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Agenda December 2014 R&D Briefing

- Welcome
  Mark Dehring
- Introduction & Highlights
  Andrew Cuthbertson
- Protein Science Research
  Andrew Nash
- Immunoglobulins & Specialty Products
  Charmaine Gittleson
  Bob Repella
- Clinical Development
- Commercial Opportunities
- Q&A

Break

- Coagulation/Haemophilia
  Charmaine Gittleson
  Bob Repella
  Andrew Cuthbertson
- Breakthrough Medicines & Licensing
- Summary
- Q&A
Introduction and Highlights
CSL Protein Therapeutics Technical Platform

- Plasma Fractionation
- Recombinant Technology

- Immunoglobulins
- Breakthrough Medicines
- Specialty Products
- Haemophilia Products

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

- >1,100 scientists globally
Building Global Recombinant Capabilities

Lengnau rCOAG Manufacturing Facility

Broadmeadows Biotech Manufacturing Facility
R&D Investment

CSL RESEARCH AND DEVELOPMENT INVESTMENT (US$ MILLIONS)

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

**December 2013**

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

### Life Cycle Management

<table>
<thead>
<tr>
<th>Research</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Registration</th>
<th>Commercial/Phase IV</th>
</tr>
</thead>
</table>

### Market Development

| New Product Development | Novel Plasma Proteins | Rec Coagulation Factors | Partnered Vaccine Programs* | P. gingivalis/POD OH-CRC/Sanofi* | Discovery Projects | FXIIa Antagonist | CSL650 rVWF-FP | CSL346 VEGFB | CSL334 IL-13R | Partnered Vaccine Programs* | CSL362 IL-3R* Janssen | CSL689 rVIIa-FP | CSL672 rVIII-SC | CSL654 rX-FP |
|-------------------------|-----------------------|-------------------------|----------------------------|-------------------------------|-------------------|----------------|----------------|----------------|---------------|----------------------------|----------------------|----------------|----------------|----------------|----------------|

### Partnered Vaccine Programs*

- P. gingivalis/POD OH-CRC/Sanofi*
- Discovery Projects
- FXIIa Antagonist
- CSL650 rVWF-FP
- CSL346 VEGFB
- CSL334 IL-13R
- Partnered Vaccine Programs*
- CSL362 IL-3R* Janssen
- CSL689 rVIIa-FP
- CSL672 rVIII-SC
- CSL654 rX-FP

### Registered Products

- Hizentra® CIDP
- CSL830 C1-INH subcut
- Fibrinogen Aortic EU
- Kcentra™ US Surgery
- Zemaira® EU

### Other Products

- Hizentra® Japan
- Privigen® CIDP
- Hizentra® biweekly
- Voncento® EU
- Kcentra™ US Bleeding

---

*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 2014
# Global R&D Portfolio

**December 2014**

<table>
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<tr>
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<tr>
<td>Life Cycle Management*</td>
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<tr>
<td>Market Development</td>
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<td>New Product Development</td>
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</table>

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

### Partnered Projects
- CSL324 G-CSFR
- CSL346 VEGFB
- CSL334 IL-13R
- CSL650 rVWF-FP
- CSL689 rVIIa-FP Congen Def
- CSL689 rVIIa-FP Inhibitors
- CSL692 rVIIa-FP
- CSL112 reconstituted HDL
- CAM3001 GM-CSFR –AZ
- Quadrivalent Flu Vaccine

### Global R&D Portfolio

**Partnered Vaccine Programs**
- CSL362 IL-3R* Janssen
- CSL627 rVIII-SC
- CSL654 rX-FP

**Immunoglobulins**
- Hizentra® CIDP
- Beriplex® Japan
- CSL830 C1-INH subcut
- Fibrinogen Aortic EU
- Zemaira® EU

**Haemophilia**
- CSL830 C1-INH subcut
- CSL654 rVIIa-FP
- Zemaira® EU

**Specialty Products**
- CSL689 rVIIa-FP
- CSL112 reconstituted HDL
- CSL654 rX-FP
- Quadrivalent Flu Vaccine

**Influenza Vaccine**
- CSL689 rVIIa-FP
- CSL112 reconstituted HDL
- Quadrivalent Flu Vaccine

**Vaccines & IP**
- CSL362 IL-3R* Janssen
- CSL627 rVIII-SC
- CSL654 rX-FP
- Quadrivalent Flu Vaccine

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*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.
Protein Science Research
CSL’s Global Research Capability

