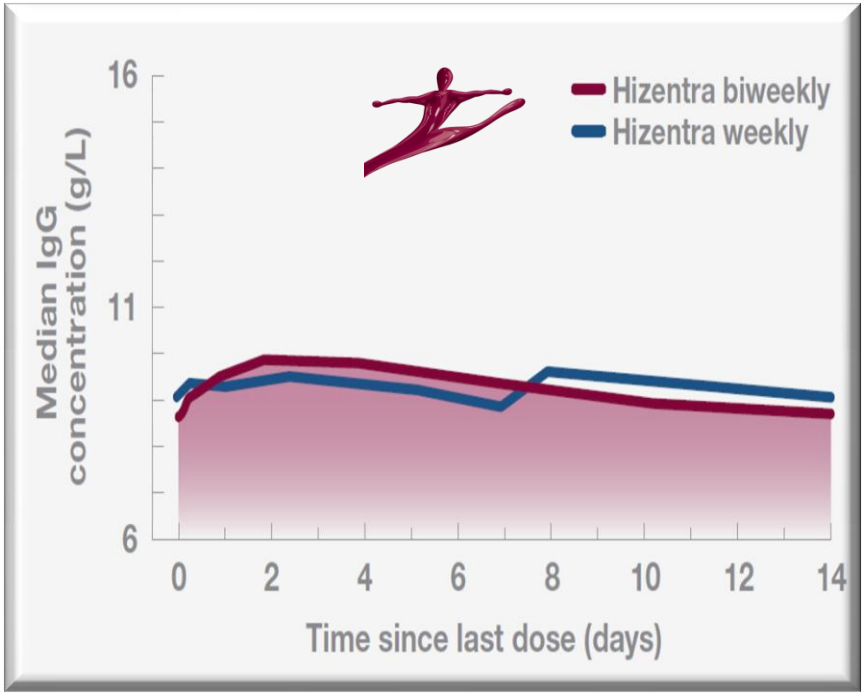
Immunoglobulins: Progress Achieved

Globalise portfolio	• Hizentra® PID in Japan – first and only SCIG product in Japan • Privigen® currently registered in 61 countries • Hizentra® currently registered in 38 countries
Expand into neurology	• Privigen® CIDP launched in Q2 2013 • Ongoing Development of Hizentra® in CIDP • Further options under evaluation
Increase convenience	• Privigen® 40 g launched in Q2 2013 • Hizentra® 10 g launched in Q3 2013 • Hizentra® Bi-weekly launched in Q3 2013 • Further activities ongoing

Benefits of SCIg: Steady-State, Convenience



Representative graph for illustration only



SCIG:

- Steady-state IgG levels[1]
- Self-administration[2]
- Flexibility in infusing[3]
- Low risk of systemic adverse events[4]

- True s.c administration profile
- Less infusions per month
- No change in safety profile
- Convenient
- No adjuncts required

1. Berger M. *Clin Immunol.* 2004;112:1-7.
2. Shapiro RS. *J Clin Immunol.* 2013;33(s2):S95-S98.
3. Younger EM, et al. *J Infusion Nurs*. 2013;36(1):1-11.
4. Gardulf A, et al. *Lancet*. 1991;338:162-166.

2 New Advances for Patients

Hizentra® Immune Globulin Subcutaneous (Human) 20% Liquid

Biweekly	10g (50mL) Vial
• Approval US: Sept 25, 2013 • Available US: Sept 25, 2013	• Approval US: Jun 12, 2013 • Available US: Oct 15, 2013

IVIg patients who:

- Have considered SCIg but felt weekly infusions were too frequent

Patients relying on caregivers who:

- Want steady state and convenience of in-home infusions but find it difficult to fit weekly infusions into everyone's schedules

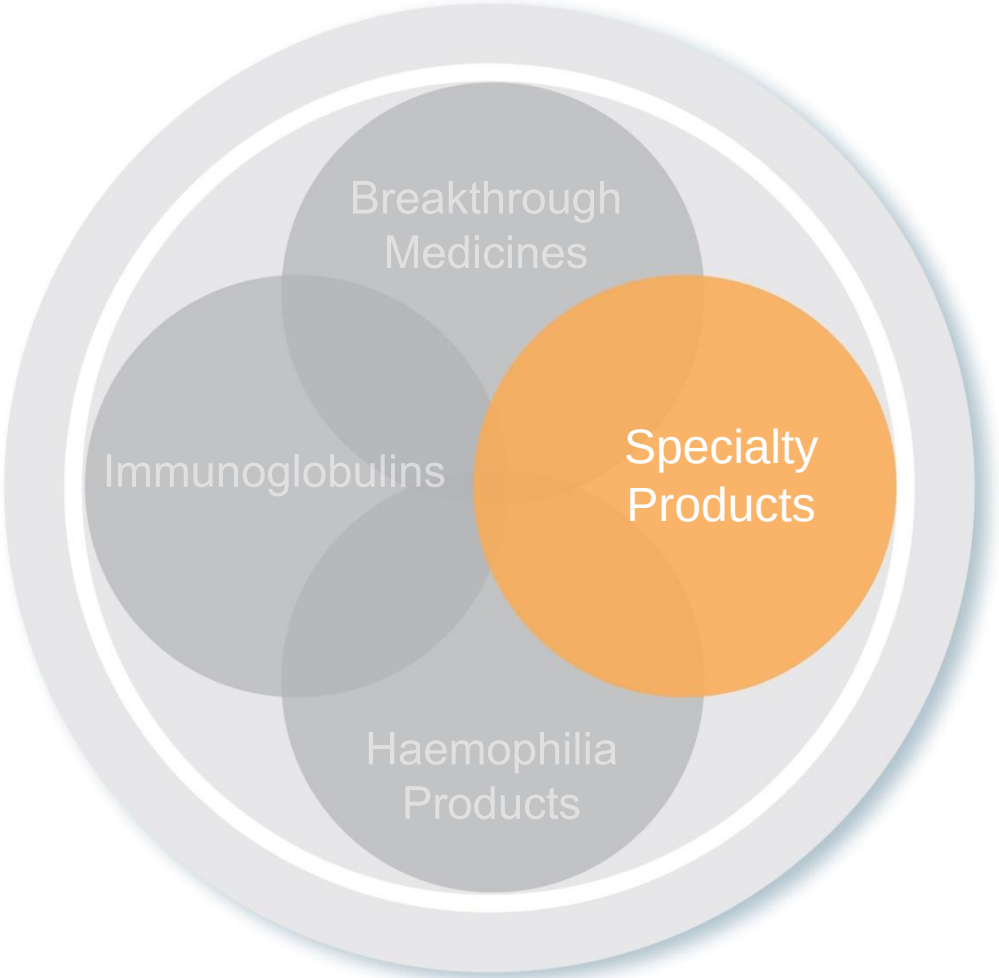
Weekly SCIG patients who:

- Are on a 10% SCIg, and want to infuse less frequently without increasing the volume per infusion
- Are on Hizentra® and want to infuse less frequently

CSL™

Specialty Products

Specialty Products



Leveraging high quality, broad product portfolio through:

- New markets
- Novel indications
- Novel modes of administration

Key Focus

- Beriplex® / Kcentra™
- Fibrinogen
- Zemaira®
- Berinert®

Kcentra™ (Beriplex®)

- Prothrombin Complex Concentrate = PCC
  - vitamin K-dependent coagulation factors (FII, FVII, FIX, FX)

Seeking approval for use of Kcentra™ to reverse the effects of vitamin K antagonists (e.g. Warfarin) for:

- Bleeding related to over-anticoagulation
- Patients needing surgery

FDA approval for urgent Warfarin reversal in patients with acute major bleeding in April 2013

- Kcentra™ launched in April as a first in class therapy

Kcentra™ (Beriplex®)

Kcentra™ Prothrombin Complex Concentrate (Human)

- Kcentra™ approved by FDA in April for bleeding indication

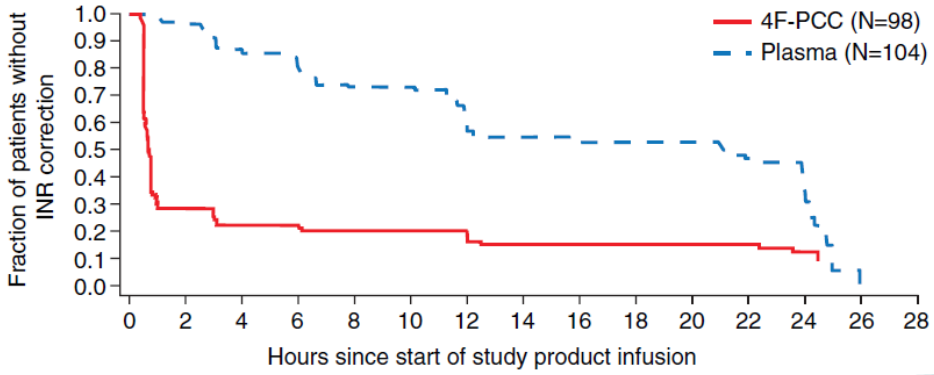
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Efficacy and Safety of a 4-Factor Prothrombin Complex Concentrate in Patients on Vitamin K Antagonists Presenting With Major Bleeding: A Randomized, Plasma-Controlled, Phase IIIb Study

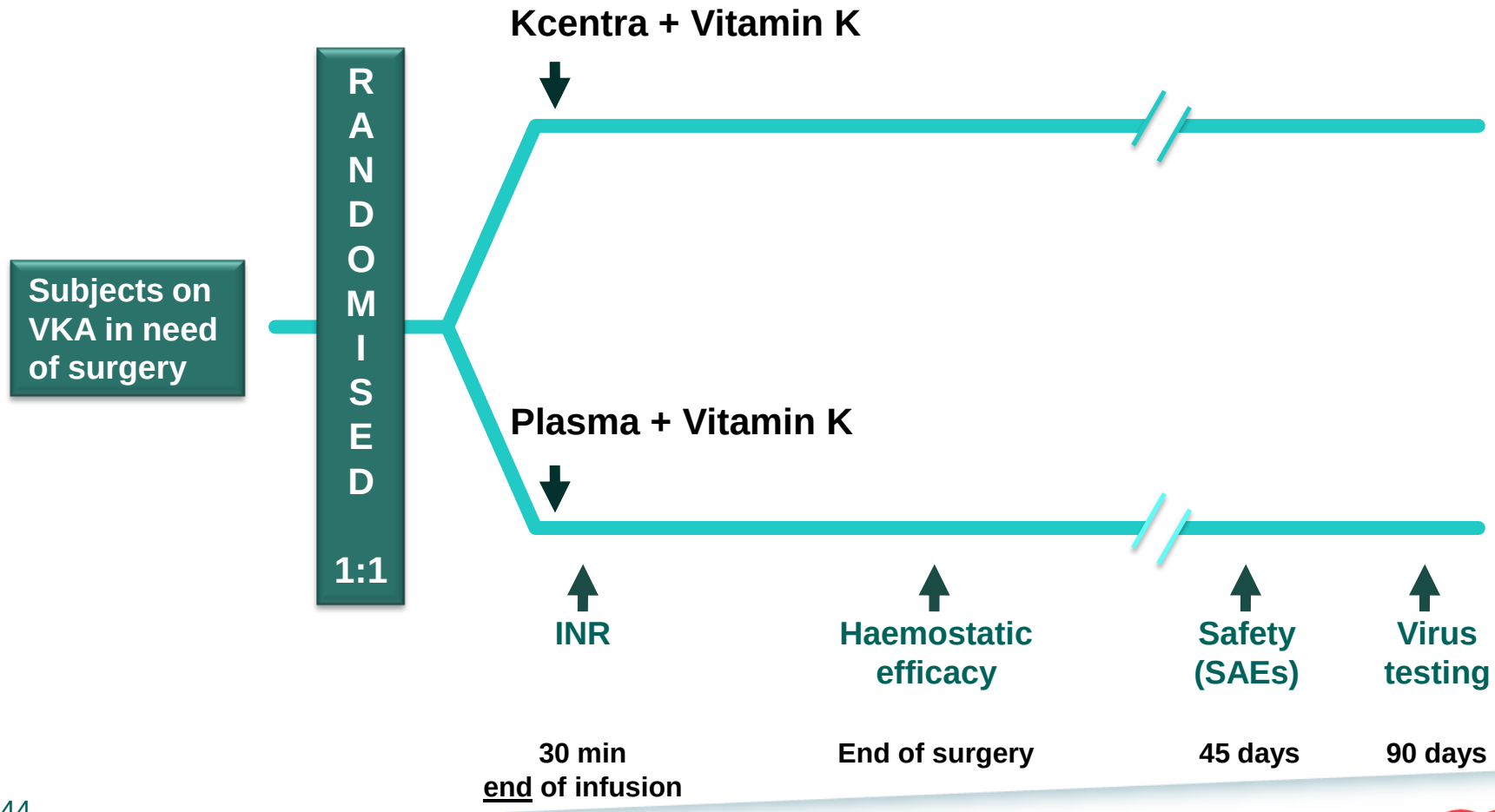
Ravi Sarode, Truman J. Milling, Jr, Majed A. Refaai, Antoinette Mangione, Astrid Schneider, Billie L. Durn and Joshua N. Goldstein

Circulation. 2013;128:1234-1243; originally published online August 9, 2013;



CSL™

Kcentra™ Surgical Study Design



Kcentra™ to reverse VKA prior to surgery

- All patients had reversal of blood thinning test (INR) to normal prior to surgery
- Those given Kcentra™ had less bleeding during subsequent surgery

	% of subjects		Difference Kcentra – plasma (%)
	Kcentra (N = 87)	**Plasma (N = 81)**	
"Effective" bleeding control	78 (90%)	61 (75%)	P <0.05

Kcentra™ Surgical Study Conclusions

Kcentra™ was:

- superior to plasma for control of bleeding
- superior to plasma for rapid reduction in INR
- as safe as plasma (safer with regard to some effects)

FDA granted priority review

- Action date 14 December 2013

Fibrinogen

RiaSTAP® Fibrinogen Concentrate

The first and only treatment approved by the US FDA for acute bleeding episodes in patients with congenital fibrinogen deficiency

Europe

- Peri-/post-operative control of coagulopathic bleeding
- REPLACE Phase III study
  - 200 subjects – recruitment commenced Jan 2012
  - Lower bleeding rate than in pilot study – longer to recruit

US

- Coagulopathic bleeding related to complex cardiac surgery
- Ongoing dialogue with FDA
- Aim to commence Phase II study in 2014

CSL™

Zemaira®

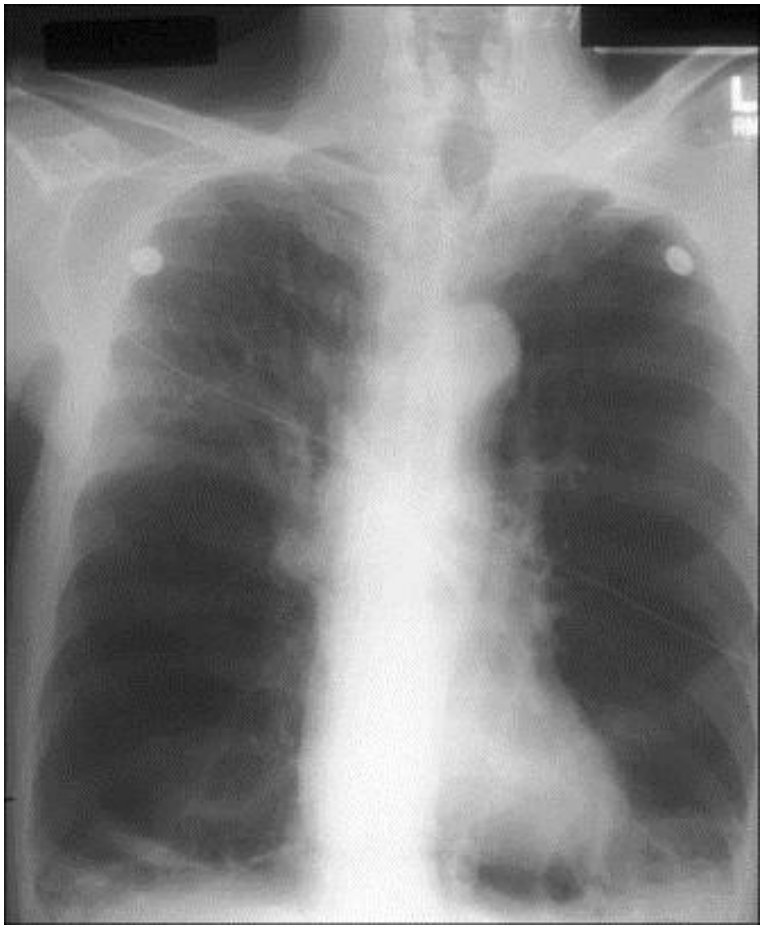
Zemaira is the first highly purified alpha-1 augmentation therapy approved by the FDA for chronic augmentation and maintenance therapy of adults with Alpha-1 and emphysema

