## Session 2

### Candidates for development

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>CS-1008 (US/EU) DJ-927 (JP) CS-7017 (US/EU)</td>
<td>DJ-927 (US/EU)</td>
</tr>
<tr>
<td>Infection</td>
<td>DC-159a (US/EU/JP) DX-619 (JP) CS-8958 (US/EU)</td>
<td>CS-023 (JP)</td>
</tr>
<tr>
<td>Immunity and allergies</td>
<td>CS-0777 (US/EU)</td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular Diseases

Prasugrel (CS-747)
CS-8663
DU-176b
DZ-697b
CS-9803

Co-developing & co-commercializing with Eli Lilly and Co.
Platelet aggregation inhibitor
- Initial submission for acute coronary syndromes (ACS)
- Phase 1 studies suggest prasugrel may have superior profile
  - Higher inhibition of platelet aggregation (IPA)
  - Faster onset of IPA
  - More consistent IPA
- Phase 2 safety study indicated acceptable bleeding profile
- Phase 3 study currently enrolling 13,000 patients
- Submission anticipated in second half of 2007
Prasugrel Phase 1 Study Results
Faster Onset of Inhibition of Platelet Aggregation

IPA (%) = 100\(\frac{[\text{Baseline MPA} - \text{MPA at timepoint}]}{\text{Baseline MPA}}\)

Results shown as mean ± sd

0 2 4 6 8 12 16 20 24

Inhibition of Platelet Aggregation (%)

Time After Administration (h)

Prasugrel 60 mg
Clopidogrel 300 mg

"Superior Responder Rate for Inhibition of Platelet Aggregation With a 60 mg Loading Dose of Prasugrel Compared With a 300 mg Loading Dose of Clopidogrel", John T. Brandt et al., presented at the American College of Cardiology, March 2005.

Prasugrel Cross-Over Study Results
More Consistent Inhibition of Platelet Aggregation

IPA at 24 hours to 20 µM ADP

Inhibition of Platelet Aggregation (%)

*Responder = >25% IPA at 4 and 24 h

"Superior Responder Rate for Inhibition of Platelet Aggregation With a 60 mg Loading Dose of Prasugrel Compared With a 300 mg Loading Dose of Clopidogrel”, John T. Brandt et al., presented at the American College of Cardiology, March 2005.
**Prasugrel Phase 2 Safety Study**

No Significant Differences in Bleeding Endpoints Measured

Primary Endpoint of JUMBO TIMI-26 Study:
Significant Non-CABG Bleeding at 30 days (Major + Minor Bleeds)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Clopidogrel*</th>
<th>Prasugrel 40/7.5</th>
<th>Prasugrel 60/10</th>
<th>Prasugrel 60/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>* At approved doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P = Not Significant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2%</td>
<td>1.7%</td>
<td>1.5%</td>
<td>2.0%</td>
<td></td>
</tr>
</tbody>
</table>


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**Prasugrel Phase 3 TRITON TIMI-38 Protocol**

Stratified Randomization:
- UA/NSTEMI vs STEMI

Planned PCI for ACS
- Mod - Hi Risk UA/NSTEMI STEMI

Antithrombin
- GP IIb/IIIa at MD discretion

- Clopidogrel 300 mg LD / 75 mg MD + ASA
- Prasugrel 60 mg LD / 10 mg MD + ASA

Secondary EPs (30, 90 d): CVD/MI/CVA ; CVD/MI/uTVR

- Clopidogrel 75 mg/day + ASA
- Last pt followed for 6 m (med =12m, max =15 m)
- Prasugrel 10 mg/day + ASA

Primary Endpoint (end of FU): CVD/MI/CVA
- Secondary EP (end of FU): CVD/MI/CVA/Hosp for Rec Isch
**Prasugrel Phase 1 TIMI 44 Protocol**

- **n < 180**
  - Planned Elective PCI
  - Aggregometry and Biomarkers
  - Clopidogrel-naive
  - Planned GP IIb/IIIa prohibited