- 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, Melbourne

• 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 Project Portfolio

Some examples from the CSL Research Project Portfolio

<table>
<thead>
<tr>
<th>Priority</th>
<th>Immunoglobulins</th>
<th>Haemophilia</th>
<th>Specialty Products</th>
<th>Breakthrough Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Ig Formulations</td>
<td>FVIII half-life ext.</td>
<td>Beriplex NOACs Reversal</td>
<td>CSL312 HAE/Throm CSL362 SLE*</td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td>P.ging vaccine / mAb*    CSL334 Asthma*</td>
</tr>
<tr>
<td>Lower</td>
<td>Ig Biomarkers</td>
<td></td>
<td>Haptoglobin / Hemopexin</td>
<td></td>
</tr>
</tbody>
</table>

* Partnered project

Current products
• new indications, new formulations, MOA, Biomarkers

New product candidates
• novel protein-based therapeutics and vaccines, plasma and recombinant
Plasma and Recombinant Proteins

• Capabilities from discovery to market
Factor IX fused to human albumin (CSL654)

CSL654 manufacturing CHO clones

CSL654 T₁/₂ extension in Haem B patients compared to Benefix

CSL654 T₁/₂ extension in Haem B dogs compared to Benefix

500L fed batch fermentation

CSL654 (rIX-FP) – Discovery to Development
CSL312 (FXIIa antagonist mAb)

Hereditary Angioedema (HAE I, II, III)

Contact activation (intrinsic) pathway

Damaged surface

FXII → FXIIa

FXI → FXIa

PXi → FXaB

Haeostasis

Fibrinogen → Fibrin

Vasodilation

BK

BK Receptor 2

Fibrinogen

Fibrin

Haemostasis

Current therapeutic strategy

- On demand treatment with:
  - plasma derived C1-Inhibitor (Berinert)
  - small molecule kalikrein inhibitor
  - small molecule BR2 inhibitor

- Prophylaxis limited by convenience issues
  - subQ Berinert

Opportunity

- Improve clinical outcomes and patient QoL by enabling prophylaxis
CSL312 (FXIIa antagonist mAb)

Generation & characterisation of a human FXIIa antagonist mAb

• screening of human Ab (Fab) phage display library

• mAb 3F7 shows complete inhibition of FXIIa

• affinity matured 3F7 (= CSL312) shows further specificity improvements
CSL312 – Hereditary Angioedema

CSL312 inhibits vascular leakage in ACEI treated C1-INH null mice

ACEI
Basal
3F7/ACEI
BM4/ACEI
Colon

OD @ 620 nm

WT KO

CSL312 inhibits vascular leakage in ACEI treated C1-INH null mice.
CSL312 – Hereditary Angioedema

CSL312 inhibits Factor XIIa activity in human plasma

Healthy Donors (n=10)

HAE Type I (n=2 pts)

Current status

• CSL312 has progressed into product development and toxicology
Haptoglobin (Hp) / Hemopexin (Hx)

Red blood cell lysis and inflammation / tissue damage

- In pathological settings, RBC lyse to release haemoglobin (Hb)
- Haemoglobin is further oxidised leading to the release of heme
- Free Hb and heme are toxic and contribute to disease pathology
  - NO scavenging
  - reactive oxygen species, oxidative stress
  - activation of inflammatory pathways (heme / TLR4)
- Acute phase proteins Hp and Hx sequester and dispose of free Hb and heme

- Hp and Hx are significantly depleted in acute and chronic disease

Opportunity for replacement therapy
Haptoglobin (Hp) / Hemopexin (Hx)

Sickle Cell Disease

- Mutation in $\beta$-Hb gene, aggregation of $\beta$-Hb, sickle-shaped RBC
- Obstruct microvasculature, prone to lysis and release of Hb / heme

Diverse manifestations

- Acute chest syndrome, severe pain, pulmonary hypertension, stroke, splenic infarction, sepsis and renal failure

Aetiology

- Chronic low level and acute higher level exposure to Hb and heme
  - Vasoconstriction, vascular damage / local inflammation
  - Vaso-occlusive crisis
    - mechanical and heme induced obstruction of capillaries

- Hp is absent and Hx significantly depleted in SCD patients
Haptoglobin (Hp) / Hemopexin (Hx)

