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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

- Breakthrough Medicines
- Specialty Products
- Immunoglobulins
- Haemophilia Products

Plasma Fractionation

Recombinant Technology

Protein Science
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

## Locations:

- Bern, Switzerland
- Marburg, Germany
- Kankakee, US
- King of Prussia, US
- Tokyo, Japan
- Melbourne Parkville, Australia
- Melbourne Broadmeadows, Australia

## Integration via Project Management Processes:

<table>
<thead>
<tr>
<th>Bern</th>
<th>Broadmeadows</th>
<th>Kankakee</th>
<th>King of Prussia</th>
<th>Marburg</th>
<th>Parkville</th>
<th>Tokyo</th>
</tr>
</thead>
</table>
R&D Investment

CSL RESEARCH AND DEVELOPMENT INVESTMENT (US$ MILLIONS)

<table>
<thead>
<tr>
<th>Year</th>
<th>New Product Development</th>
<th>Market Development</th>
<th>Life Cycle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>08-09</td>
<td>120</td>
<td>22</td>
<td>90</td>
</tr>
<tr>
<td>09-10</td>
<td>140</td>
<td>28</td>
<td>72</td>
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<tr>
<td>10-11</td>
<td>170</td>
<td>32</td>
<td>88</td>
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<tr>
<td>11-12</td>
<td>190</td>
<td>36</td>
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</tr>
<tr>
<td>12-13</td>
<td>210</td>
<td>40</td>
<td>90</td>
</tr>
</tbody>
</table>

- **New Product Development** activities focus on innovative new therapies for life-threatening diseases.
- **Market Development** strategies seek to bring therapies to new markets and new indications.
- **Life Cycle Management** ensures continuous improvement of existing products.
**Global R&D Portfolio**

### Life Cycle Management
- Market Development
- New Product Development

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

### Partnered Projects
*Partnered Vaccine Programs*
- P. gingivalis/POD OH-CRC/Sanofi*
- Discovery Projects

### Research → Pre-clinical → Phase I → Phase II → Phase III → Registration → Commercial/Phase IV

#### New Product Development
- Novel Plasma Proteins
  - rvWF-FP
  - Rec Coagulation Factors
  - Partnered Vaccine Programs*
  - P. gingivalis/POD OH-CRC/Sanofi*
- Discovery Projects

#### Phase I
- Fibrinogen New Indications
- PCC New Indications

#### Phase II
- CSL627 rVIII-SC
- CSL689 rVIIa-FP
- Partnered Vaccine Programs*
- CSL362 IL-3R

#### Phase III
- CSL112 reconstituted HDL
- CAM3001 GM-CSFR –AZ*

#### Registration
- CSL654 rX-FP

#### Commercial/Phase IV
- Immunoglobulins
  - Haemophilia
  - Specialty Products
  - Influenza Vaccine
  - Hizentra® US/EU

### Pre-clinical Research
- Phase I
- Phase II
- Phase III
- Registration
- Commercial/Phase IV

---

*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

1. New Product Opportunity
   - Enter Research
   - rvWF-FP
   - Anti-FXIIa

2. Research
   - Enter Product Development & GLP Toxicology
   - rVIIa-FP

3. Phase I (FIH)
   - Enter Phase I
   - rVIII-SC
   - Beriplex®
   - Japan

4. Phase II
   - Enter Phase II
   - Berinert®
   - s.c.
   - CSL112
   - CSL362* Janssen

5. Phase III
   - Enter Phase III
   - Zemaira®
   - EU
   - Kcentra™
   - Surgery US

6. Registration & Launch
   - Enter Register & Launch
   - Hizentra®
   - Bi-weekly
   - Japan

7. Post Registration
   - Enter Post Registration
   - Privigen®
   - CIDP
   - Hizentra®
   - Japan
   - Voncento™
   - EU
   - FXIII
   - Japan
   - Kcentra™
   - Bleeding US
   - Berinert®
   - EU S-T prophy
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

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

Assess new product opportunities and emerging threats
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
CSL654 (rIX-FP) – Discovery to Development

Factor IX fused to human albumin (CSL654)

CSL654 manufacturing CHO clones

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

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

Marburg

Bio21

CSL654 manufacturing CHO clones

Marburg

Parkville

King of Prussia

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

500L fed batch fermentation

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

Marburg
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 Triado, Ingrid Pabinger-Fasching, Christine Voigtl, Iris Jacob, and Massimo Morfini