- **n = 100**
  - High Dose Clopidogrel
  - ASA
  - Prasugrel 60 mg
  - 0.25, 0.5, hour post-LD Aggregometry and biomarkers
  - Diagnostic catheterization anatomy suitable for PCI
  - Post cath aggregometry

- **Primary Endpoint:** Mean IPA (6h) in all treated subjects

**Prasugrel Phase 2 TIMI 44 Protocol**

- **PCI**
  - High Dose Clopidogrel x 14d
  - Prasugrel 10 mg x 14d
  - 14 d clinical events, biomarkers, aggregometry, CROSSOVER

- **Primary Endpoint:** Mean IPA (14d&30d) in all treated subjects
Prasugrel Japan Clinical Development

Current Status
- Phase 1 study is on-going

Target Indications
- The following have been considered as target indication
  - Prevention of atherothrombotic events in patients who undergo percutaneous coronary intervention (PCI) while having acute coronary syndrome (ACS)
  - Secondary prevention of thrombotic vascular events in patients with cerebrovascular accident (CVA)

CS-8663

- A fixed dose combination of two antihypertensives, amlodipine (most widely used CCB) and olmesartan medoxomil (fastest growing ARB)
  - ARBs continue to be the fastest growing anti-hypertensive class
  - Life cycle management strategy to grow Benicar®(US) /Olmetec®(Europe) franchise

- Target indication: second line therapy for hypertensive patients who fail monotherapy
  - Over 120 million hypertensive patients in the US/EU and still growing
  - Only 40 - 50% of hypertensive patients are being treated, and only about half of them achieving target blood pressure goals
  - Addresses unmet medical need, getting more patients to treatment goals recommended by the guidelines

- Phase 3 studies on-going
  - Target market entry soon after amlodipine (Norvasc®) patent expiry (US)
Grows to third-largest seller in US ARB market – Benicar/Benicar HCT

Accounts for approx. 15% of new prescriptions to join the top 3, aiming for No. 2 spot

Trends in share of new prescriptions in US ARB market since Benicar went on the market:

Benicar HCT Launch

15.7% 2006/3

2004 Sales Share of Anti-Hypertensive Class
US, EU5 (DE, UK, FR, ES & IT) & JP

22.0% 26.5% 14.1% 4.9% 4.6%

Angiotensin Receptor Blocker Calcium Channel Blocker

Diuretics Others Beta-blocker CCB ARB Franchise ACEI Franchise

[Source: IMS]
**DU-176b**

- Best in class inhibitor of blood coagulation factor Xa.
- Oral doses inhibit thrombin generation dose-dependently in human volunteers.
- VTE prevention was confirmed by QD and BID dosing in the patients with total hip replacement without causing increased bleeding (605 pts).
- Phase 2b studies are under preparation.
  - Targets: AF
  - VTE
- Clinical data is consistent with preclinical data including toxicogenomics that suggests a low risk of hepatotoxicity.
- Significant market opportunity but with many competitors.
  - $11 billion
  - 9% increase every year

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**Mechanism of DU-176b**

**Blood Coagulation Stimulus**

- Extrinsic (Endothelial damage)
- Intrinsic (XII a)

**DU-176b**

Xa ➔ Thrombin ➔ Fibrin Clotting

- **Prothrombin** ➔ Thrombin
- **Fibrinogen** ➔ Fibrin Clotting

<<Vessel occlusion>>
Greater separation of anti-thrombotic effect and bleeding risk with DU-176b

DU-176b

Warfarin

Heparin

0.01 0.1 1 10 100
DU-176b (mg/kg, p.o.)
Warfarin (mg/kg/day, p.o.)
Heparin (U/kg/h, i.v., infusion)

○, □, △ Anti-thrombotic effect
●, ■, ▲ Bleeding time

Platinum-wire induced venous thrombosis model and tail cut bleeding time in rats

DU-176b was scarcely metabolized and QD dosing was suggested in human volunteers

Thrombin generation was measured by F1+2 formation

[DSK] [JPSY 2006]
DZ-697b

- **First in class anti-platelet agent**
  - Inhibit platelet adhesion to the injured endothelium
  - Inhibit high-shear stress induced platelet aggregation
  - Little inhibition on aggregation at low-shear stress suggests lower bleeding risk