Hx therapy normalises blood pressure in SCD mice

- Transgenic mice that express human α-globlin and β-globin incorporating the sickle mutation (HbS), no expression of mouse Hb genes
- 0.7mg Hx, 2x per week for 4 weeks from 1 month of age

Vinchi et al., Circulation 2013
CSL Research on Hp / Hx

- Swiss government funding since 2011
- Collaborators: University of Zurich, University of Torino, FDA CBER
- Processes for purification of Hp and Hpx from plasma developed
- Initial pre-clinical proof-of-concept data generated *in vitro* and *in vivo*
- Planning to progress into product development during 2015
Immunoglobulins
Immunoglobulins

Maintaining leadership position through focus on:
- Patient convenience
- Yield
- Label
- Formulation science
- Specialty Igs

Key Focus
- Hizentra®
- Privigen®
The first and only 10% liquid intravenous immunoglobulin (IVIg) therapy that is proline stabilised with room temperature storage up to 36 months.

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.
Benefits of Hizentra®: Steady-State Kinetics

Pharmacokinetic Profile of IVIG vs. SCIG

- SCIG weekly dosing results in steady IgG levels (no peaks, no troughs) \(^1\)
- Patients report less wear off effect switching from IVIG to Hizentra® \(^2\)

---

1. Data shown for a patient with X-linked agammaglobulinemia who received a single infusion of 5% IVIG (30 g followed by 16% SCIG (12 g) every 7 days.
2. Igarashi A. *Clin Ther.* 2014 Sep 15
Hizentra® Schedules Beyond Biweekly

Individualised dosing strategies for patient protection

- More optionality, better management of dosing holiday
- Approved by EMA
- Under FDA review

Data on file CSL Behring
*Hizentra® pharmacometric modeling and simulation
Chronic Inflammatory Demyelinating Polyneuropathy

- Increased use of Privigen® across Europe and Canada in patients with CIDP
- Hizentra® CIDP orphan designation in the US
- Ongoing progress in Hizentra® Path study
Path Phase III Study Design

IgG dependency Test

- Screening
- IVIG Withdrawal
- IVIG Re-stabilization
- SC Treatment

Regular monitoring until CIDP relapse: monthly visits + biweekly phone calls

1x IVIG loading
3x or 4x IVIG maintenance

1, 4, 7, 10, (13)

R

- IgPro20 (0.4 g/kg bw) (N=50)
- IgPro20 (0.2 g/kg bw) (N=50)
- Placebo (N=50)

IVIG rescue medication

Visits (weeks [wk])
2 wk
Up to 12 wk
10 or 13 wk IVIG
24 wk weekly SC

BL = Baseline
R = Randomization
Path Study Progress

- 60 patients completed
- 114 / 174 randomised
- Expect to close recruitment in late 2015
- Last patient completing late 2016
- FDA and EMA submissions Q3/4 2017
Commercial Opportunities
and Activities
Global Immunoglobulin Market

- Ig volume continues to grow globally
- Increased competition particularly in SCIg
- CSL is well positioned

2013/14 Sales (USD)

~ $8b

Sources: Company annual reports / earnings releases, CSL Estimates of Target Markets
CSL’s Immunoglobulin Portfolio

- Increased presence in neurology in Europe
- Maximise patient convenience
- Geographical expansion

2013/14 Sales (USD)

- IVIG
- SCIG
- Hyper IG

$2,320m
Immunoglobulins: Progress Achieved

Increased presence in neurology
- Privigen® CIDP launched in Europe and Canada
- Ongoing development of Hizentra® in CIDP
- Additional indications under evaluation

Maximise patient convenience
- Individualised therapy from daily to bi-weekly
- Further activities ongoing

Geographical expansion
- Hizentra® biweekly approved in major regions
- Hizentra® flexible dosing in EU
- Hizentra® registered in 39 countries
- Privigen® registered in 66 countries
Advantages of individualised therapy with Hizentra®

• Dosing flexibility provides more freedom to patients, allowing them to manage their condition based upon their specific needs and lifestyle

• All dosing options with Hizentra® result in steady-state IgG levels, avoiding the monthly IVIG wear-off effects
Specialty Products
Specialty Products

Leveraging high quality, broad product portfolio through:

• New markets
• Novel indications
• Novel modes of administration

Key Focus

• Beriplex®/Kcentra™
• Berinert®
• Zemaira®
• Fibrinogen
Kcentra™ (Beriplex®)

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

Kcentra™ launched in April in the US as a first in class therapy to reverse the effects of vitamin K antagonists (e.g. Warfarin) for:
- Bleeding related to over-anticoagulation
- Patients needing urgent surgery
- Included in treatment guidelines

Clinical Program commenced in Japan to register Beriplex® for vitamin K antagonist reversal
- PMDA submission Q1 2016
Kcentra™ (Beriplex®)

- Potential clinical application for new oral anticoagulant reversal?