Seeking to broaden commercial reach through:

- Launch in EU, Canada, Brazil
  - EU requires demonstration of a clinical outcome (disease modification)
  - Increase diagnosis and treatment
- Broaden label in US

Alpha-1-antitrypsin Deficiency

Zemaira®
alpha$_1$-proteinase inhibitor (Human)

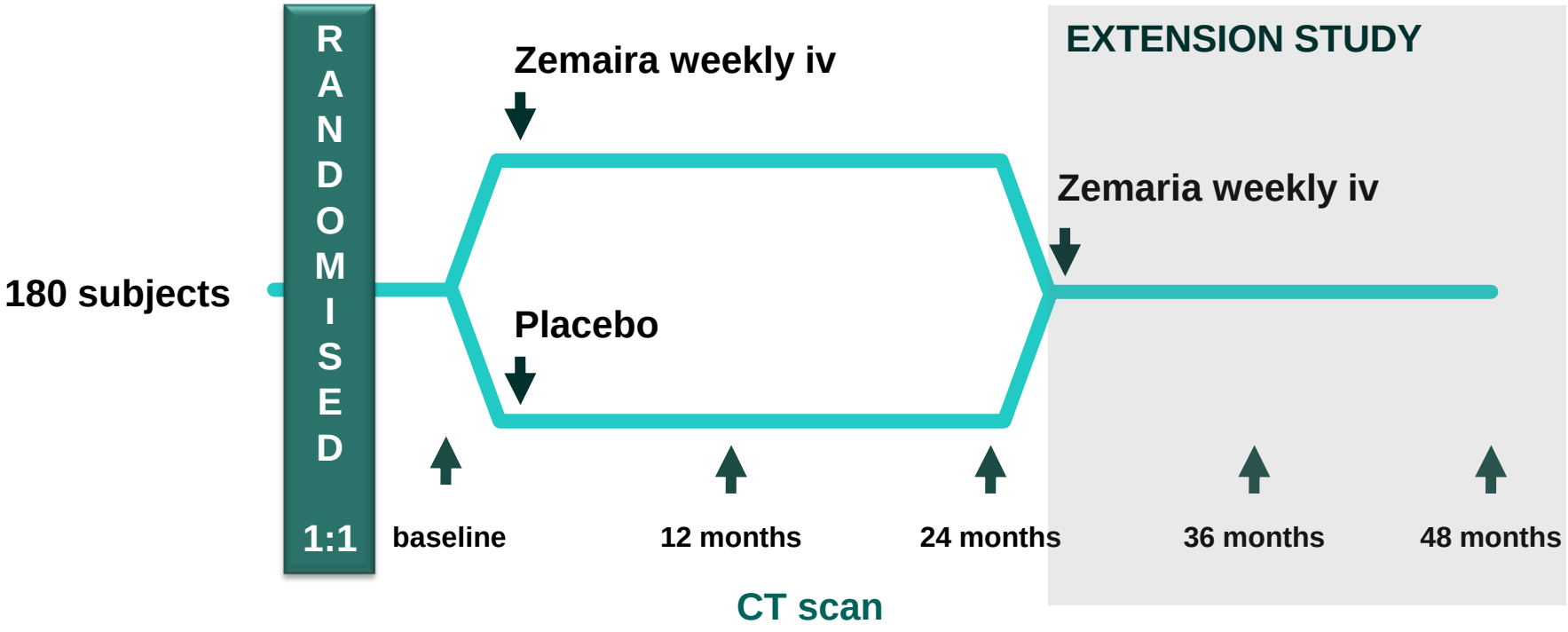


- Chronic obstructive pulmonary disease (COPD) or emphysema
- Cirrhosis and liver failure less commonly

- Under-diagnosed
- Lung disease usually presents in 30-40’s

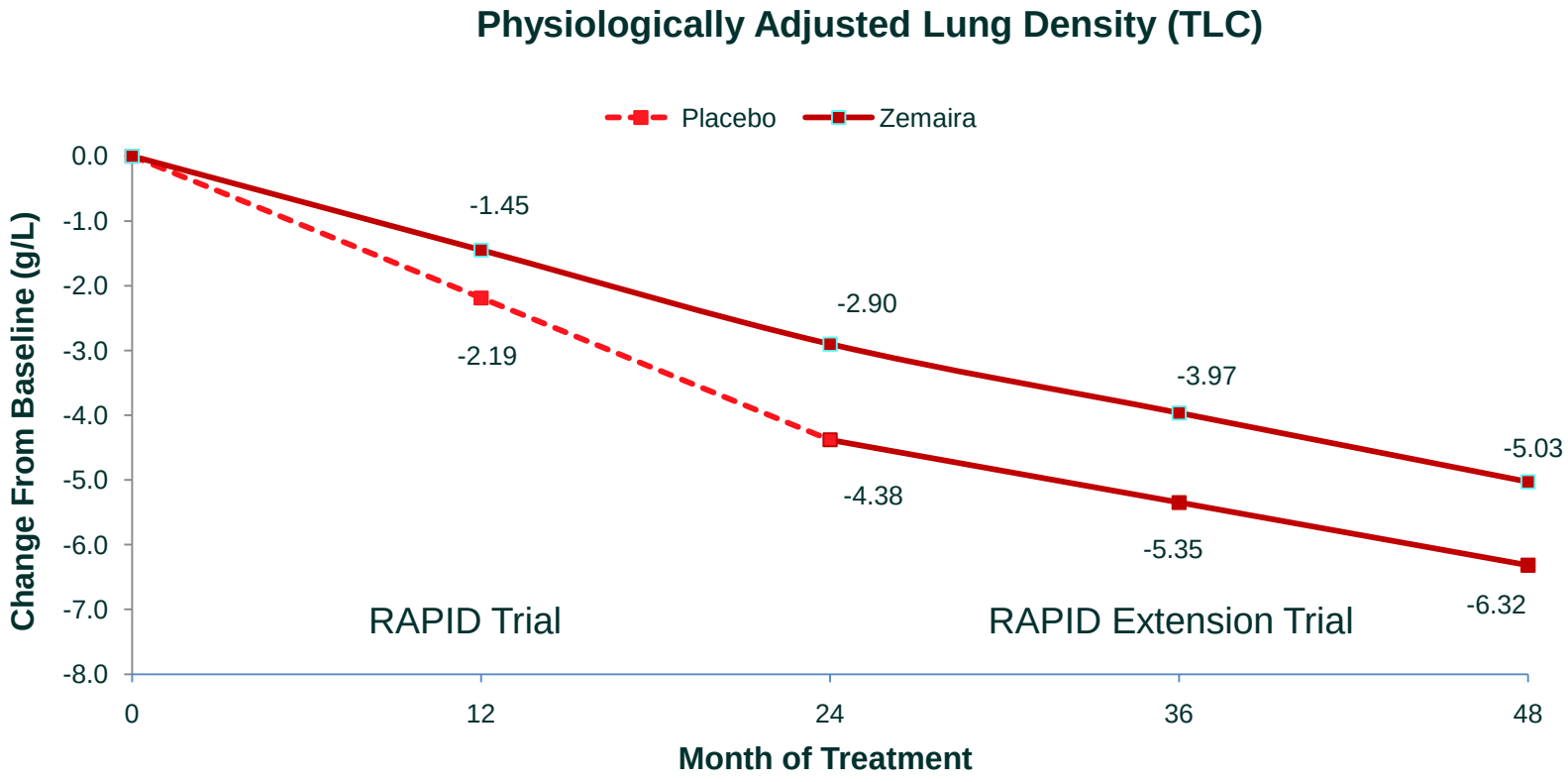
CSL™

RAPID Study Design



RAPID Study Data

Zemaira®
alpha$_1$-proteinase inhibitor (Human)



Zemaira® slows damage to lung tissue

- Efficacy supplement submitted to FDA late Nov 2013
- MAA submitted to EMA early Dec 2013

CSL™

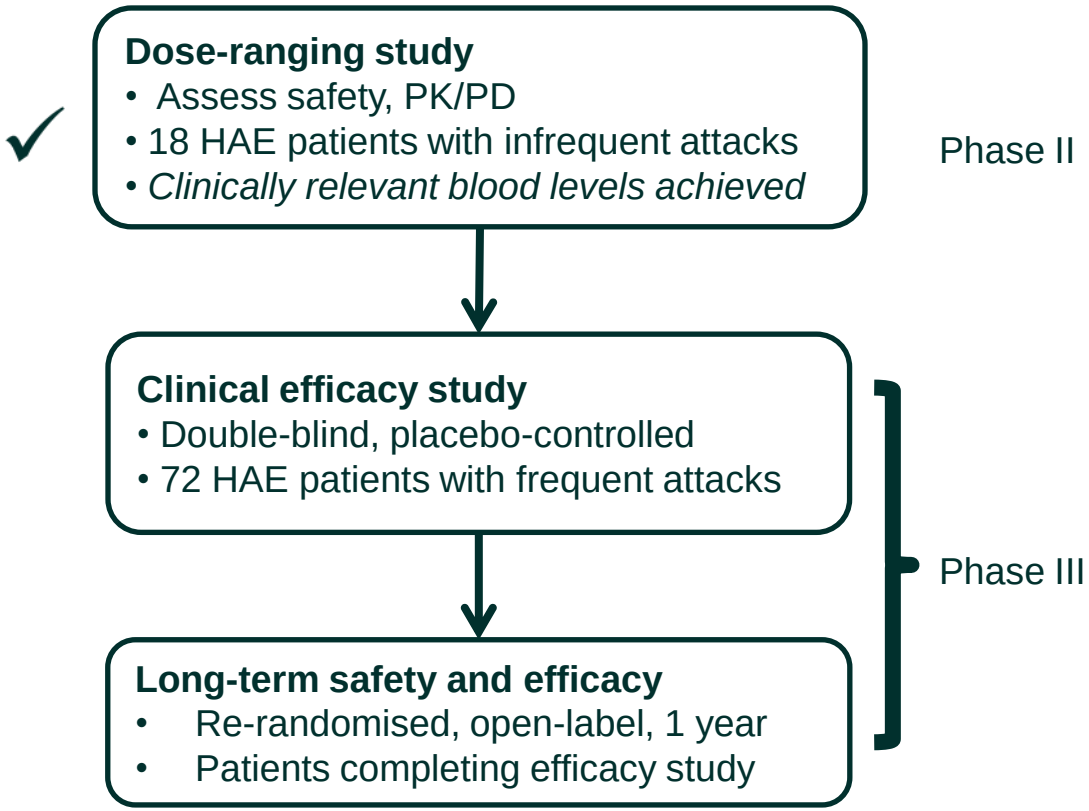
Berinert®

Plasma derived, pasteurised & nanofiltered concentrate of C1 Esterase Inhibitor indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adults and adolescents

- US and European approved label expansion for self administration of HAE in 2012
- EMA approval for short term prophylaxis in adults and children in April 2013
- Phase I/II high concentration, subcutaneous prophylaxis study complete

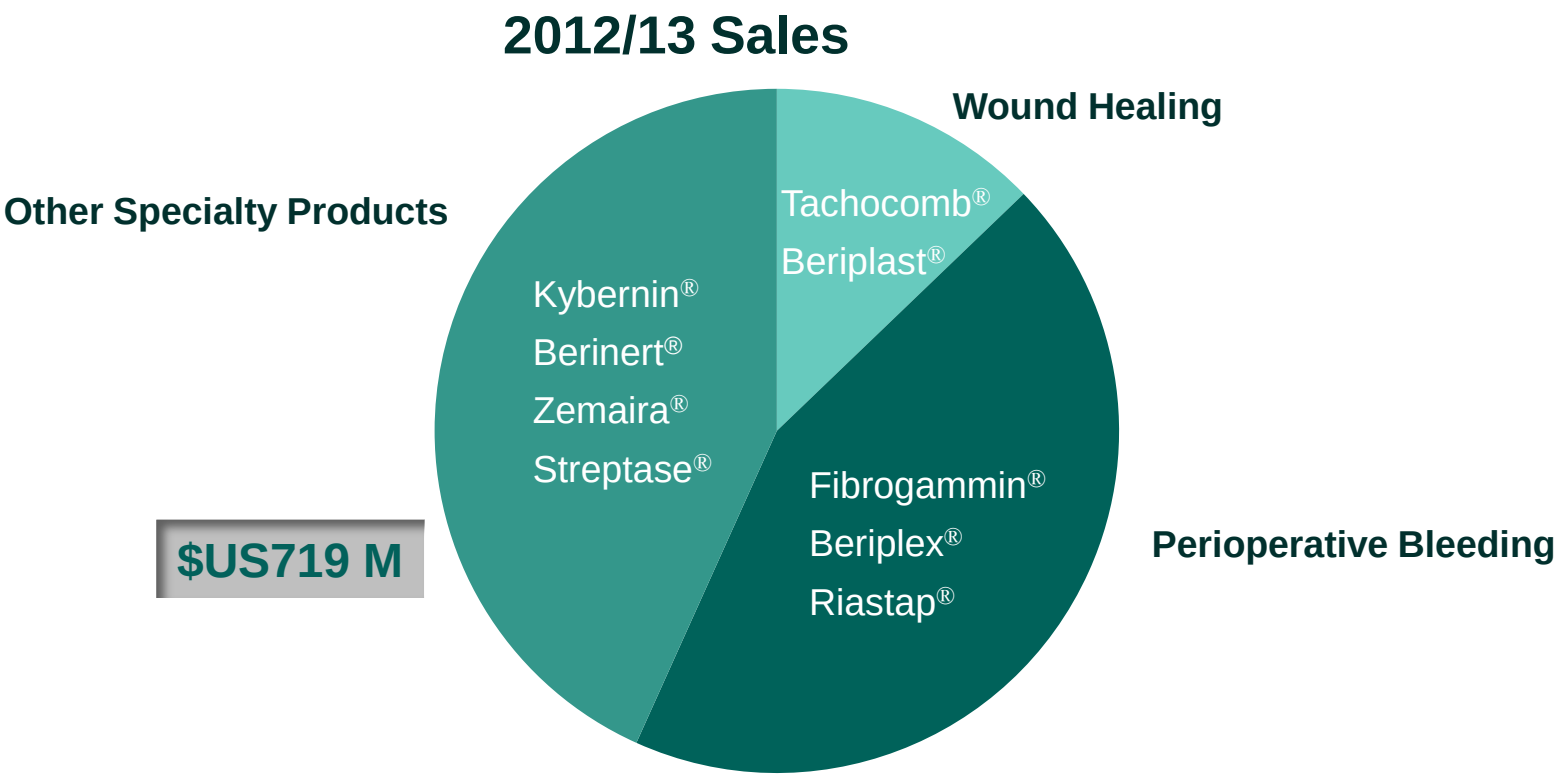
COMPACT

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



Commercial Opportunities and Activities

CSL's Specialty Products Portfolio



- Increase clinical data set
- Add indications
- Expand regionally

Blood Components vs. Concentrates

FFP

Fibrinogen concentration at ≈2.3g / L

Not virus inactivated

Frozen, requires time (<50 minutes) to thaw

Red Blood Cells

Need to be matched to blood type

Not virus inactivated

Platelets

Short shelf life (5 days)

Risk of bacterial contamination

Cryo

- Frozen, require time to thaw
- Pooled from 10 bags of FFP in the blood bank
- Average Fibrinogen concentration ≈ 6g /L

Beriplex® P/N

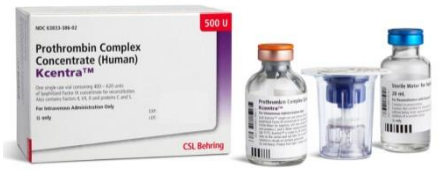
Kcentra™ Prothrombin Complex Concentrate (Human)

RIASTAP® Fibrinogen Concentrate

Corifact® Factor XIII Concentrate (Human)

Concentrated, virus inactivated, room temperature storage, Fibrinogen concentration 20g / L

Kcentra™



Kcentra™, Prothrombin Complex Concentrate (Human), is indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g. warfarin) therapy in adult patients with acute major bleeding

2013

Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec

- **Apr**: FDA APPROVAL
- **Jun**: First Sale
- **Jul**: New Technology Add-On Payment Approval
- **Sep**: 

Pivotal Manuscript Published
- **Nov**: 1,000 IU Vial Size Action Date
- **Dec**: Surgical Indication Action Date

CSL™

Kcentra™ Awarded New Technology Add-On Payment

Medical Community Support for Kcentra NTAP

Centers for Medicare and Medicaid Services (CMS) approved a new technology add-on payment (NTAP) for Kcentra

"AABB strongly believes that Kcentra provides a significant improvement in care for patients in life-threatening circumstances ……."