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

Carolina E. Hagberg, Anna Mehlert, Annelle Falkevall, Lars Mulh, Barbara C. Fam, Henrik Ortsa, Pierre Scowney, Daniel Nyqvist, Erik Samuelsson, Li Li, Sharon Stone-Elansier, Joseph Proietto, Sofianus Andrikopoulos, Akke Stahl, Andrew Nash, and Ul Eriksson

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

Eugene Maraskovsky, Steve Rockman, Allison Dyson, Sandra Koernig, Dorit Becher, Adriana Baz Morelli, Megan Barnden, Sarina Camuglia, Jesse Bodie, Kirsten Vandenberg, I-Ming Wang, Razvan Cristescu, Andrey Loboda, Mike Citron, Jane Fontenot, Derchie Hung, Peter Schoofs, and Martin Pearse

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

Tracy L. Potter, JAA, JAA, JAA, JAA, Andrea Lovington, Rita Buoncristiani, Nicholas J. Wilson, Paul K. Ziegler, Paul M. Nguyen, JAA, JAA, Adele Pecorari, JAA, JAA, Ryan Fan, JAA, JAA, Kirsten M. Edwards, JAA, JAA, Yeliz Bogul, JAA, Rodney B. Lusson, JAA, Andrew Janicki, JAA, David Holt, JAA, Alex Boussiotis, JAA, Joan K. Heath, JAA, JAA, Oliver M. Seibel, JAA, JAA, and Ira Plesner, JAA, Benjamin T. Ukle, JAA, Andrew Nash, JAA, Florian R. Greten, JAA, Brent S. McKenzie, JAA, and Matthias Ernst, JAA, JAA, JAA, JAA

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

Susann Cattepor, Alexei Schaub, Miriam Ender, Annette Gaida, Alain Kroff, Ursula Guggisberg, Marc W. Nolte, Louis Fabri, Paul A. Adlard, David I. Finkelstein, Reinhard Bolli, Sylvia M. Miescher

PLOS ONE

Cancer Cell

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

**Rat PK study**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Half-life extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>VWF k.o. mouse</td>
<td>4x</td>
</tr>
<tr>
<td>rat</td>
<td>5x</td>
</tr>
<tr>
<td>rabbit</td>
<td>4x</td>
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**Table:**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Half-life extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>vWF:Ag [mIU/mL]</td>
<td></td>
</tr>
<tr>
<td>time [minutes]</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120</td>
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<td>240</td>
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<td>360</td>
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<td>480</td>
<td>480</td>
</tr>
<tr>
<td>1440</td>
<td>1440</td>
</tr>
</tbody>
</table>
FXIIa Antagonists

Auto-activation pathways

FXIIa

- FXI → FXIa
- PK → KAL
- HK → BK → BR2
- C1qr,s → C1qr,s

Mitogenes

- +FXIIa/β

FXII

- Berinert
- Kalbitor
- Icatibant

Hemostasis

- Vasodilation, vascular permeability
- Complement activation

Thrombosis

- Hemostasis
- Vasodilation, vascular permeability
- Complement activation

Thrombosis

- HAE
- Transplantation
- IPF

Fibroblast/endothelial cell
FXIIa Antagonist mAb - HAE

Percutaneous anaphylaxis, a mouse model of HAE

- anti-FXIIa mAb 3F7 inhibits edema

![Graph showing inhibition of edema by 3F7 and BM4](image)
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
Proposed role for pDC’s in SLE

- Dying cell
- IFNα
- RNA/DNA
- Immune complex
- Autoantibodies
- Plasma B cell
- CD4+ T cell
- CD8+ T cell
- Presentation of autoantigens
- T cell help
- Complement-dependent cell cytotoxicity
- Phagocytosis
- Cytotoxicity
- TLR7/9 activation
- CSL362 targets and kills pDC’s

CSL362 for the Treatment of SLE
CSL362 for the Treatment of SLE (Lupus)

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

![Graph showing IFNα concentration in Healthy controls and SLE patients](image-url)