![Graph showing reversal effects of Beriplex® on Edoxaban* in healthy volunteers.]

- 50IU/kg Beriplex® dose reversed the anticoagulant effect of edoxaban

* Potential clinical application for new oral anticoagulant reversal?

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02047565. (Zahir H. Circulation. 2015;131:00-00. Published online November 17, 2014)

* Edoxaban - Daiichi Sankyo Pharma Development, Edison, NJ
Berinert®

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

• Post marketing safety studies completed
  • No antibody generation
  • No increased thrombo-embolic risk
CSL830 (Subcutaneous C1-INH)

Plasma derived, pasteurised & nanofiltered highly concentrated C1 Esterase Inhibitor indicated for subcutaneous administration in the prophylaxis of hereditary angioedema (HAE) in adults and adolescents

- Patients with frequent attacks (50 to <100/year):
  - Treat acute attack, loss of life quality
- High frequency attacks (>100/year)
- Prophylaxis with intravenous C1 Esterase Inhibitor
  - Limited by venous access, break though attacks in some patients

Zuraw B. Allergy, Asthma & Clinical Immunology 2010, 6:23
Vulnerable Period (time <40% C1-INH activity)

SC CSL830 maintains trough levels above “protective” C1 levels

(a) 1000 IU IV pdC1-INH

<table>
<thead>
<tr>
<th>Peak</th>
<th>Trough</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>63.9</td>
<td>29.4</td>
<td>2.2</td>
</tr>
</tbody>
</table>

(b) 3000 IU SC CSL830

<table>
<thead>
<tr>
<th>Peak</th>
<th>Trough</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.3</td>
<td>42.9</td>
<td>1.4</td>
</tr>
</tbody>
</table>
CSL830 Clinical Program

Phase II
Dose-ranging study
- Safety
- PK/PD
- 18 HAE patients with infrequent attacks

Completed

Phase III
Clinical efficacy study
- Efficacy
- PK
- Safety

Ongoing

Phase IIIb
Long-term safety

Commencing Dec 14
CSL830 Phase II COMPACT Study Results

Primary Endpoint

- Mean modelled trough C1-INH functional activity
- Mean as-observed trough C1-INH functional activity

Protective Level

Modified from Zuraw et al; EEACI 2014
CSL830 Phase III Study Design

Modified from Zuraw et al; EEACI 2014
CSL830 COMPACT Program Progress

- 84/100 patients randomised
- Last Patient visit Q4 2015
- Long term Safety study to commence Dec 2014
- Submission to FDA Q2/3 2016
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 use through approval in EMA in 2015

- Completed RAPID trial in 2013
- Under review with EMA
Zemaira® Biochemical Efficacy

Study CE1226_2002
Equivalence to Prolastin®

RAPID Study

www.clinicaltrials.gov
Zemaira® Continues to Slow the Rate of Lung Density Decline Over 4 Years

Estimated Rate of Decline in Physiologically Adjusted P15 at TLC

RAPID Study
N=97
- Annual Rate of Decline
  -2.06 g/L/Year

RAPID Extension (Dec 2013)
N=97
- Annual Rate of Decline
  -1.08 g/L/Year

Annual Rate of Decline
-1.37 g/L/Year

Early Start Group (n=50)
- Annual Rate of Decline
  -1.31 g/L/Year

Delayed Start Group (n=47)

Estimated Decline from Baseline

Months

0 12 24 36 48

www.clinicaltrials.gov
Commercial Opportunities and Activities
Select Specialty Products – Global Markets

- Rare diseases
- Unmet medical need
- High value
- Increasing awareness

Sources: Company annual reports / earnings releases, CSL Estimates of Target Markets
CSL’s Specialty Products Portfolio

2013/14 Sales (USD) $848m

- Peri-Operative Bleeding
- Other Specialty Products

- Berinert®
- Zemaira®
- Ristap®
- Kcentra®
- Beriplex®

- Increase demand
- Geographical expansion
- Education and diagnosis
Kcentra™, Prothrombin Complex Concentrate (Human), is the first non-activated 4-factor PCC approved in the U.S. for the urgent reversal of vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding or needing an urgent surgery or other invasive procedure.