Letter of support from AABB to CMS dated June 25, 2013.

"…Kcentra represents a substantial improvement compared to existing therapeutic technologies (i.e. plasma therapy). …."

Letter of support from the American Society of Hematology to CMS dated June 24, 2013.

Riastap®

RIASTAP® Fibrinogen Concentrate

REPLACE RiaSTAP Exploration in Patients with Low Fibrinogen in Aortic Cardiotomy trial with global impact, Europe, Japan, Canada

- Obtain US acquired bleeding label
- Initiate acquired label expansion
- Central role of fibrinogen in severe bleeding discussed in scientific literature[1]
- Early intervention with concentrates further recommended in guidelines[2,3] and transfer into local algorithms[4]

Davenport and Brohi *Critical Care* 2013, 17:190
http://ccforum.com/content/17/5/190

CRITICAL CARE

COMMENTARY

Fibrinogen depletion in trauma: early, easy to estimate and central to trauma-induced coagulopathy

Ross Davenport and Karim Brohi*

See related research by Schlimp et al., http://ccforum.com/content/17/4/R137

Critical Care

CRITICAL CARE

This Provisional PDF corresponds to the article as it appeared upon acceptance. Copyedited and fully formatted PDF and full text (HTML) versions will be made available soon.

Management of bleeding and coagulopathy following major trauma: an updated European guideline

Critical Care 2013, **17**:R76 doi:10.1186/cc12685

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Yves Ozier (yves.ozier@chu-brest.fr)

EJA

Eur J Anaesthesiol 2013; **30**:270–382

GUIDELINES

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

Sibylle A. Kozek-Langenecker, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa Alvarez Santullano, Edoardo De Robertis, Daniela C. Filipescu, Dietmar Fries, Klaus Görlinger, Thorsten Haas, Georgina Imberger, Matthias Jacob, Marcus Lancé, Juan Llau, Sue Mallett, Jens Meier, Niels Rahe-Meyer, Charles Marc Samama, Andrew Smith, Cristina Solomon, Philippe Van der Linden, Anne Juul Wikkelsø, Patrick Wouters and Piet Wyffels

Journal of Anesthesiology & Clinical Science

HOAJ Herbert Open Access Journals

Original Open Access

Prevention and treatment of trauma induced coagulopathy (TIC). An intended protocol from the Italian trauma update research group

Giuseppe Nardi[1*], Vanessa Agostini[2], Beatrice Rondinelli Maria[3], Grazia Bocci[4], Stefano Di Bartolomeo[5], Giovanni Bini[6], Osvaldo Chiara[7], Emiliano Cingolani[3], Elvio De Blasio[8], Giovanni Gordini[9], Carlo Coniglio[3], Concetta Pellegrini[8], Luigi Targa[4] and Annalisa Volpi[10]

*Correspondence: gnardi@scamilloforlanini.rm.it
[1]Shock and Trauma Centre, S. Camillo-Forlanini Hospital, Roma Italy.
[2]Department of Clinical Pathology, Transfusion Medicine Service, Bufalini Hospital, Cesena, Italy.
[3]Department of Immunoematology and Transfusion Medicine, S. Camillo-Forlanini Hospital, Roma, Italy.
[4]Department of Intensive Care, Catholic University, Roma, Italy.
[5]Department of Anesthesia and Intensive Care, Hospital and University, Udine, Regional Health Agency Emilia-Romagna, Italy.

[1]Davenport and Brohi Critical Carre 2013, 17:190

[2]Spahn et al. Critical Care 2013 Apr 19;17(2):R76

[3]Kozek-Langenecker et al. Eur J Anaesthesiol 2013; 30:270–382

[4]Nardi et al. Journal of Anesthesiology and Clinical Science 2013

CSL™

Zemaira® and the RAPID results

Zemaira®
alpha$_1$-proteinase inhibitor (Human)

The first and only proven disease-modifying A1-PI therapy shown to slow damage to lung tissue and delay the progression of emphysema

RAPID data

- Data rollout initiated at ATS
- Will provide clinical differentiation supporting preferred formulary placement

Targeted to be:

- First and only A1-PI with pan EU approval
- First and only A1-PI that will have clinical efficacy data in package insert
  - Will allow sales rep promotion
  - May expand market to convince A1-PI "non-believer" physicians

CSL™

Berinert®

Berinert treats the fundamental cause of HAE symptoms by providing C1-Inhibitor deficient patients with the missing human protein[1]

Berinert has demonstrated that it provides fast relief of pain and swelling within 30 minutes[2]

- Obtain Prophylaxis indication COMPACT Clinical Studies for Optimal Management in Preventing Angioedema with low-volume subcutaneous C1-inhibitor Replacement Therapy
  - Increase convenience with s.c. treatment option
- Continuous Life Cycle Management to improve product profile
  - Self administration, nano-filtration, and most recently “short term prophylaxis” approval in EU
- Continue geographical expansion

1) Agostini et al. J Allergy Clin Immunol. 2004
2) Craig et al. J Allergy Clin Immunol 2009

Berinert® Key Features

Product Advantages

- Efficacy: Almost no redosing required to treat attacks
- Early onset of relief
- Excellent Safety and tolerability

Manufact-uring

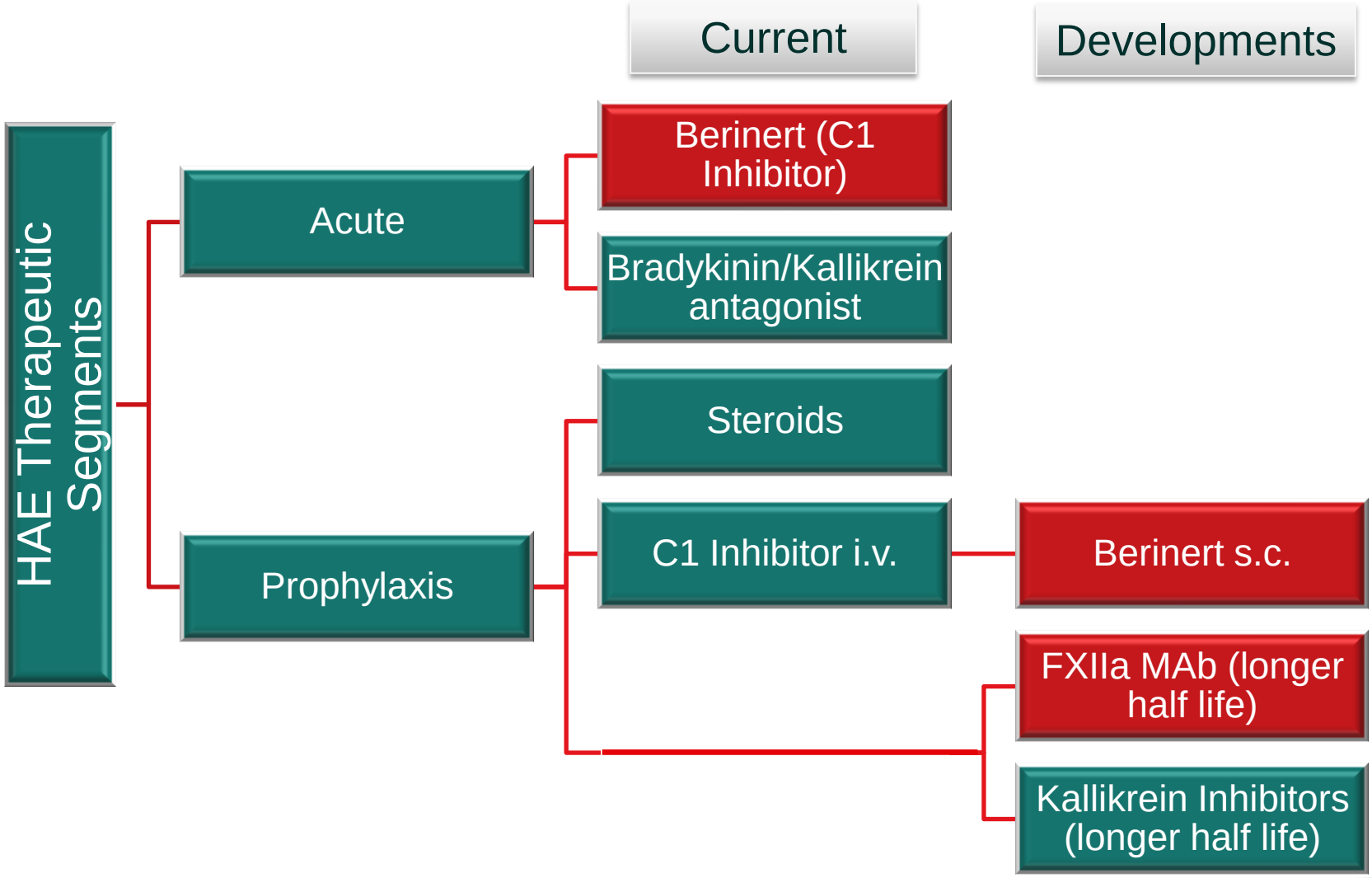
- Control of product supply - own plasma collection centers and manufacturing sites

Life Cycle Management

- s.c. prophylaxis
- Low Volume formulation
- Further LCM indications under evaluation

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

HAE Therapeutic Segments



Q&A

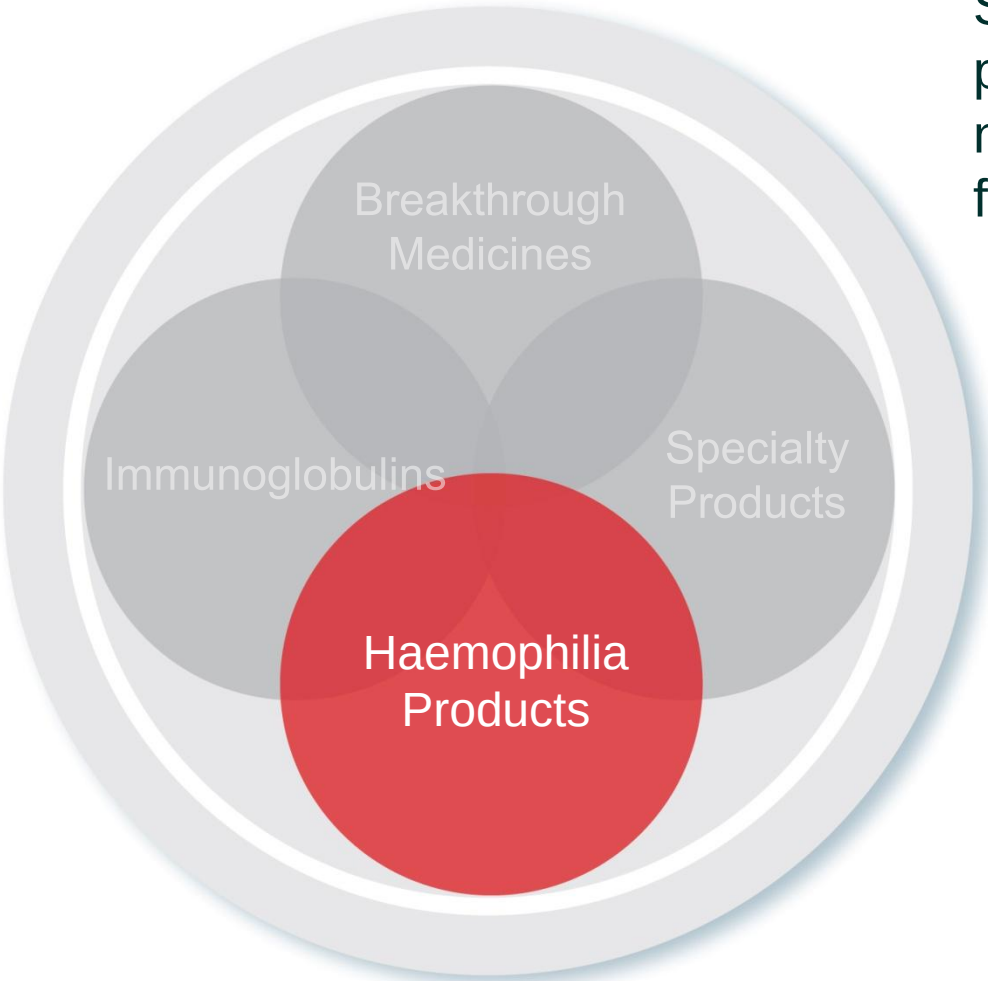
Break

R&D Briefing

December 5, 2013

Haemophilia Products

Haemophilia



Supporting and enhancing plasma products and developing novel recombinant portfolio with focus on:

- Scientific and product innovation
- Patient benefit

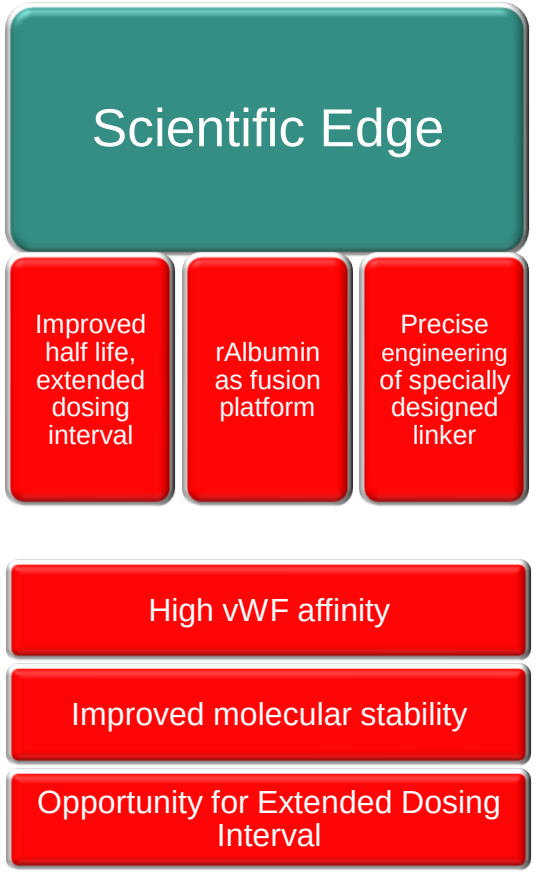
Key Focus

- Long acting rIX-FP
- Long acting rVIIa-FP
- rVIII-Single Chain
- Research into long acting rvWF-FP