- **Phase 1 study**
  - Rapid onset and prolonged inhibition
  - Inhibited platelet aggregation induced by shear stress (PFA-100), collagen and ristocetin
  - Excellent PK profiles in oral absorption and AUC
  - High tolerance without increase in bleeding time

- **Phase 2a study**
  - The clinical plan was reviewed with FDA and obtained agreement to proceed with stroke and stable CVD (Pre IND meeting)

- **Potential Indications**
  - Stroke, ACS, Microcirculation disorders

DZ-697b, Prasugrel, DU-176b
**DZ-697b Lower Bleeding Risk than Aspirin**

![Graph showing comparison between DZ-697b and Aspirin](image)

DZ-697b, an Anti-thrombotic effect agent, is expected to be a first in class agent for reduction of reperfusion injury in acute myocardial infarction patients undergoing revascularization procedures.

*PKC: protein kinase C

Currently a Phase 1/2 study ("DELTA-MI") is ongoing in US/EU in acute heart attack patients undergoing balloon angioplasty.

Promising pre-clinical efficacy in models of ischemic stroke

FDA fast track designation

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**CS-9803**

- Co-developing with KAI pharmaceuticals, South San Francisco, CA
- Delta PKC* inhibitor, is expected to be a first in class agent for reduction of reperfusion injury in acute myocardial infarction patients undergoing revascularization procedures
  
  *PKC: protein kinase C

Currently a Phase 1/2 study ("DELTA-MI") is ongoing in US/EU in acute heart attack patients undergoing balloon angioplasty.

Promising pre-clinical efficacy in models of ischemic stroke

FDA fast track designation
Mechanism of CS-9803

- CS-9803 is a small peptide that works by inhibiting the translocation of delta PKC to its specific intracellular receptor.
- Delta PKC activation during reperfusion initiates the inflammatory molecular processes leading to cell death and damage to the heart.
- CS-9803 inhibits both apoptotic and necrotic pathways of myocardial cell death and heart muscle damage.

CS-9803 AMI Model for Reperfusion Injury

Pig model of acute MI by occluding LAD coronary artery with a balloon
CS-9803 Reduces Infarct Size in Pig Model

From pharmacology studies using healthy pig model with induced MI by balloon-occlusion of LAD. Treatment with CS-9803 resulted in:

• 70% reduction in infarct size (seen 4 hr, 5 and 14 days post-reperfusion)

Oncology

DJ-927
CS-7017
CS-1008
New Oral Taxane anticancer

- Excellent antitumor activity in oral administration
- Less affected by P-gp, a drug excretion pump, and effective in multidrug resistant (MDR) cell lines such as colorectal cancer
- Reduced risk of peripheral neuropathy

1. Phase 1 study

- Oral absorption confirmed
- MTD: 27–35 mg/m²
- DLT: Neutropenia
- Potential anti-tumor activity in breast cancer and bladder cancer
**DJ-927**

2. **Phase 2a study**
   - **Colorectal cancer:**
     Response (CR and PR) observed after failure of Oxaliplatin- or Irinotecan-based chemotherapy
     First Taxane effective for Colorectal cancer
   - **Breast cancer:**
     Response (PR) observed after failure of anthracycline-based chemotherapy
   - **Gastric cancer:**
     Response (PR) observed after failure of 5-FU based chemotherapy
   - **Predominant ADR:**
     Neutropenia
     Gastrointestinal toxicities (nausea and vomiting)

3. **Phase 2b study**
   - **Under consultation with FDA**
     Colorectal cancer
     Breast cancer

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**CS-7017**

- **Antitumor PPARγ activator**
- A positive correlation between PPARγ activation and inhibition against colony formation of tumor cells have been demonstrated in vivo
- Effective against human tumor-implanted in vivo models
- Inhibits growth of tumor cells in vitro without killing those cells
- Expected to be less toxic compared to standard chemotherapeutics
- Could be used either alone or in combination with other chemotherapeutic agents
- Phase 1 study is on-going in US
**Mechanism of CS-7017**

- PPARγ activator (ligand)
- Gene transcription activation
- Gene expression
- aP2 (differential regulation gene), PTEN (tumor suppressor gene) etc.