**Sustain momentum in US**
- Surgical indication and launch
- Hospital account expansion

**Key tactics**
- Pivotal publication in Lancet
- Broad customer education

**Geographical expansion\(^1\)**
- Eastern Europe
- Japan

**Life cycle management**
- Improved virus filtration
- New 1000IU vial

---

1) Beriplex®
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\(^2\)

Geographical expansion
- Asia
- Latin America
- Russia

Patient care and convenience
- Short term prophylaxis in Europe
- Self-administration education and expansion
Berinert® Key Features

- Improved patient convenience
  - Low volume formulation

- New method of use
  - subQ prophylaxis

- New Indications
  - Explore new indications (e.g. Transplantation)
Indicated in the US for chronic augmentation and maintenance therapy in adults with alpha-1 deficiency and clinical evidence of emphysema.

Has been shown to slow the progression of emphysema as measured by CT lung density.

DNA\textsubscript{1} is the first and only test to confirm known and unknown variants of alpha-1 proteinase inhibitor.

**Increased diagnosis**
- Approximately 100K patients in US
- 10% of patients diagnosed
- Established DNA\textsubscript{1} test

**Geographical expansion**
- EU registration process ongoing
- Launched in Brazil
- Dossier submitted in Mexico

**Continued investment**
- Expand US sales force
- Explore new formulations

**RAPID data**
- Publish in high impact journal
- Medical Affairs education

**Continued investment**
- Expand US sales force
- Explore new formulations
Q&A
Break
Haemophilialia 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 benefit primary driver of innovation

- Albumin fusion technology
  - rIX-FP, rVIIa-FP, rvWF-FP

- Factor VIII
  - Innovative SingleChain design

Scientific Edge

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

- Strong vWF binding
- Greater molecular integrity and stability
- Opportunity for Extended Dosing Interval
PROLONG-9FP Clinical Development Program: rIX-FP
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-9FP Clinical Development Program: rIX-FP

**Phase I**
- PK
- Safety

**Phase I/II**
- PK
- Long-term safety
- Weekly prophylaxis
- On-demand treatment

**Phase II/III**
- PK
- Long-term safety
- 7, 10 and 14-day prophylaxis
- On-demand treatment
- Surgical prophylaxis

**Phase III**
- Pediatric

**Completed**

**Extension**

**PUP Surgery**

**Completed**

**Completed**

**Completed**

**Completed**

**Ongoing**

www.clinicaltrials.gov
PROLONG-9FP Clinical Results Summary

• Excellent safety profile
  • Well tolerated
  • No inhibitors
  • No adverse events related to CSL654

• Meets all criteria for registration
  • Effectively treats bleeding episodes
  • Offers benefit for prophylaxis
  • Effective in 7-day, 10-day and 14-day regimens
**FIX Activity: rIX-FP vs. rFIXFc**

**rIX-FP shows higher activity at the 240 hour time point**

![Graph showing FIX activity-time profiles](image)

**Paired comparison: Mean (SD) Plasma FIX activity-time Profiles after 50 IU/kg in ≥12 year olds**

- rIX-FP (n=12)
- Previous FIX (n=12)

Plasma FIX activity (IU/dL) at the 240 hour time point:
- rIX-FP shows higher activity.

*With baseline correction

**plasma-derived and recombinant products**

Plasma FIX activity-time profiles in ≥12-year olds
rIX-FP (CSL654) Clinical Development

- All patients now in extension study
- Dossier submission for adult and paediatric indications
  - FDA Dec 2014
  - EMA Q2 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)
rVIIa-FP Clinical Development Program

Congenital Factor VII Deficiency

- Phase I PK/PD study in congenital FVII deficiency patients
  - PK and safety in patients
  - To commence December 2014
rVIIa-FP Clinical Development Program

Congenital Haemophilia with Inhibitors

- Pivotal Phase II/III trial in haemophilia A & B patients with inhibitors
  - Dose finding, safety & efficacy on-demand therapy
  - To commence first half 2015
rVIII-SingleChain (CSL627)
AFFINITY Clinical Development Program: rVIII-SingleChain