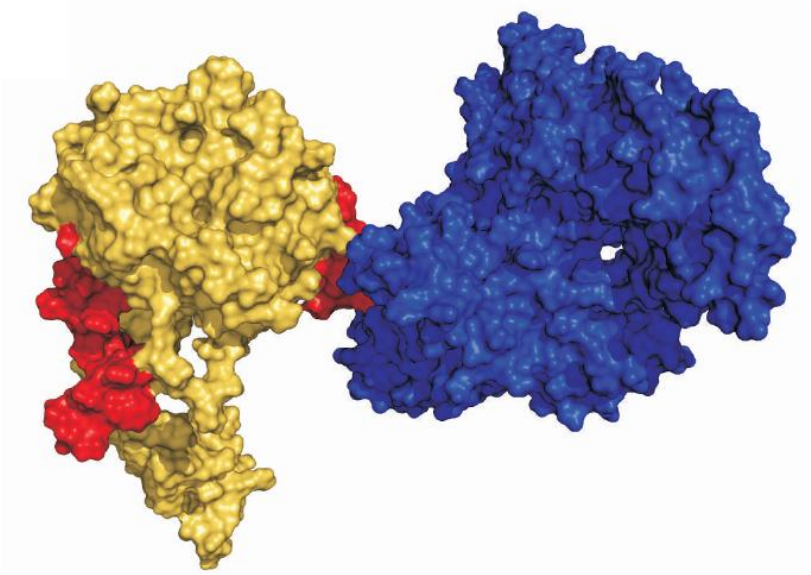
Innovation to Drive Growth

Patient convenience primary driver of innovation

- Albumin fusion technology
  - rIX-FP, rVIIa-FP, rvWF-FP
- Factor VIII
  - biobetter rVIII-SingleChain



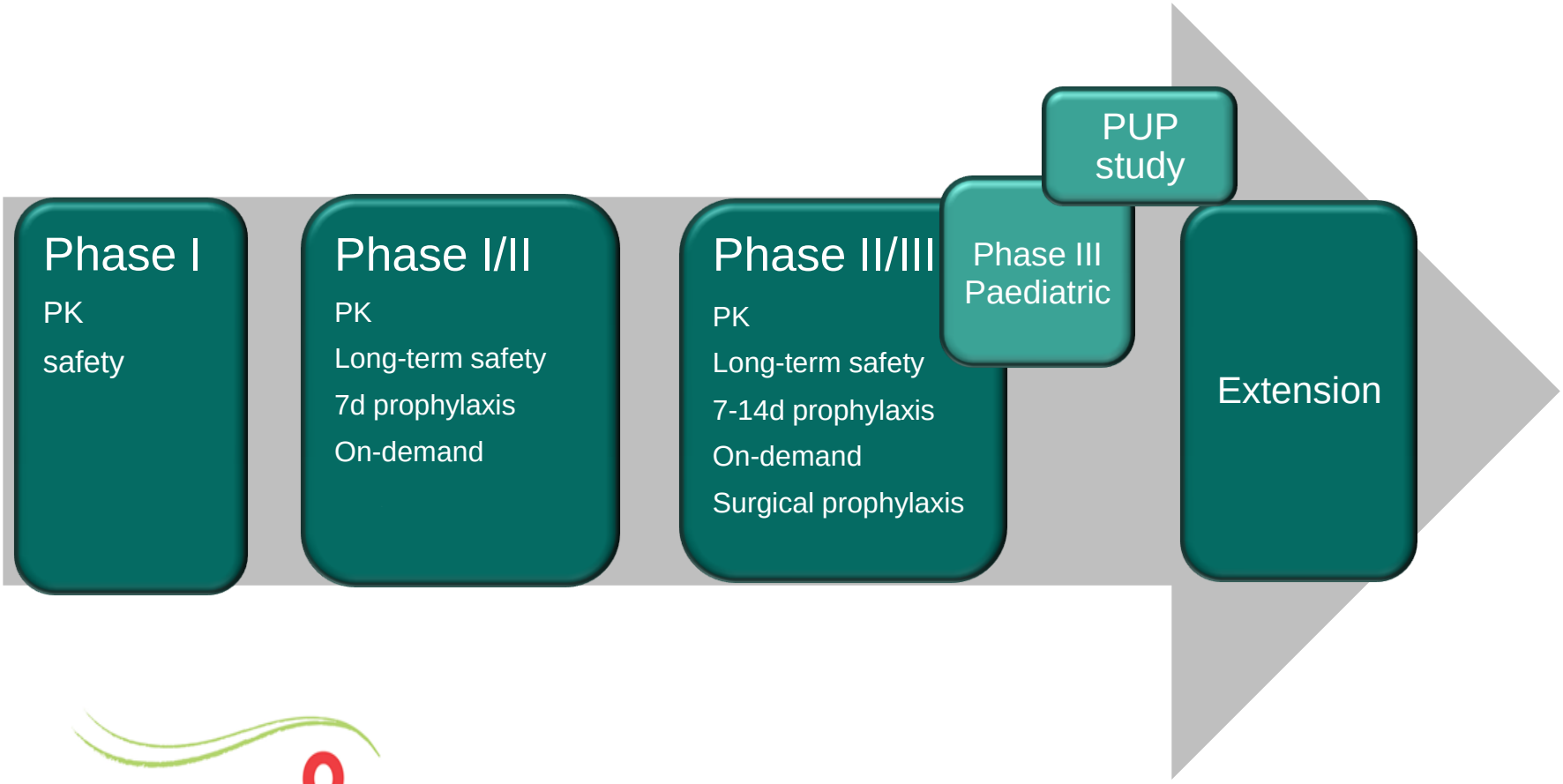
rIX-FP (CSL654)



PROLONG 9 FP

CSL™

rIX-FP (CSL654) Global Clinical Program



PROLONG 9 FP

CSL

blood

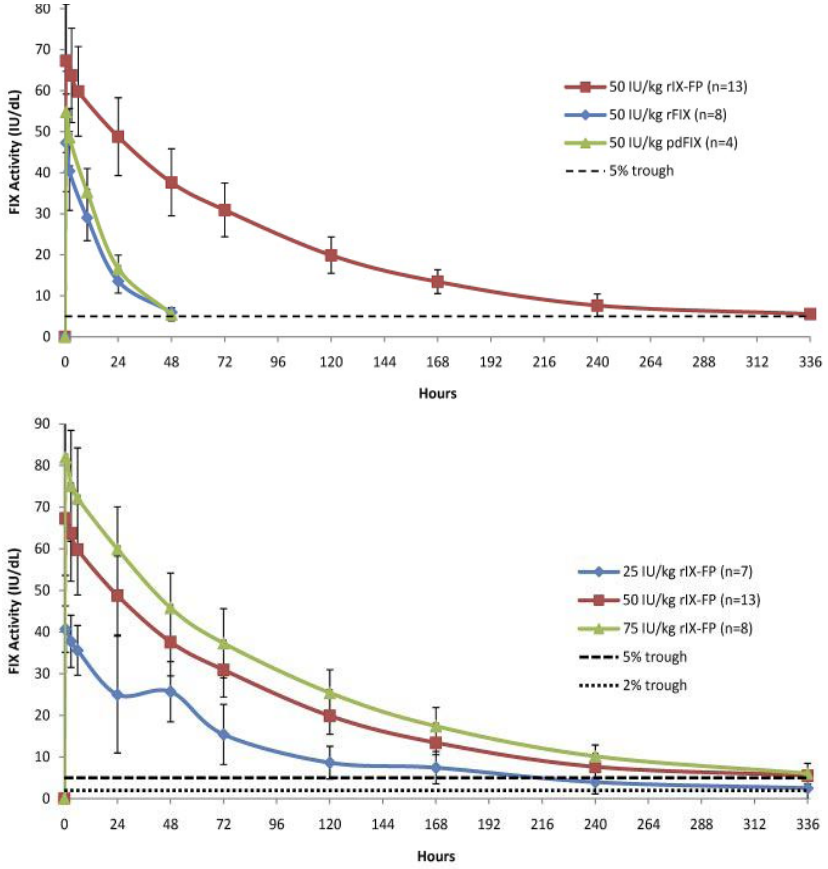
2012 120: 2405-2411
Prepublished online August 2, 2012;
doi:10.1182/blood-2012-05-429688

Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients

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

Compared with in market rFIX

- 5.3-fold longer half-life (92hrs)
- ~ 45% higher incremental recovery
- ~7-fold larger AUC
- ~7-fold slower clearance



PROLONG 9 FP

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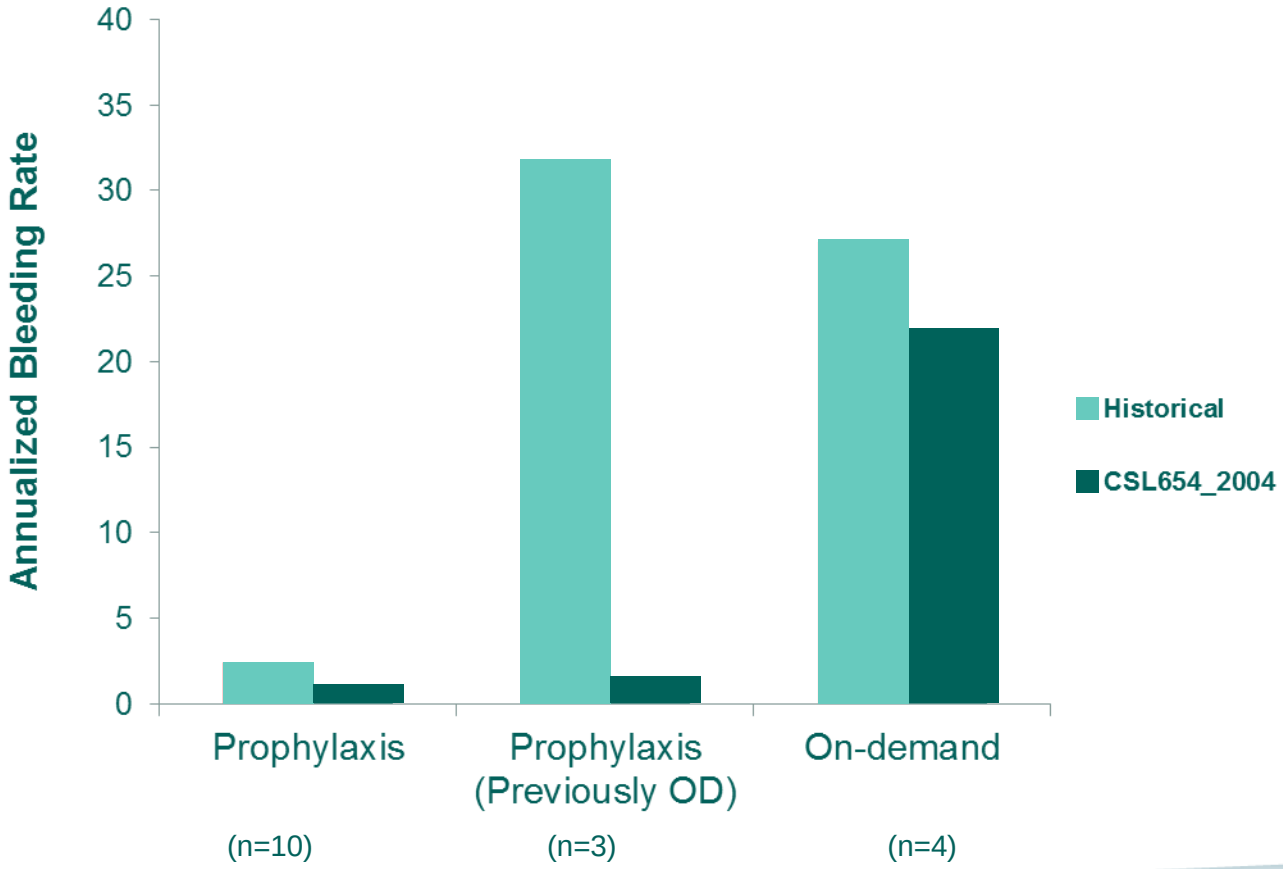
rIX-FP (CSL654) Efficacy in Phase I/II Study

- Annualised spontaneous bleeding during the study vs previous 12 months



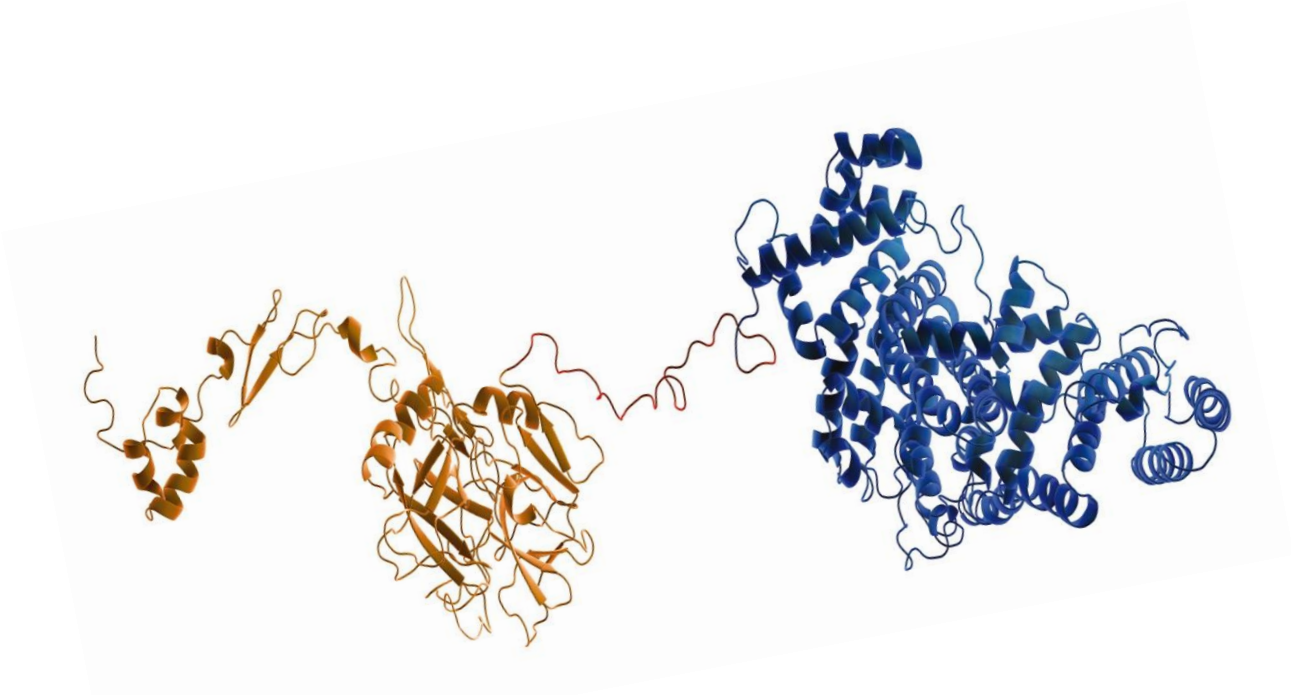
rIX-FP (CSL654) Clinical Development

- Excellent safety profile
  - Well tolerated
  - No inhibitors
  - No adverse events related to CSL654
- All patients now enrolled in Phase II/III and Paediatric studies
- Dossier submission now planned early 2015

PROLONG 9 FP

CSL

rVIIa-FP (CSL689)