- **Healthy controls**
  - Unstimulated
  - CPG 1uM
  - CSL362 10μg/ml + CPG 1uM

- **SLE patients**
  - Unstimulated
  - CPG 1uM
  - CSL362 10μg/ml + CPG 1uM

n = 5
Mean ± SEM

*IFNa concentration (pg/ml)*

**CSL362 10μg/ml**
- **Healthy**
  - -
- **SLE**
  - +

**CpG 1μM**
- **Healthy**
  - -
- **SLE**
  - +

*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
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
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

Simulation of SCIG q1W & q2W PK

From Landersdorfer et al, Postgrad Med 2013
Commercial Opportunities and Activities
Global Immunoglobulin Market

- Market includes IVIG, SCIG and Hyperimmunes
- Growing, but competitive, market
- CSL is well positioned:
  - privigen
  - Hizentra
  - Sandoglobulin®/CARMU®NF

2012/13 Sales

$US 7+ B
CSL’s Immunoglobulin Portfolio

• Globalise portfolio
• Expand into neurology
• Increase convenience

2012/13 Sales

- Privigen®
- Hizentra®
- IVIG
- Other
- Specific IG

$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

SCIG:
- Steady-state IgG levels
- Self-administration
- Flexibility in infusing
- Low risk of systemic adverse events

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

New Advances for Patients

**Biweekly**
- Approval US: Sept 25, 2013

**10g (50mL) Vial**
- Approval US: Jun 12, 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
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™ approved by FDA in April for bleeding indication

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;*
Kcentra™ Surgical Study Design

Subjects on VKA in need of surgery

Randomised 1:1

Kcentra + Vitamin K

Plasma + Vitamin K

INR

Haemostatic efficacy

Safety (SAEs)

Virus testing

30 min end of infusion

End of surgery

45 days

90 days
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

<table>
<thead>
<tr>
<th>% of subjects</th>
<th>Kcentra (N = 87)</th>
<th>Plasma (N = 81)</th>
<th>Difference Kcentra – plasma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Effective” bleeding control</td>
<td>78 (90%)</td>
<td>61 (75%)</td>
<td>P &lt;0.05</td>
</tr>
</tbody>
</table>
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

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
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

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

• Under-diagnosed
• Lung disease usually presents in 30-40’s
RAPID Study Design

180 subjects

1:1

Randomised

Zemaira weekly iv

Placebo

CT scan

12 months

24 months

36 months

48 months

EXTENSION STUDY

Zemaira weekly iv

50
Zemaira® slows damage to lung tissue

- Efficacy supplement submitted to FDA late Nov 2013
- MAA submitted to EMA early Dec 2013
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
**Dose-ranging study**
- Assess safety, PK/PD
- 18 HAE patients with infrequent attacks
- *Clinically relevant blood levels achieved*

**Clinical efficacy study**
- Double-blind, placebo-controlled
- 72 HAE patients with frequent attacks

**Long-term safety and efficacy**
- Re-randomised, open-label, 1 year
- Patients completing efficacy study

---

Phase II

Phase III
Commercial Opportunities and Activities
CSL’s Specialty Products Portfolio

2012/13 Sales

- Wound Healing
- Perioperative Bleeding
- Other Specialty Products
  - Tachocomb®
  - Beriplast®
  - Fibrogammin®
  - Beriplex®
  - Riastap®
  - Kybernin®
  - Berinert®
  - Zemaira®
  - Streptase®

$US719 M

- 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

Concentrated, virus inactivated, room temperature storage, Fibrinogen concentration 20g / L
Kcentra<sup>TM</sup>, 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.
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.
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
  
- Early intervention with concentrates further recommended in guidelines and transfer into local algorithms

---

1. Davenport and Brohi Critical Care 2013, 17:190
2. Spahn et al. Critical Care 2013 Apr 19;17(2):R76
Zemaira® and the RAPID results

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
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
  - 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

---

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

Manufacturing

• 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
HAE Therapeutic Segments

**Acute**
- Bradykinin/Kallikrein antagonist
- Steroids
- C1 Inhibitor i.v.

**Prophylaxis**
- Berinert (C1 Inhibitor)

**Current**
- Berinert s.c.
- FXIIa MAb (longer half life)
- Kallikrein Inhibitors (longer half life)

**Developments**
Break
R&D Briefing

December 5, 2013
Haemophilia Products
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

Scientific Edge

- Improved half life, extended dosing interval
- rAlbumin as fusion platform
- Precise engineering of specially designed linker