Phase I/III 1001
- PK
- Long-term safety
- On-demand treatment
- Long-term prophylaxis
- Surgical prophylaxis

Phase III
- Pediatric

Extension

Completed Ongoing Ongoing

www.clinicaltrials.gov
CSL627 PK Evaluation: Area Under the Curve

*Dose-normalised baseline-corrected FVIII activity $AUC_{0-\text{last}}$ and $AUC_{0-\infty}$ 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

CSL627 PK Evaluation: Clearance and $t_{1/2}$

*Dose-normalised baseline-corrected FVIII activity Clearance and half-life 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. n=27

CSL627 PK Supports Dosing Twice-Weekly

<table>
<thead>
<tr>
<th>Product</th>
<th>Time to 2% (hr)</th>
<th>Time to 1% (hr)</th>
</tr>
</thead>
<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

50 IU/kg, twice per week

Time (day)

0.2 0.5 1.0 2.0 5.0 10.0

FVIII Activity (IU/dL)

CSL627 Advate

rVIII-SingleChain Phase I/III Study

- Very well tolerated
- No inhibitors
- All bleeding events effectively treated
- All surgeries successfully treated

- Pivotal study primary endpoint reached
  - US dossier submission first half 2015
  - EMA dossier submission Q4 2015
Commercial Opportunities
and Activities
Coagulation: Key Market Segments (USD)

**Hem A ~$5.4b**
- Haemate P®
- rVIIa-FP
- Helixate®
- rVIII-Single Chain

**Inhibitor bleed treatment ~$1.4b**
- Voncento®
- Haemate P®
- rvWF-FP

**VWD ~$0.5b**
- Mononine®
- Berinir®
- rIX-FP

**Hem B ~$0.9b**
- Beriate®

Sources: Company annual reports / earnings releases, CSL Estimates of Target Markets
Global Haemophilia Market (USD)

- Trend toward recombinants in major markets
- New longer-acting competition
- Pd highly competitive tender markets

Sources: Company annual reports / earnings releases, CSL Estimates of Target Markets
CSL Coagulation Sales 2013/14 (USD)

- Broad portfolio presence
- Growth in developed and emerging markets
- Helixate® strong foundation for recombinant pipeline

$1,064m
rVIII-SingleChain (CSL627)

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

**Single Chain Design**
- Binds strongly to vWF
- Greater molecular integrity and stability
- Improved PK profile

**Potential Differentiated Profile**
- Effective bleeding control
- Favorable tolerability profile
- Low potential for inhibitors
- Longer lasting therapeutic effect
- Twice-weekly dosing
rIX-FP (CSL654)

Unique recombinant albumin fusion protein molecule

Enhanced pharmacokinetic profile including five-fold half-life extension, seven fold increase in AUC* and higher trough levels

Attributes of Albumin
- Natural protein
- Transports natural components
- Not associated with immune response
- Long half-life

Potential Differentiated Profile
- Effective bleeding control
- Favorable tolerability profile
- Minimising the potential for immunologic response
- Dosing interval 7 to 14 days

Coagulation: Growth Drivers

| Increased diagnosis                        | • Estimated 1 in 1,000 people have inherited blood disorders  
|                                         | • 75% inadequate or no care; disorder not diagnosed          |
| Awareness of benefits of prophylaxis      | • Publications and presentations  
|                                         | • Benefits of long/longer acting products                   |
| Growth in recombinant market             | • Hemophilia B – long acting  →  rIX-FP  
|                                         | • Hemophilia A – longer acting  →  rVIII-SingleChain         |
|                                         | • Inhibitors – long acting  →  rVIIa-FP                       |
| CSL leadership                           | • Strong heritage in therapeutic category                      |
|                                         | • Understanding of physician and patient community           |
|                                         | • Robust pipeline of recombinant products                    |
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)

- Reduction of early recurrent cardiovascular events represents a substantial unmet medical need

![Graph showing the incidence of vascular death, MI, or stroke over days after randomization.](image)

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

Figure adapted from PLATO Trial, Kohli P et al. Circulation 2013;127:673-680
CSL112

- Novel Mechanism of Action for Early Reduction of Recurrent CV Events
- Produces an immediate and robust increase in the efflux of cholesterol from cells, including lipid-rich macrophages in coronary arteries