PROLONG 7 FP

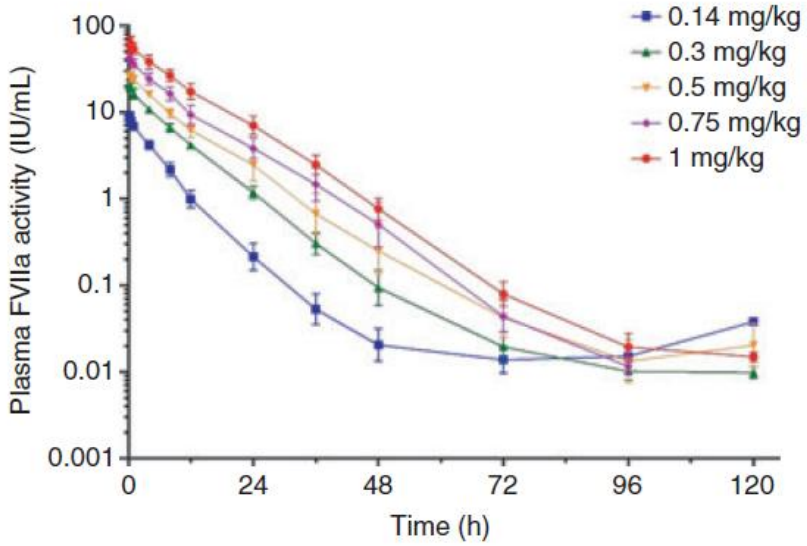
CSL™

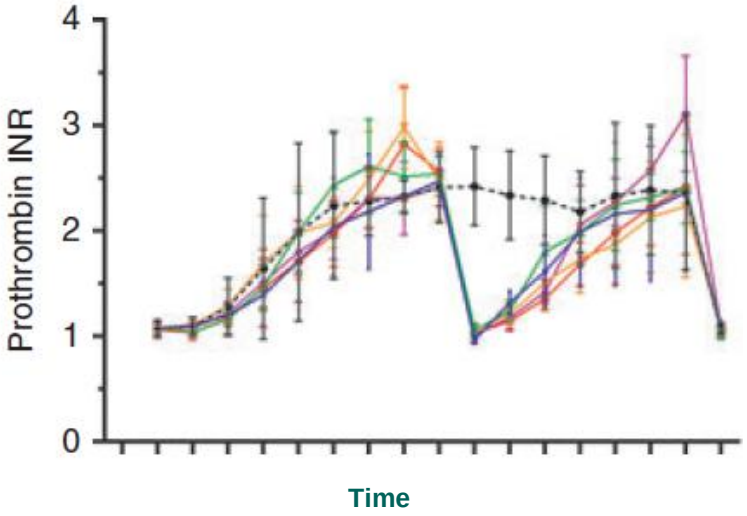
Journal of Thrombosis and Haemostasis, **11**: 1977–1985

ORIGINAL ARTICLE

Safety and pharmacokinetics of a recombinant fusion protein linking coagulation factor VIIa with albumin in healthy volunteers

G. GOLOR,* D. BENSEN-KENNEDY,† S. HAFFNER,* R. EASTON,† K. JUNG,‡ T. MOISES,‡ J.-P. LAWO,‡ C. JOCH‡ and A. VELDMAN‡





- Half-life = 8.5 hrs (vs rFVIIa ~2-3hrs)
- Well tolerated, no serious adverse events

rVIIa-FP (CSL689) Global Clinical Program

- Pivotal Phase II/III trial in haemophilia A & B patients with inhibitors
  - Dose finding, safety & efficacy on-demand therapy
  - Ongoing discussions with regulatory agencies (FDA, PEI, PMDA)
- Anticipate commencing in 2014

PROLONG 7 FP

CSL

Potential of rVIIa-FP (CSL689)

For patients with inhibitors

- Single dose for treatment of bleeding
- Prevention of bleeding in patients undergoing surgery
- Prophylaxis

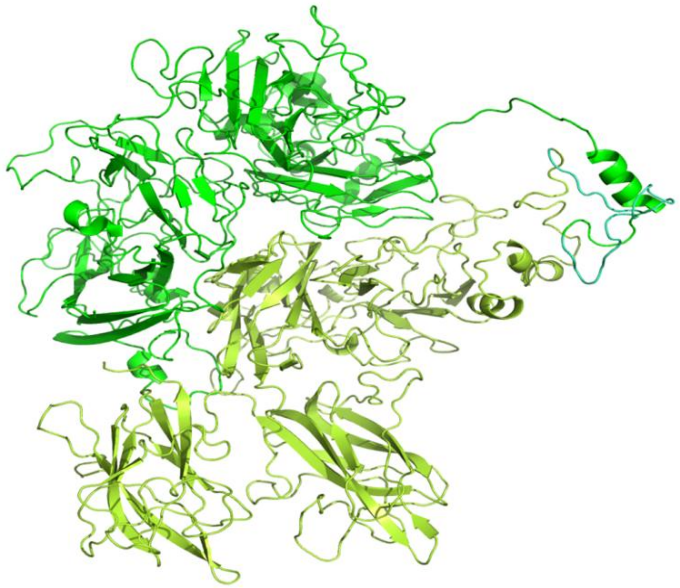
Other indications

- Congenital Factor VII deficiency
- Acquired haemophilia
- Glanzmann's thrombasthenia

PROLONG 7 FP

CSL

rVIII-SingleChain (CSL627)



AFFINITY
rVIII-SingleChain Clinical Trial Program

CSL™

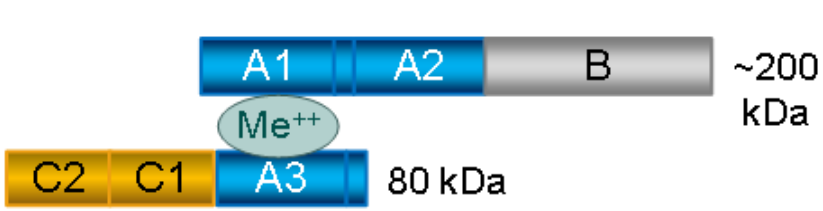
rVIII-SingleChain: approach for improved FVIII

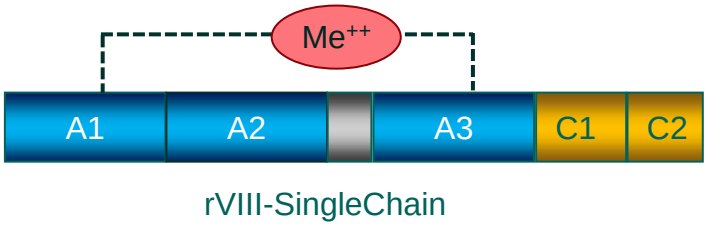
FVIII's physiological partner in plasma is von Willebrand factor (vWF)

- FVIII/vWF complex is important role in the physiological activity and clearance of FVIII
- *Aim - improve binding to vWF*

FVIII is an unstable molecule in the manufacturing environment

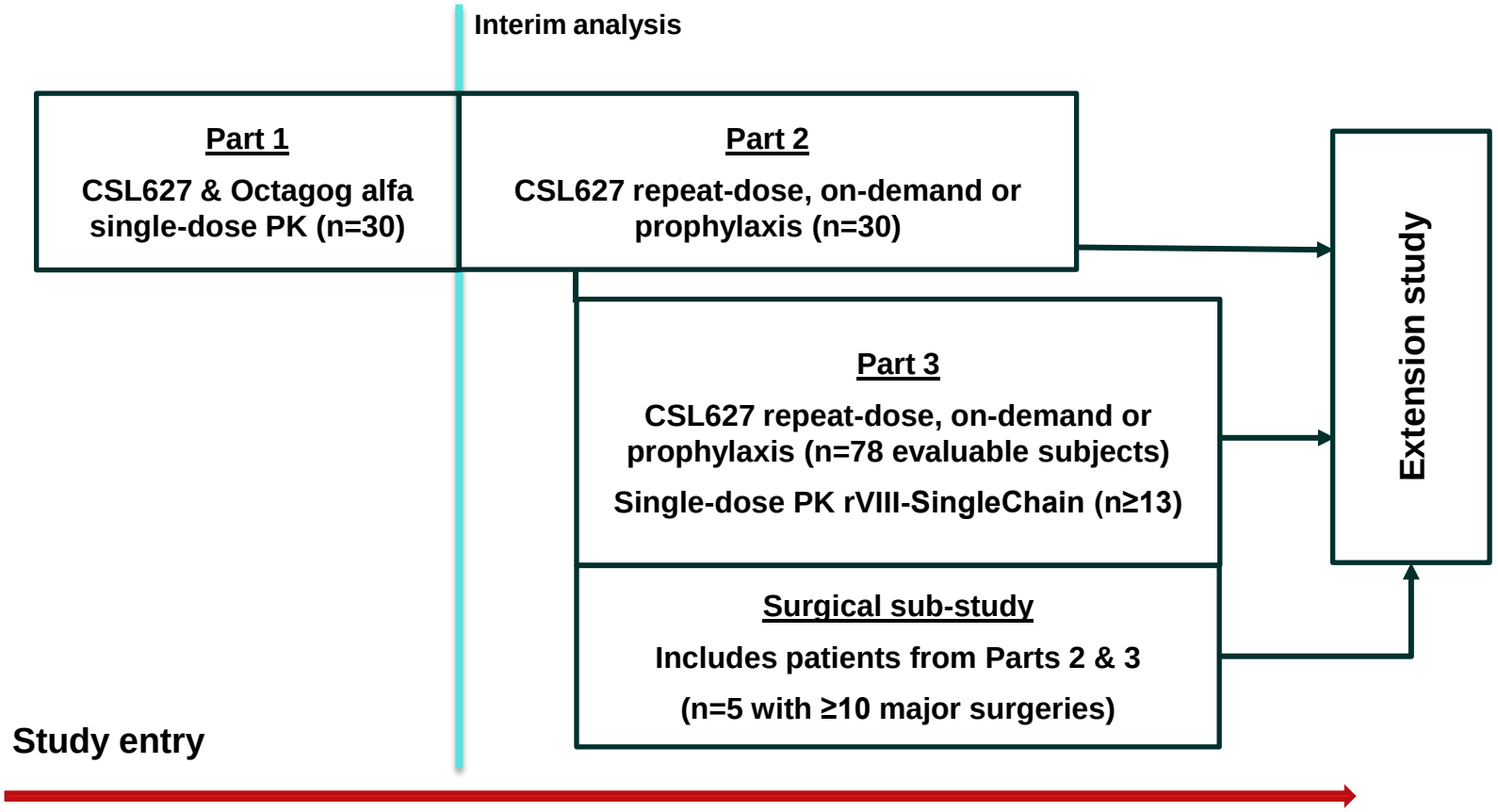
- Potential for dissociation and loss of procoagulant activity of FVIII
- *Aim - improve molecular stability*





rVIII-SingleChain

rVIII-SingleChain Phase I/III Study Design



- Part 1 completed enrolment Q1 2013
- Part 3 commenced Q2 2013 – now scheduled to complete early 2014

AFFINITY
rVIII-SingleChain Clinical Trial Program

CSL

CSL627 PK Supports Dosing Twice-Weekly

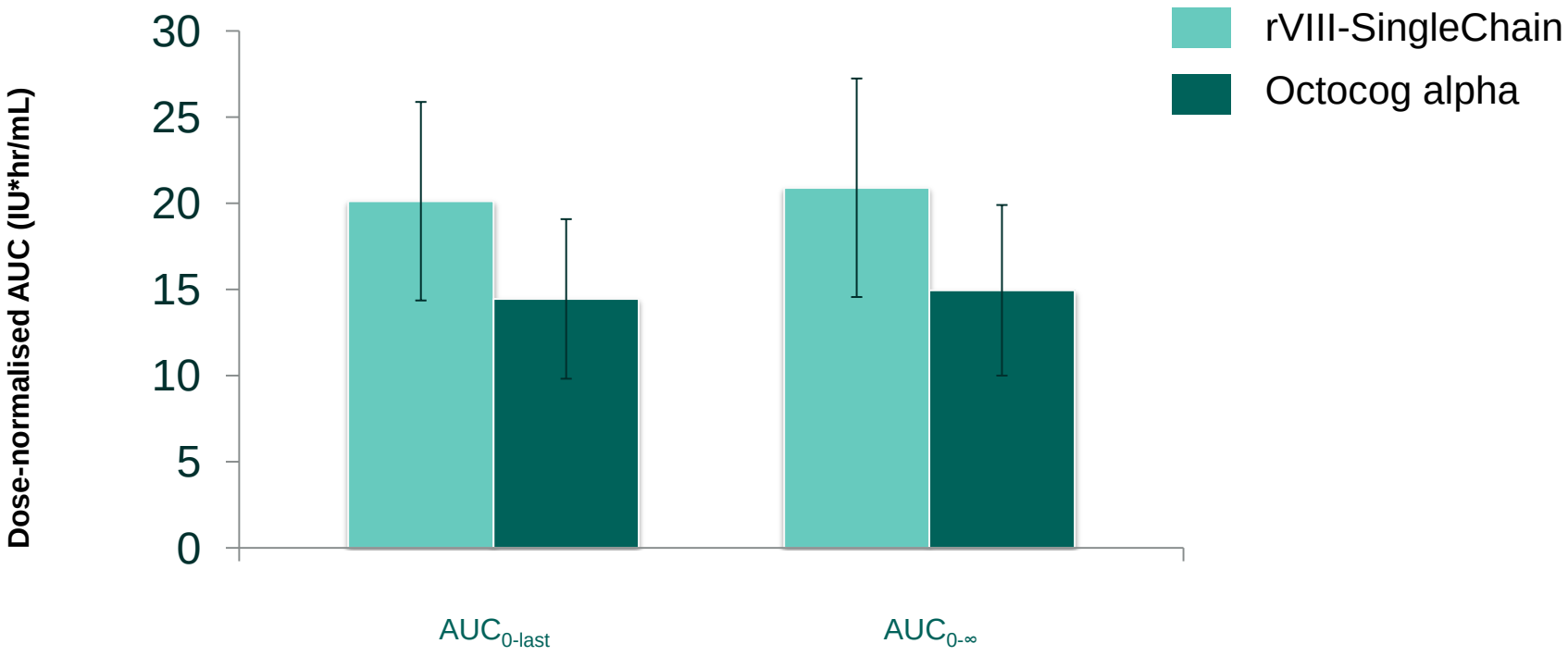
Product	Time to 2% (hr)	Time to 1% (hr)
rVIII-SingleChain	78.0	91.9
Octocog alpha	65.2	77.2

Data presented are mean values. n=22

AFFINITY
rVIII-SingleChain Clinical Trial Program

CSL

CSL627 PK Evaluation: Area Under the Curve



*Dose-normalised baseline-corrected FVIII activity $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ in plasma following a single intravenous administration of rVIII-SingleChain or Octocog alpha. FVIII activity determined by chromogenic assay and normalised by individual dose to 50 IU/kg. Data presented are mean ±SD n=27

rVIII-SingleChain Phase I/III Study

Results to Date

- Very well tolerated
- No inhibitors
- All bleeding events effectively treated
- Last patient now to be enrolled early 2014
  - recruitment challenges
- Dossier submission now planned early 2015

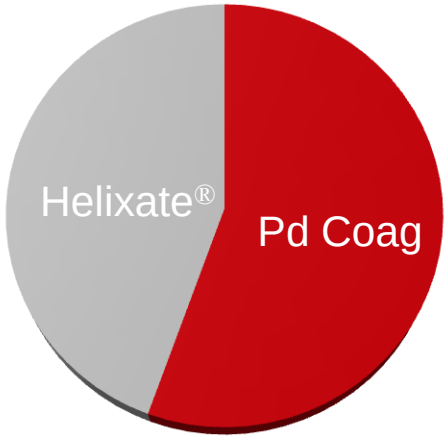
AFFINITY
rVIII-SingleChain Clinical Trial Program