- High vWF affinity
- Improved molecular stability
- Opportunity for Extended Dosing Interval
rIX-FP (CSL654)
rIX-FP (CSL654) Global Clinical Program

Phase I
PK
safety

Phase I/II
PK
Long-term safety
7d prophylaxis
On-demand

Phase II/III
PK
Long-term safety
7-14d prophylaxis
On-demand
Surgical prophylaxis

Phase III
Paediatric

PUP study

Extension
Compared with in market rFIX

- 5.3-fold longer half-life (92 hrs)
- ~45% higher incremental recovery
- ~7-fold larger AUC
- ~7-fold slower clearance
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
rVIIa-FP (CSL689)
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
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
rVIII-SingleChain (CSL627)
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*
Part 1
CSL627 & Octagog alfa single-dose PK (n=30)

Part 2
CSL627 repeat-dose, on-demand or prophylaxis (n=30)

Part 3
CSL627 repeat-dose, on-demand or prophylaxis (n=78 evaluable subjects)
Single-dose PK rVIII-SingleChain (n≥13)

Surgical sub-study
Includes patients from Parts 2 & 3
(n=5 with ≥10 major surgeries)

Interim analysis

Extension study

Study entry

- Part 1 completed enrolment Q1 2013
- Part 3 commenced Q2 2013 – now scheduled to complete early 2014
CSL627 PK Supports Dosing Twice-Weekly

<table>
<thead>
<tr>
<th>Product</th>
<th>Time to 2% (hr)</th>
<th>Time to 1% (hr)</th>
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<tbody>
<tr>
<td>rVIII-SingleChain</td>
<td>78.0</td>
<td>91.9</td>
</tr>
<tr>
<td>Octocog alpha</td>
<td>65.2</td>
<td>77.2</td>
</tr>
</tbody>
</table>

Data presented are mean values. n=22
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
Commercial Opportunities and Activities
Coagulation Sales

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

$US1,090M
Coagulation: Key Market Segments and Products

**Target Segments**

- Hem A ~ $5.2B
  - FX P ~ $2M
  - Inhibitor bleed treatment ~ $1B
- Hem B ~ $0.9B
  - VWD ~ $0.5B
  - pd ITT management ~ $0.4B
- VWD ~ $0.5B
  - VWD ~ $0.5B
- Hem B ~ $0.9B
  - Hem B ~ $0.9B

**Products**

- Factor X P®
- Hem A ~ $5.2B
- pd ITT management ~ $0.4B
- Inhibitor bleed treatment ~ $1B
- VWD ~ $0.5B
- Hem B ~ $0.9B
- Beriate®
- Helixate® NexGen/FS/81
- rVIII-Single Chain
- rVIIa-FP
- Factor X P®
- Hem A ~ $5.2B
- pd ITT management ~ $0.4B
- Inhibitor bleed treatment ~ $1B
- VWD ~ $0.5B
- Hem B ~ $0.9B
- Beriate®
- Helixate® NexGen/FS/81
- rVIII-Single Chain
- rVIIa-FP
- Factor X P®
- Hem A ~ $5.2B
- pd ITT management ~ $0.4B
- Inhibitor bleed treatment ~ $1B
- VWD ~ $0.5B
- Hem B ~ $0.9B
- Beriate®
- Helixate® NexGen/FS/81
- rVIII-Single Chain
- rVIIa-FP

**Key Market Segments**

- FX P ~ $2M
- Voncento®
- Haemate P®
- rvWF-FP
- Voncento®
- Haemate P®
- rvWF-FP
- Mononine®
- Berinin®
- rIX-FP
- CSL Market Estimate 2013
Coagulation: Factors with Market Impact

Diagnosis

Treatment Options

Product Choice

rIX-FP

rVIIa-FP

rVIII-SingleChain
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) WFH Guidelines for the Management of Hemophilia, 2nd edition
Coagulation: Factors with Market Impact

- Effective
- Safe
- Low inhibitor risk
- Fewer needlesticks
rIX-FP (CSL654)

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.
rVIIa-FP (CSL689)

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
rVIII-SingleChain (CSL627)

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.
Presenting Data: Active Scientific Presence

Extending the pharmacokinetic half-life of coagulation factors by fusion to recombinant albumin
Hubert J. Meissner1,*, Steven W. Pope2, Thomas Werner3, Stefan Schulte4
1CSL Behring GmbH, Marburg, Germany; 2Department of Biochemistry and Molecular Biology, University of Michigan Medical Center, Ann Arbor, Michigan, USA
doi:10.1160/TH13-03-0213
Thromb Haemost 2013; 110:

Safety and Pharmacokinetics of a Recombinant Fusion Protein Linking Coagulation Factor VIII with Albumin (rVIIa-FP) in Healthy Volunteers
Georg Golo1, Debra Benssen-Kennedy1, Steffen Haffner1, Rachael Easton1, Kerstin Jung1, Tina Mokbel2, John-Philip Lavo3, Christine Joch3, Alex Veldman3

Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients
Elena Santagatino, Claude Negrier, Robert Klannroth, Andreas Tiade, Ingrid Pabinger-Fasching, Christine Voigt, Ira Jacobs and Massimo Morini

blood
2012 120: 2405-2411
Prepublished online August 2, 2012;
doi:10.1182/blood-2012-06-429688
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

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
• 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

\[\text{VLP 45mcg} \]
\[\text{Low-dose IMX 5mcg} \]
\[\text{Low-dose IMX 15mcg} \]
\[\text{Med-dose IMX 5mcg} \]
\[\text{Med-dose IMX 15mcg} \]

\[\text{IMX = ISCOMATRIX® adjuvant} \]
Summary
### Core Capabilities:
- **Immunoglobulins**
- **Haemophilia**
- **Specialty Products**
- **Breakthrough Medicines**
- **Vaccines & IP**

### Partnered Projects
- P. gingivalis/POD OH-CRC/Sanofi
- FXIIa Antagonist
- CSL324 G-CSFR
- CSL346 VEGFB
- CSL334 IL-13R
- CSL689 rVIIa-FP
- CSL627 rVIII-SC
- CSL654 rX-FP
- CAM3001 GM-CSFR – AZ
- CSL112 reconstituted HDL

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

### Global R&D Portfolio December 2013

#### Research
- Life Cycle Management

#### Pre-clinical
- Market Development
- New Product Development
- Novel Plasma Proteins
- Rec Coagulation Factors
- Partnered Vaccine Programs*
- P. gingivalis/POD OH-CRC/Sanofi*
- Discovery Projects
- FXIIa Antagonist

#### Phase I
- Fibrinogen New Indications
- PCC New Indications
- rWF-FP
- Partnered Vaccine Programs*
- CSL362 IL-3R Janssen

#### Phase II
- Partnered Vaccine Programs*
- CSL324 G-CSFR
- CSL346 VEGFB
- CSL334 IL-13R

#### Phase III
- CSL689 rVIIa-FP
- CSL627 rVIII-SC
- CSL654 rX-FP
- CSL112 reconstituted HDL

#### Registration
- Hizentra® CIDP
- Berinert® subcut
- Fibrinogen Aortic EU
- Kcentra™ US Surgery
- Zemaira® EU
- Hizentra® Japan
- Privigen® CIDP
- Hizentra® biweekly
- Voncento® EU
- Kcentra™ US Bleeding

#### Commercial/Phase IV
- Immunoglobulins
- Haemophilia
- Specialty Products
- Influenza Vaccine
- Partnered Vaccine Programs*
Expected Progress in next 12 Months

- **New Product Opportunity**
- **Research**
- **Product Development & GLP Toxicology**
- **Phase I (FIH)**
- **Phase II**
- **Phase III**
- **Registration & Launch**
- **Post Registration**

**Steps:**
1. Enter Research
2. Enter Product Development & GLP Tox
3. Enter Phase I
4. Enter Phase II
5. Enter Phase III
6. Enter Register & Launch
7. Enter Post Registration

**Products:**
- **Anti-FXIIa**
- **Fibrinogen Aortic US**
- **rVIIa-FP**
- **CSL112**
- **Beriplex® Japan**
- **Berinert® s.c.**
- **Fibrinogen Aortic Japan**
- **Zemaira® EU**
- **Kcentra™ Surgery US**
## Significant Target Launch Dates

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<tr>
<th>2013</th>
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<th>2016</th>
<th>2017</th>
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<tr>
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<td>Voncento™ EU</td>
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<td>CSL627 rFVIII</td>
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<td>Kcentra™ Bleeding</td>
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<td>Fibrinogen EU Aortic Surgery</td>
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<td>Hizenta® Biweekly</td>
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### 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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