- Expected to rapidly stabilise plaque and reduce the incidence of early recurrent cardiovascular events
Further elucidation of mechanisms by which CSL112 may rapidly stabilise plaque at risk of rupture

**Mechanism of HDL Remodeling Induced by CSL112**
- Prebeta-1 HDL levels correlate strongly with ABCA1 mediated cholesterol efflux
- Infusion of CSL112 rapidly produces large increases in prebeta-1 HDL

**CSL112 Enhances Cholesterol Efflux In Patients with Low HDL Function**
- CAD* patients have impaired ability to efflux cholesterol from cells
- CSL112 caused strong and quantitatively similar elevation in cholesterol efflux in patients with coronary artery disease and healthy subjects

*Coronary artery disease
CSL112
AHA announcement of Phase 2b start

Randomisation
N = 1200

Four Weekly Infusions

High dose (6 gms)
N = 400

Low Dose (2 gms)
N = 400

Placebo
N = 400

Administered in acute MI setting
Primary endpoint: liver and renal safety
To be followed by Phase 3 morbidity/mortality trial

Target indication
Reduction of early atherothrombotic events in acute MI patients
at high risk of recurrent events
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)
  - CSL334 (ASLAN)
- ISCOMATRIX® adjuvant
• Impact of Australia’s HPV Vaccination Program

Genital warts
• 93% reduction in genital warts in females less than 21 years
• 82% reduction in genital warts in heterosexual males less than 21 years
• Rates of treatment for genital warts in private hospitals have also declined

Cervical disease
• Current Australian cervical screening program data show that rates of high grade cervical disease are declining in both the <20 year old age group and in women aged 20–24 years

HPV Prevalence
• Substantial fall in vaccine-targeted HPV types in vaccinated women
• Also lower prevalence of vaccine-targeted types in unvaccinated women, suggesting herd immunity
GARDASIL®

• 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
  • Phase III data: prevented 97% cervical, vaginal and vulvar pre-cancers caused by additional 5 types
  • US - BLA Dec 2013 for 2015 launch
  • Australia - Submitted registration package to TGA June 2014
Mavrilimumab (GM-CSFRα mAb)

Phase IIb (EARTH EXPLORER 1) study:

- 326 patients with moderate-to-severe RA and an inadequate response to at least one disease-modifying anti-rheumatic drug
- Dosing (30, 100, 150mg) every 2 weeks for 24 weeks
- Co-primary endpoints
  - Mean change from baseline in DAS28-CRP at Week 12
  - ACR20 response rate at Week 24
- Other endpoints
  - Multiple disease activity parameters
  - Safety and tolerability profile
- Patients eligible to enter open-label extension (OLE) study
Mavrilimumab

Phase IIb study met DAS28-CRP co-primary endpoint:

- At Week 12, a statistically significant difference in DAS28-CRP was seen for all doses of mavrilimumab versus placebo

- Sustained at Week 24 versus placebo

![Graph showing mean ±SE DAS28-CRP change from baseline at Week 12 and Week 24, with significant differences indicated by ***p<0.001 for mavrilimumab compared to placebo.]

- A significantly greater percentage of mavrilimumab-treated patients met the ACR20 co-primary endpoint versus placebo for all doses

***p<0.001, mavrilimumab versus placebo
Mavrilimumab

Phase IIb study conclusions:

• Study met both co-primary endpoints at all mavrilimumab doses

• All secondary endpoints (including ACR50, ACR70 response) achieved statistical significance for the 150 mg dose

• Rapid (after one week of initiation of treatment) and sustained improvement in multiple symptoms of RA observed in patients receiving mavrilimumab

• Improvements demonstrated in patient-reported outcomes (pain, health-related quality of life, physical function, fatigue)

• An acceptable safety and tolerability profile, with no apparent safety signals, demonstrated over the 24-week study period
CSL362 (anti-IL-3Rα mAb)

- Initial indication: Acute myeloid leukaemia
- Enhanced recruitment of tumour killing NK cells
- Phase I study in progress
- Other high quality opportunities in autoimmunity eg. SLE
- Partnership with Janssen Biotech, Inc
Summary
# Global R&D Portfolio