CSL

Commercial Opportunities and Activities

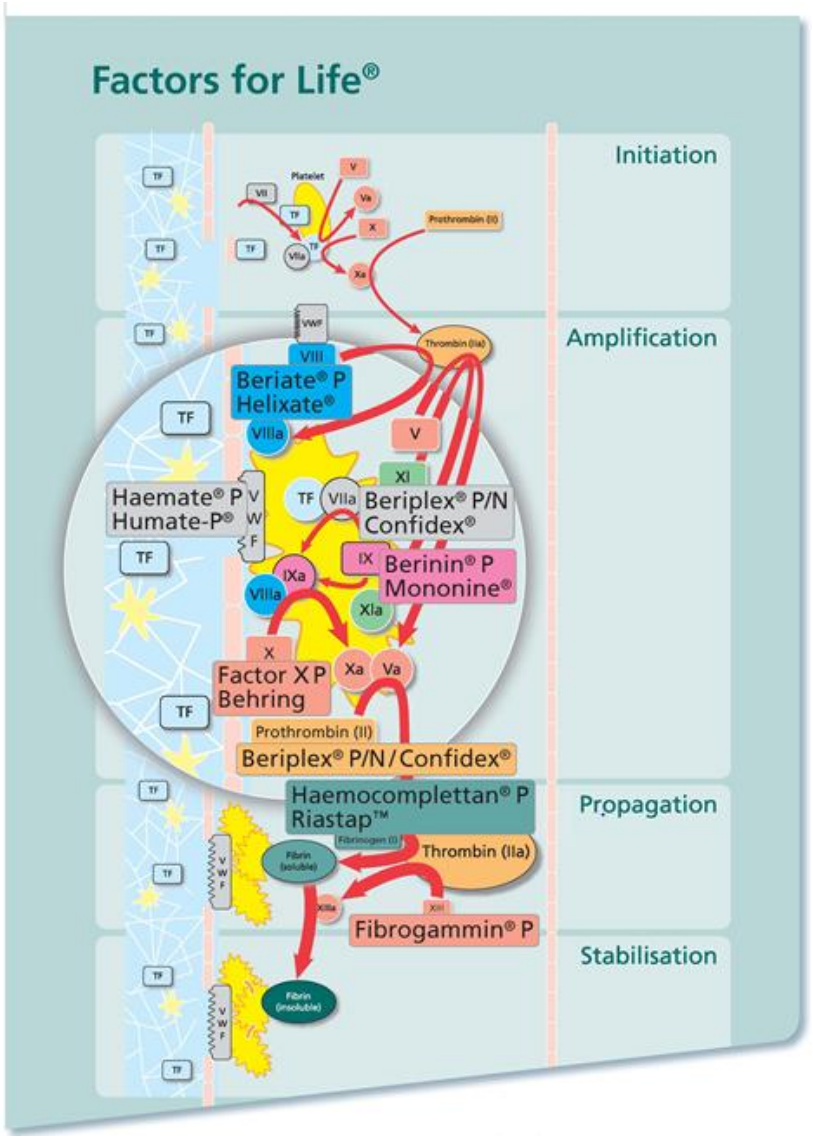
Coagulation Sales

2012/13

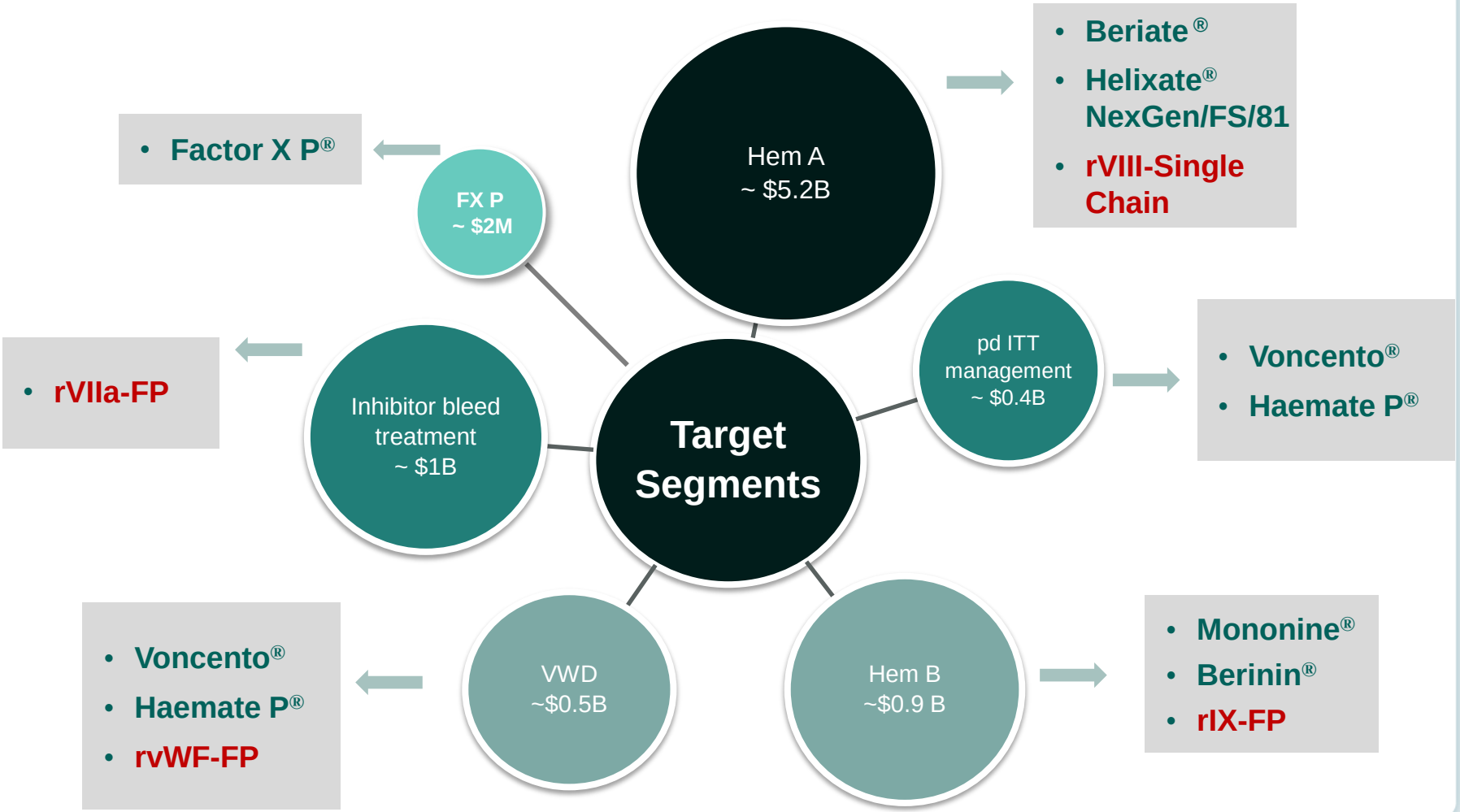


$US1,090M

- Broad portfolio presence
- Growing pd portfolio
- Helixate® as a strong foundation for recombinant pipeline



Coagulation: Key Market Segments and Products



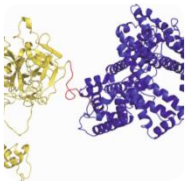
Coagulation: Factors with Market Impact

Diagnosis

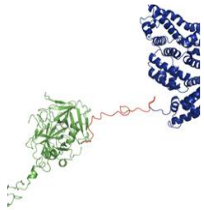
Treatment Options

Product Choice

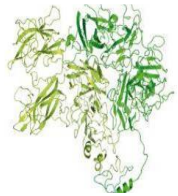
rIX-FP



rVIIa-FP



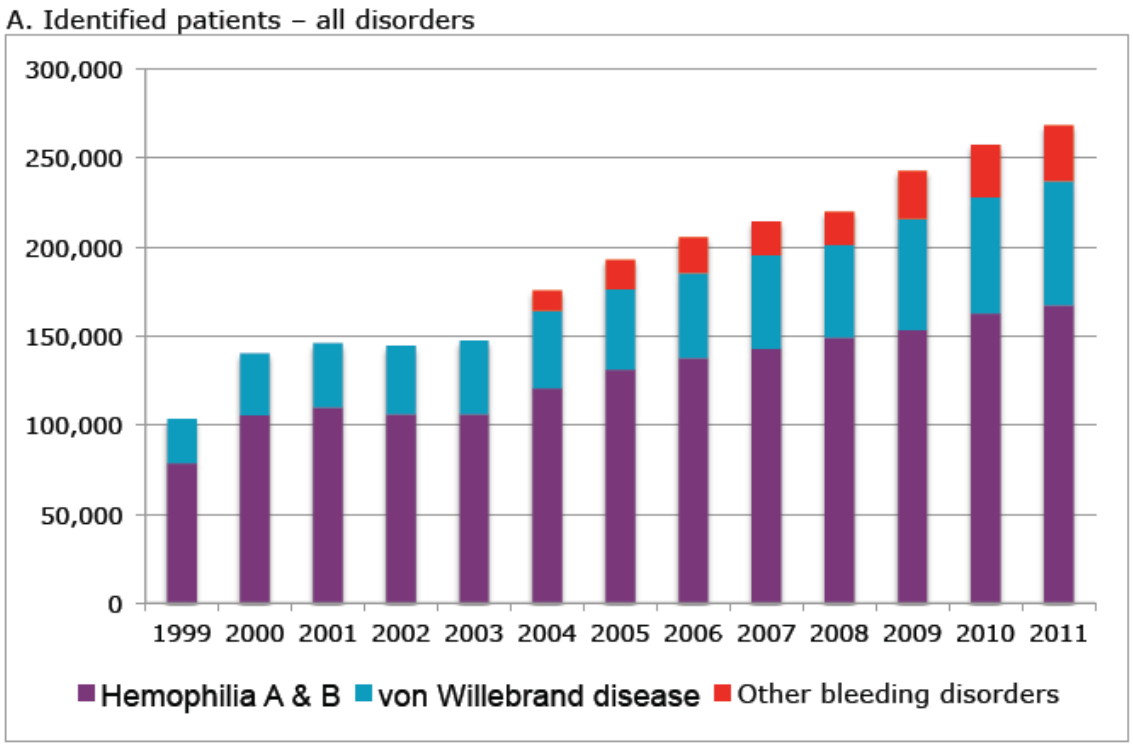
rVIII-SingleChain



Coagulation: Factors with Market Impact

Diagnosis

World Federation of Hemophilia Global Survey 2011



Identification of patients with bleeding disorders is still ongoing [1)]

[1)] WFH Global Survey 2011

Coagulation: Factors with Market Impact

Treatment Options

On Demand

- Episodic, fewer infusions
- Addresses bleed

Prophylaxis

- Regular, more infusions
- Avoids bleeds

WFH/ISTH recommendation: “Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function. (Level 2)” [1)]

[1)] WFH Guidelines for the Management of Hemophilia, 2nd edition

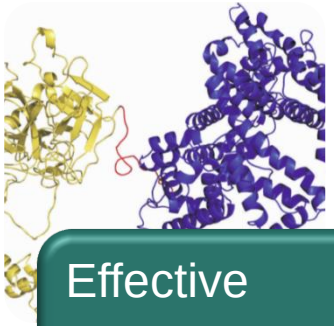
Coagulation: Factors with Market Impact

Product Choice

- Effective
- Safe
- Low inhibitor risk
- Fewer needlesticks

rIX-FP (CSL654)

PROLONG 9 FP
Prophylaxis using longer half-life fusion protein

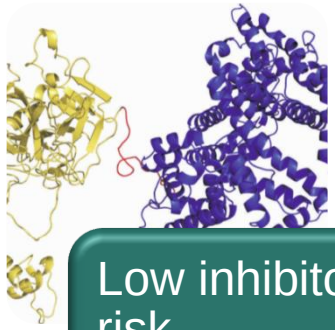


Effective

- Bleeding events effectively treated
- Successful prophylaxis maintained
- Access to site of bleed

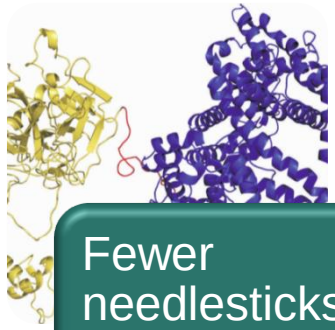
Safe

- Recombinant Albumin as fusion partner
- Well tolerated, locally and systemically to date



Low inhibitor risk

- Specifically designed linker
- Recombinant Albumin as fusion partner



Fewer needlesticks

- T/2 at 92h
- Supports dosing every 2+ weeks
- Approx. 80 fewer needle sticks p.a.

CSL

rVIIa-FP (CSL689)

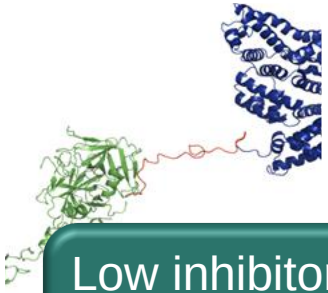
PROLONG 7 FP
Prophylaxis using longer half-life fusion protein

Effective

- Effective in range of animal models

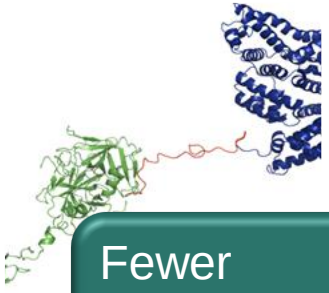
Safe

- Recombinant Albumin as fusion partner
- Well tolerated locally and systemically to date



Low inhibitor risk

- Specifically designed flexible linker
- Recombinant Albumin as fusion partner
- Native FVIIa



Fewer needlesticks

- T/2 at 8.5h
- Supports on demand and prophylactic therapy options

CSL

rVIII-SingleChain (CSL627)

AFFINITY
rVIII-SingleChain Clinical Trial Program

Effective

- Bleeding events effectively treated
- Improved molecular stability
- Access to site of bleed

Safe

- Well tolerated locally and systemically to date

Opportunity for low inhibitor risk

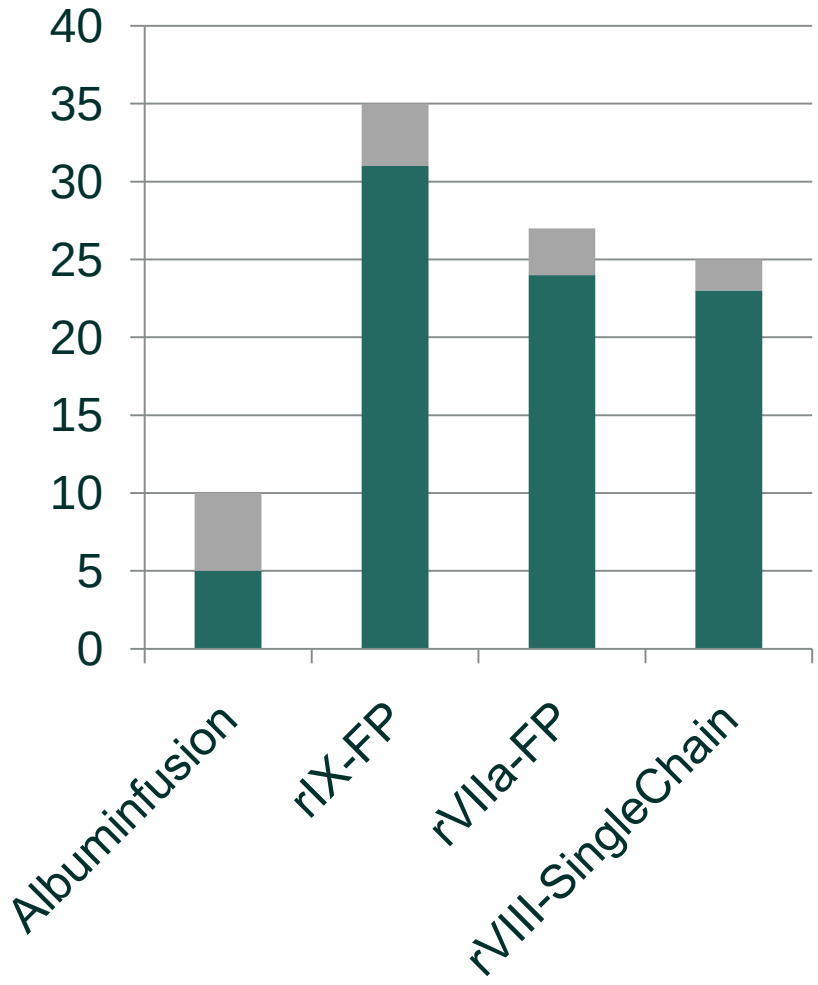
- High binding affinity to VWF
- No inhibitors to date

Fewer needlesticks

- Time to 1% FVIII level supports 2x per week dosing
- Up to 52 fewer needle sticks p.a.

CSL™

Presenting Data: Active Scientific Presence



Extending the pharmacokinetic half-life of coagulation factors by fusion to recombinant albumin

Hubert J. Metzner[1]; Steven W. Pipe[2]; Thomas Weimer[1]; Stefan Schulte[1]
[1]CSL Behring GmbH, Marburg, Germany; [2]Departments of Pediatrics and Pathology, University of Michigan Medical Center, Ann Arbor, Michigan, USA

doi:10.1160/TH13-03-0213
Thromb Haemost 2013; 110:

Received Date : 21-May-2013
Accepted Date : 04-Sep-2013
Article type : Original Article - Clinical Haemostasis and Thrombosis

Safety and Pharmacokinetics of a Recombinant Fusion Protein Linking Coagulation Factor VIIa with Albumin (rVIIa-FP) in Healthy Volunteers

Georg Golor*, Debra Bensen-Kennedy*, Steffen Haffner*, Rachael Easton*, Kerstin Jung§, Tina Moises§, John-Philip Lawo§, Christine Joch §, Alex Veldman§

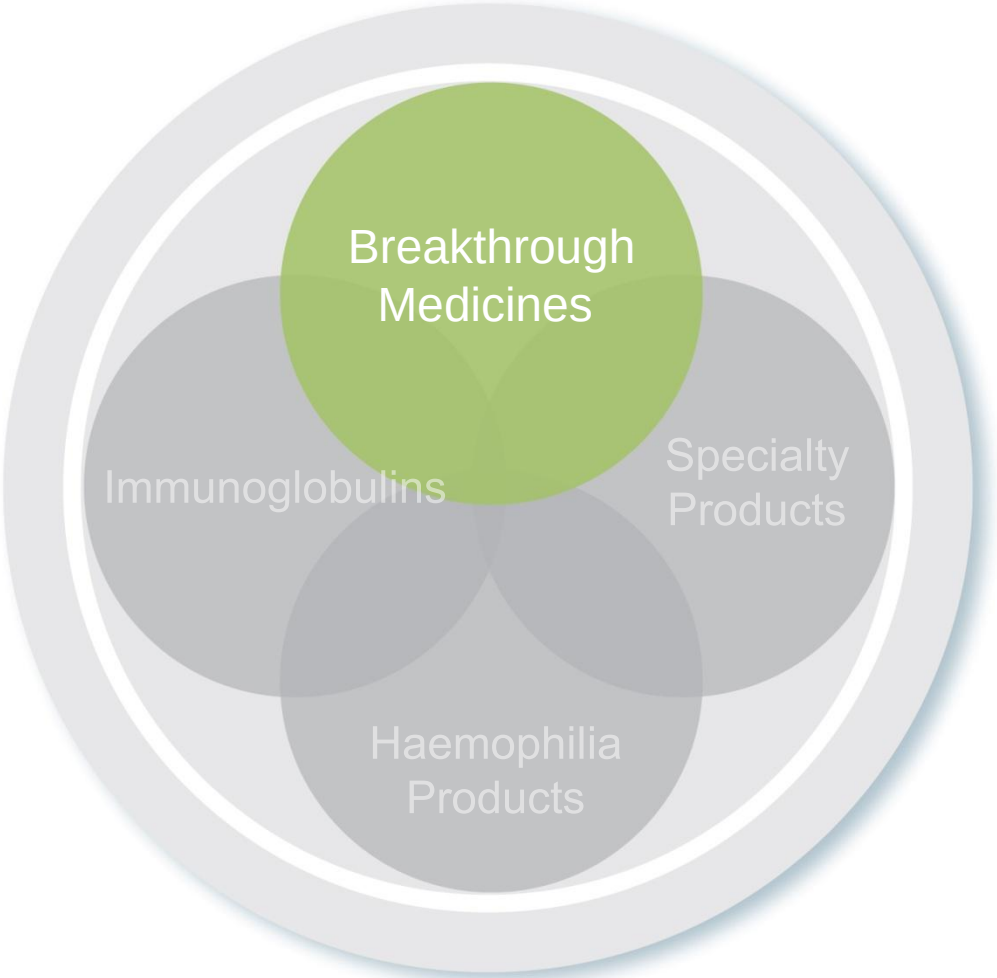
blood
2012 120: 2405-2411
Prepublished online August 2, 2012;
doi:10.1182/blood-2012-05-429688

Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients

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

Breakthrough Medicines

Breakthrough Medicines



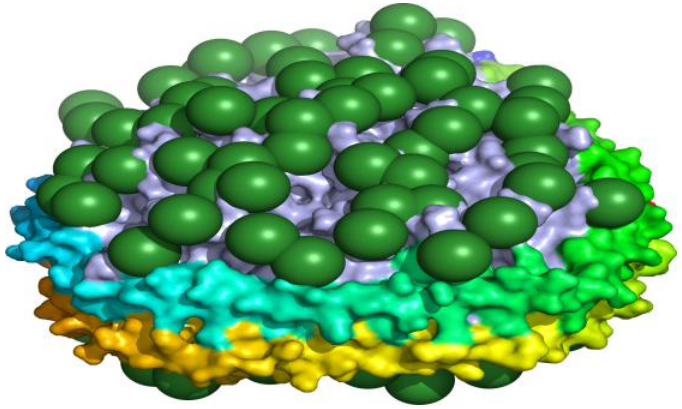
Leveraging clinical and technical insight in developing novel protein-based therapies

- Significant unmet need
- Multiple indications

Key Focus

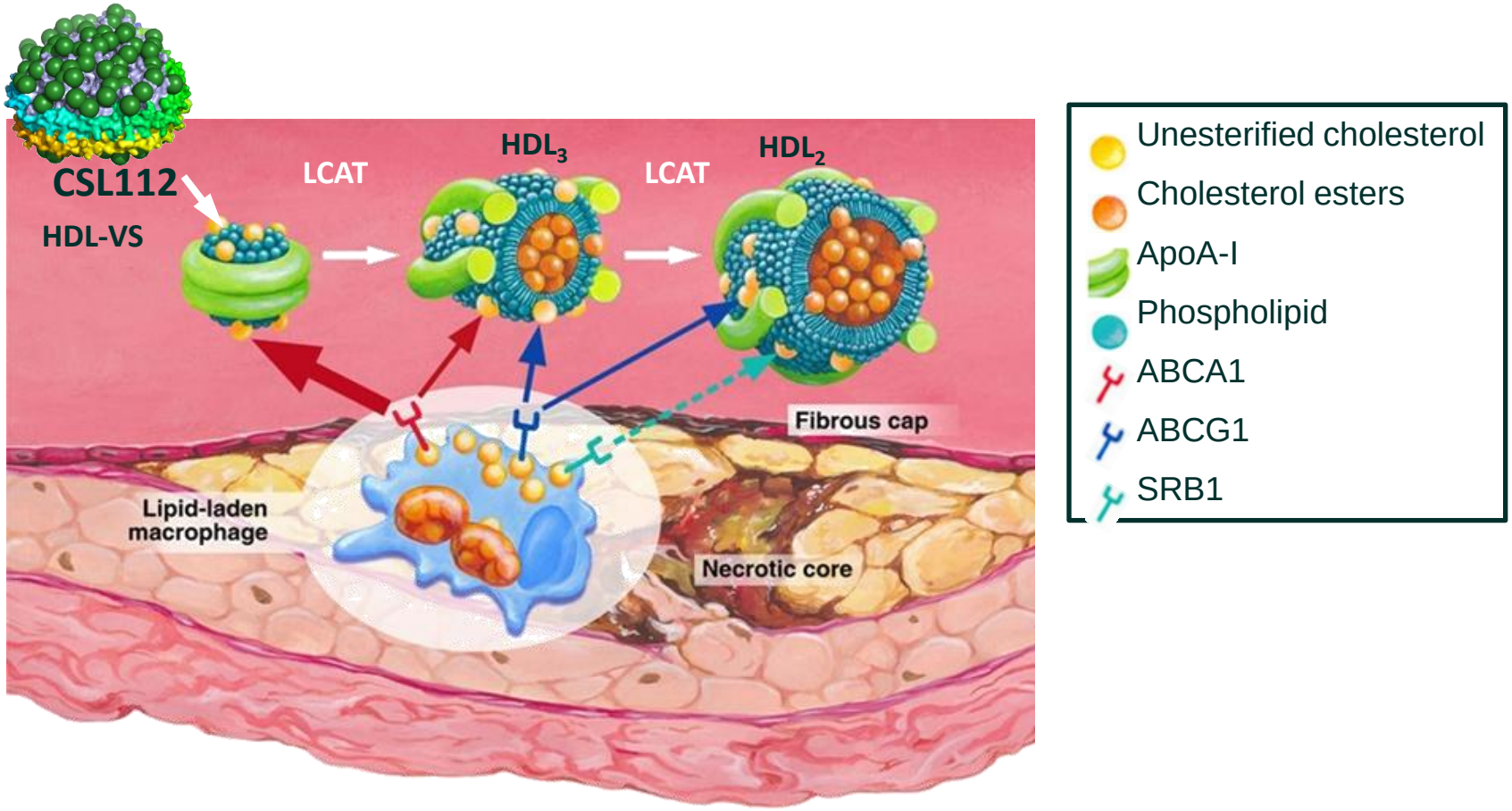
- CSL112 (Apo AI)
- CSL346 (anti-VEGF-B mAb)
- FXII Antagonist

CSL112 (Apolipoprotein A-I)



- CSL112 is natural apolipoprotein A-I (apoA-I) the chief protein component of HDL
- Rapidly and robustly enhances capacity of plasma to promote cholesterol efflux
- Potential to address significant gap in acute coronary syndrome
- Cholesterol removal from atherosclerotic plaque and its proposed removal by CSL112 demonstrated in Phase IIa study

CSL112 Mechanism of Action

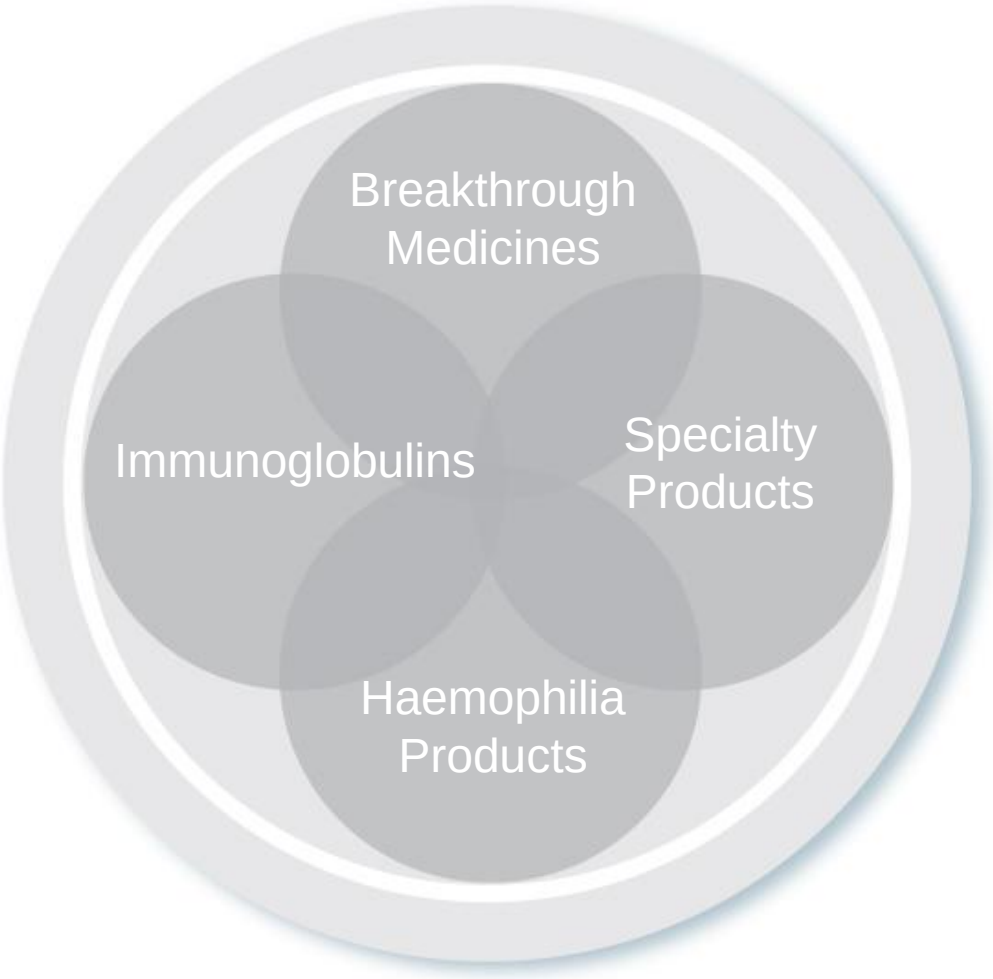


- Global Phase IIb clinical program to initiate early 2014

Modified from Kingwell & Chapman. *Circulation* 2013;128:1112-21

Licensing and Collaborations

Licensing

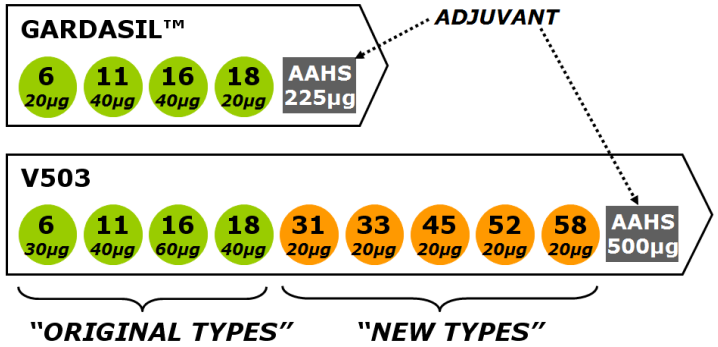


Optimising value of IP Portfolio and assets

- Partner high opportunity products
  - GARDASIL®
  - Mavrilimumab (GM-CSFRα - Medi/AZ)
  - Periodontal disease (Sanofi)
  - CSL362 (Janssen)
- Continue broad licensing strategy for ISCOMATRIX® adjuvant

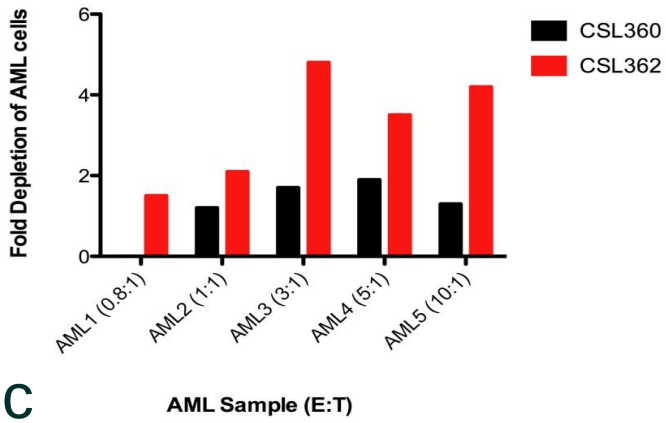
GARDASIL®

- Impact of Australian HPV Vaccination Program
  - 93% reduction in genital warts in females less than 21 years
  - 82% reduction in genital warts in heterosexual males less than 21 years
  - 48% less high grade pre-cancers in women vaccinated in catch-up program (12-17 years in 2007)
- Long term protection
  - Follow up studies up to 8 years demonstrate no break through disease
- V503: 9-Valent HPV Vaccine
  - Merck's 2nd generation HPV vaccine
  - BLA Dec 2013 for 2015 launch
  - Phase III data: prevented 97% cervical, vaginal and vulvar pre-cancers caused by additional 5 types