**December 2014**

<table>
<thead>
<tr>
<th>Core Capabilities:</th>
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<tbody>
<tr>
<td>Immunoglobulins</td>
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<td>Haemophilia</td>
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<td>Specialty Products</td>
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<tr>
<td>Breakthrough</td>
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<tr>
<td>Medicines</td>
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<tr>
<td>Vaccines &amp; IP</td>
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</tbody>
</table>

### Life Cycle Management®

- Fibrinogen New Indications
- PCC New Indications

### Market Development

- **New Product Development**
  - Novel Plasma Proteins
  - Rec Coagulation Factors
  - Partnered Vaccine Programs* P. gingivalis/POD OH-CRC/Sanofi*
  - Discovery Projects
  - CSL650 rVWF-FP
  - CSL699 rVIIa-FP Congen Def
  - CSL362 IL-3R* Janssen
  - CSL112 reconstituted HDL
  - CAM3001 GM-CSFR –AZ*

### Registration

- **Hizentra® CIDP**
- **Beriplex® NOACs** Daiichi*
- **CSL689 rVIIa-FP** Inhibitors
- **CSL689 rVIIa-FP** Congen Def
- **CSL362 IL-3R** Janssen

### Commercial/Phase IV

- Immunoglobulins
- Haemophilia
- Specialty Products
- Influenza Vaccine
- Hizentra® Japan
- Privigen® CIDP
- Hizentra® biweekly
- Voncento® EU
- Kcentra™ US Bleeding/Surgery

---

*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

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

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

**Privigen**
- **MG**
- **Japan**

**Hizentra**
- **US Flex Dosing**

**rIX-FP**
- **US Approval**

**rVIIa-FP**
- **Inhibitors**

**Haptoglobin/Hemopexin**

- **CSL12**
  - Anti-FXIIa

- **CSL324**
  - G-CSFR

- **CSL334**
  - ASLAN

- **CSL362**
  - Janssen

- **CSL830**
  - C1-INH s.c.

- **Beriplex®**
  - Japan

- **QIV**
  - 18+ years

- **Zemaira® EU**

**CSL**
## Significant Target Launch Dates

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<tbody>
<tr>
<td><strong>Voncento™ Haem A EU</strong></td>
<td><strong>Voncento™ V WD EU</strong></td>
<td><strong>CSL654 rIX-FP US</strong></td>
<td><strong>CSL654 rIX-FP EU</strong></td>
<td><strong>CSL654 rIX-FP Japan</strong></td>
<td><strong>CSL654 rIX-FP US</strong></td>
</tr>
<tr>
<td><strong>Kcentra™ Surgical</strong></td>
<td><strong>Zemaira® EU</strong></td>
<td><strong>CSL654 rIX-FP EU</strong></td>
<td><strong>CSL654 rIX-FP EU</strong></td>
<td><strong>CSL830 C1-INH SubCut</strong></td>
<td><strong>CSL689 rVIIa-FP Congen Def</strong></td>
</tr>
<tr>
<td><strong>Hizentra® Japan</strong></td>
<td><strong>CSL627 rFVIII-SC US</strong></td>
<td><strong>CSL627 rFVIII-SC US</strong></td>
<td><strong>CSL627 rFVIII EU/Japan</strong></td>
<td><strong>Fibrinogen EU Aortic Surgery</strong></td>
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<tr>
<td><strong>Quadrivalent Flu Vaccine 18+</strong></td>
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**Core Capabilities:**
- Immunoglobulins
- Haemophilia
- Specialty Products
- Vaccines & IP

* Calendar Years
2014 Highlights

Immunoglobulins
- Hizentra® flexible dosing registration in EU
- Hizentra® CIDP orphan drug designation
- Ongoing global Privigen CIDP registrations

Specialty Products
- Kcentra™ registration for surgical indication in US
- Berinert® s.c. Pivotal Phase III rapid recruitment
- Commencement of Beriplex™ Japan Phase III study

Haemophilia
- rIX-FP Phase III efficacy data supports 7-14 day dosing
- rVIII-SingleChain Phase I/III supports twice-weekly dosing
- rVIIa-FP congenital deficiency Phase I/II commenced

Breakthrough Medicines
- Commencement of CSL112 (Apo A-1) Phase IIb study
- Anti-FXIIa mAb progressed into product development

Licensing & Vaccines
- Quadrivalent Flu (QIV-01) study 18+ yrs fully recruited
- Mavrilimumab positive additional Phase II data
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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