CSL362 (anti-IL-3Rα mAb)

- Initial indication: Acute myeloid leukaemia
- Enhanced recruitment of tumour killing NK cells
- Phase I trial in progress
- Other high quality opportunities in autoimmunity eg. SLE

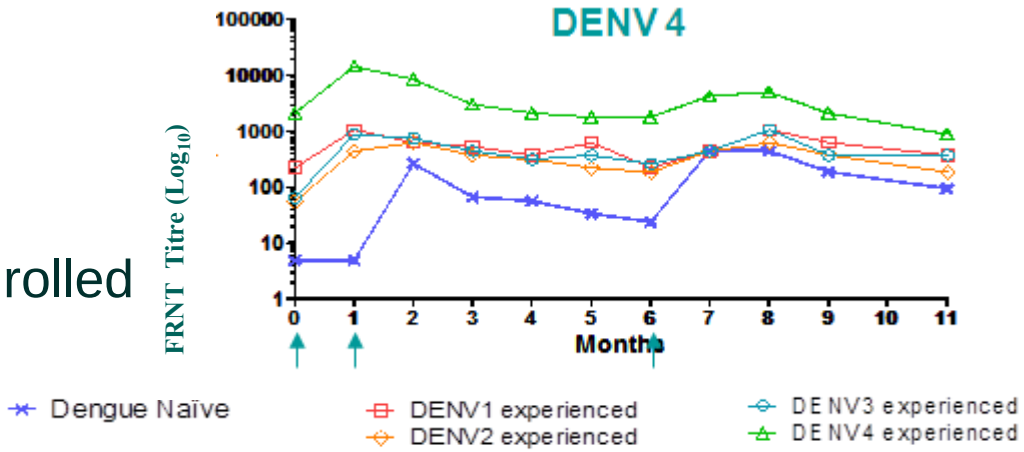


- Agreement with Janssen Biotech, Inc
  - Exclusive worldwide license to develop and commercialise CSL362
  - Collaborative research program to support the use of CSL362 in other indications

ISCOMATRIX® Adjuvant

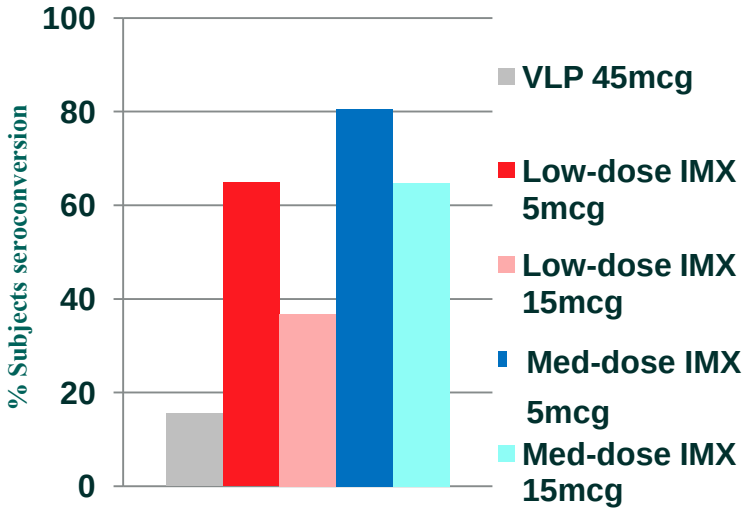
Merck Research Laboratories

- Dengue Phase 1 fully enrolled
- Long lived antibodies in pre exposed NHPs



Novavax

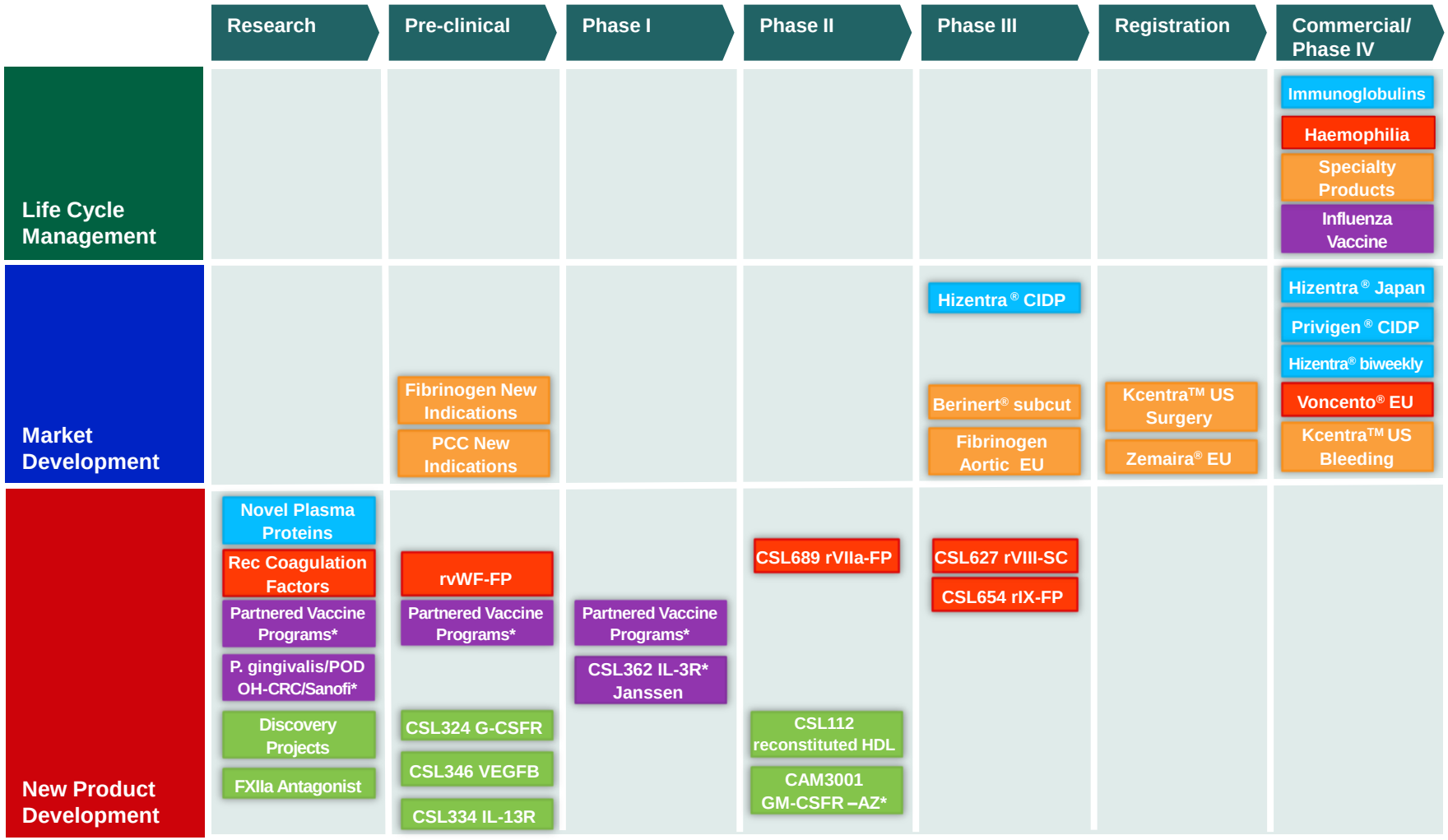
- H5N1
  - WVC 2013
- H7N9
  - NEJM Nov 2013



IMX = ISCOMATRIX® adjuvant

Summary

Global R&D Portfolio December 2013

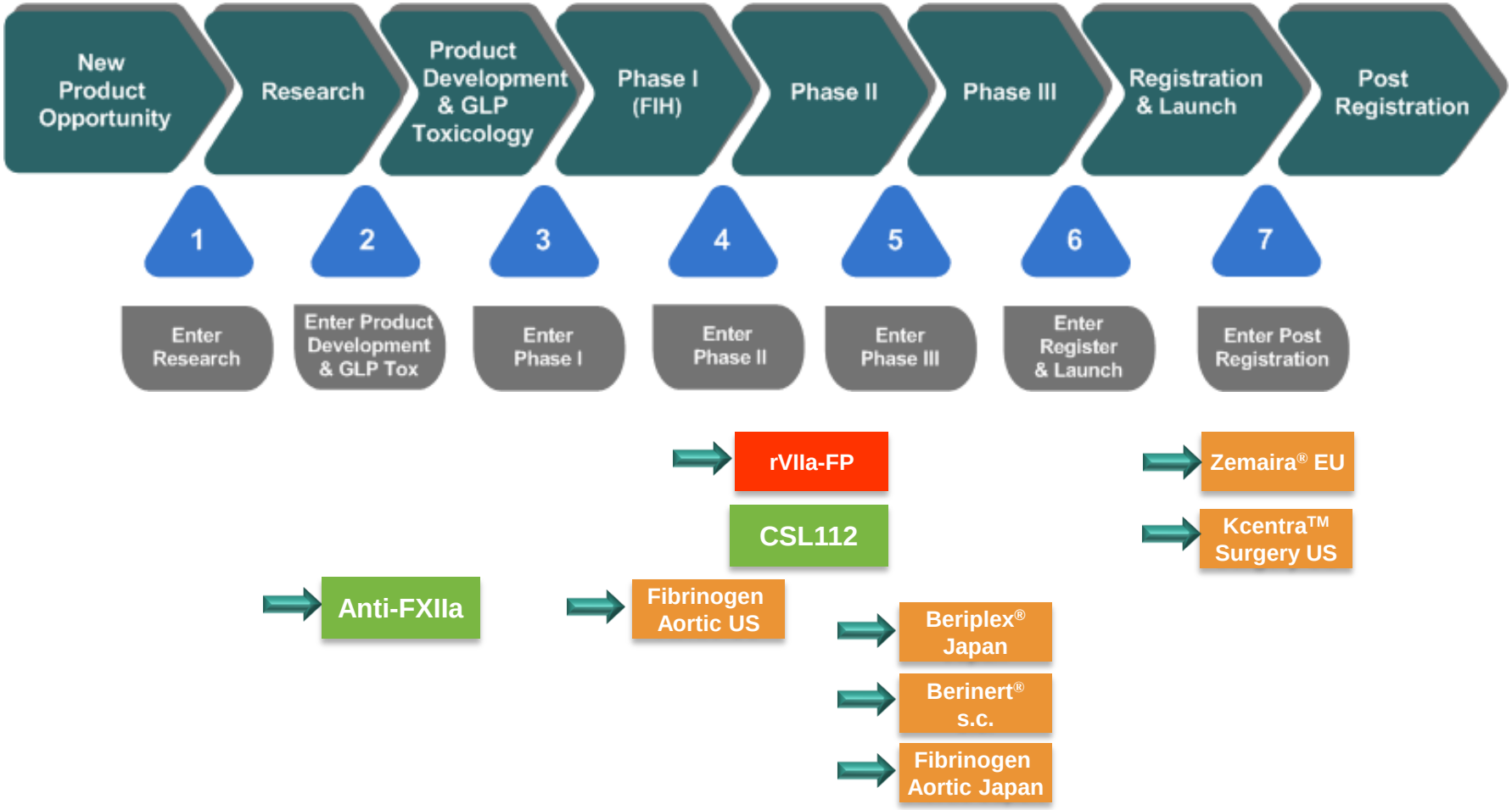


Core Capabilities: Immunoglobulins | Haemophilia | Specialty Products | Breakthrough Medicines | Vaccines & IP

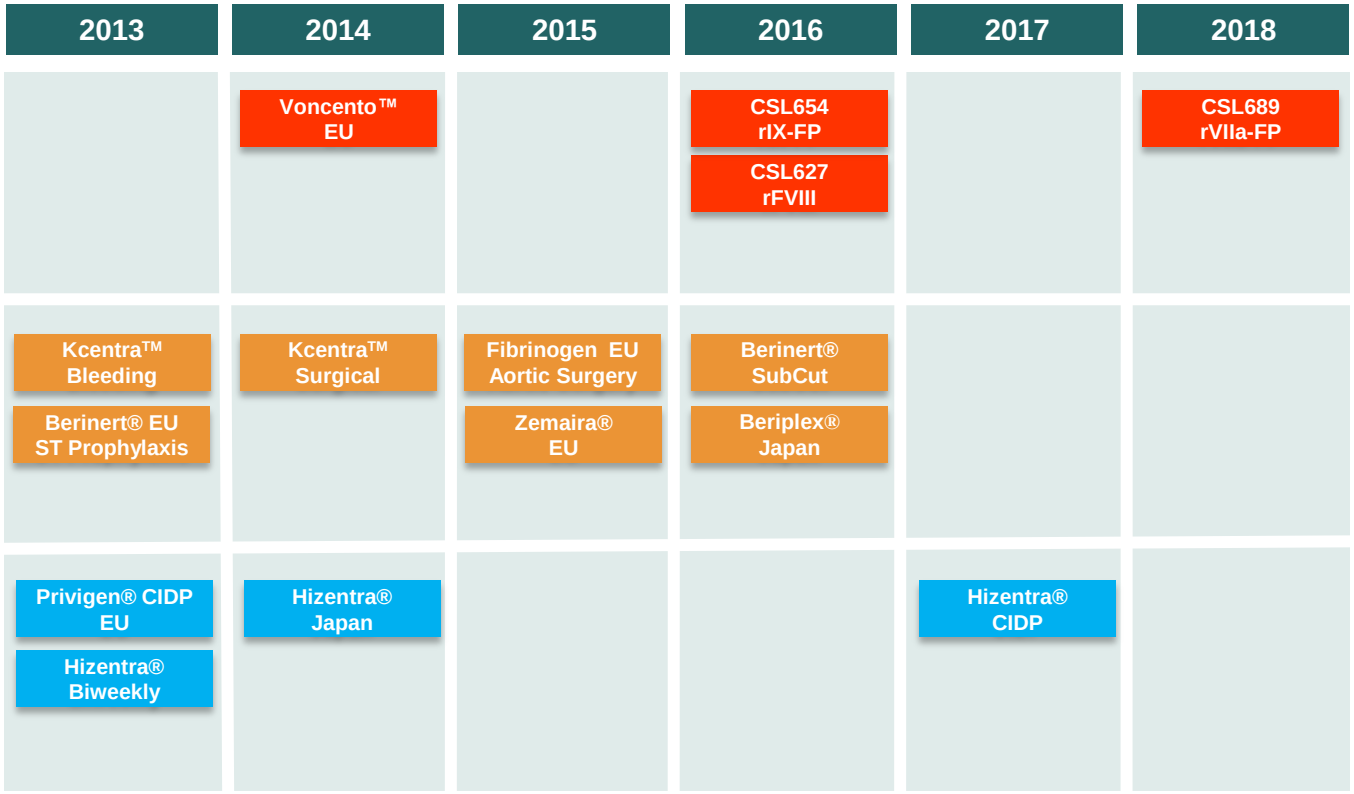
***Partnered Projects**

#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



Core Capabilities: Immunoglobulins | Haemophilia | Specialty Products

* Calendar Years
* Based on estimated first approval

2013 Highlights

Immunoglobulins	• Privigen® CIDP registration in EU • Hizentra® BiWeekly registration in US and EU • Hizentra® registration in Japan
Specialty Products	• Kcentra™ registration for bleeding indication in US • Zemaira® efficacy data submitted in EU and US • Berinert s.c. Pivotal Phase III commenced
Haemophilia	• rIX-FP pivotal Phase III enrolment complete • rIX-FP preliminary data demonstrates efficacy • rVIII-SingleChain Phase I/III supports twice-weekly dosing
Breakthrough Medicines	• CSL112 (reconstituted HDL) Phase IIa data supports mechanism of action and further development
Licensing	• CSL362 (IL-3Rα mAb) partnership with Janssen

Q&A

Further Information

Presentation Playback

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