**CS-1008**

- A humanized version TRA-8, a murine agonistic moAb raised against human death receptor 5 (DR5)
- Discovered through collaboration with the University of Alabama at Birmingham in U.S.
- CS-1008 induces apoptosis of tumor cells expressing DR5 on the cell surface
- Pre-clinical studies showed an anti-cancer effect against human cancer cell lines *in vitro* and in tumor-bearing mice *in vivo*
- Good safety profile demonstrated in pre-clinical studies
- DR5 is rarely expressed in normal tissues, CS-1008 is expected to show selective activity against tumor cells
- IND was filed Dec 2005 and Phase 1 study will start this April
CS-1008 induces apoptosis in tumor cells through binding to DR5. CDC or ADCC may also contribute to antitumor activity of CS-1008.

**Mechanism of CS-1008**

**Conventional antibodies**

**CS-1008 induces apoptosis in tumor cells through binding to DR5. CDC or ADCC may also contribute to antitumor activity of CS-1008.**

**Infection**

- DX-619
- DC-159a
- CS-023
- CS-8958
DX-619

- Best in class quinolone injection against multi-drug resistant Gram(+) bacteria.
  - MRSA
  - VRE
  - MRCNS
  - PRSP
- Did not induce resistant mutants \textit{in vitro}, possibly due to dual mechanisms: DNA gyrase & TopoIV
- Enhanced relative efficacy and rapid speed of onset of bactericidal activity
- Phase 1 program is on-going

DX-619, Most Potent against Resistant Gram(+) bacteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>( \text{MIC}_{90} (\mu g/mL) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>DX-619</td>
<td>0.25</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>32</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>4</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>32</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>4</td>
</tr>
<tr>
<td>Linezolide</td>
<td>1</td>
</tr>
</tbody>
</table>

Vancomycin-resistant MRSA (VRSA) USA 2002

[ Hershey Medical Center]
DX-619 Cures Severe Infection Model

Endocarditis due to LVFX-R MRSA in rats [ICAAC 2003]

DC-159a

- Best in class respiratory quinolone with broad spectrum enabling empiric therapy
  - QR *S. pneumoniae*
  - MDR *S. pneumoniae*
  - *Mycoplasma pneumoniae*
  - RFP-R *M. tuberculosis*

- Covering Major Gram-(+) & (-) pathogens and atypical pathogens

- Faster cure is expected with its rapid bactericidal action

- Preferable penetration into target organs

- Phase 1 study under preparation
DC-159a has broader anti bacterial spectrum than LVFX against clinical isolates

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC90 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycoplasma pneumoniae</em> (5)</td>
<td>≤0.06</td>
</tr>
<tr>
<td>Community-acquired MRSA (44)</td>
<td>0.25</td>
</tr>
<tr>
<td>MSSA (48)</td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> (56)</td>
<td>4</td>
</tr>
<tr>
<td>Ampicillin-susceptible <em>H. influenzae</em> (22)</td>
<td>58</td>
</tr>
<tr>
<td>Ampicillin-resistant <em>H. influenzae</em> (23)</td>
<td>1</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> (47)</td>
<td>2</td>
</tr>
<tr>
<td>Penicillin-intermediate &amp; resistant <em>S. pneumoniae</em> (50)</td>
<td>4</td>
</tr>
<tr>
<td><em>S. pyogenes</em> (49)</td>
<td>8</td>
</tr>
<tr>
<td>Penicillin-susceptible <em>P. aeruginosa</em> (48)</td>
<td>10</td>
</tr>
</tbody>
</table>

Bactericidal activity of DC-159a against QR S.pneumoniae

- Control
- ½ MIC (0.5 μg/ml)
- 1 MIC (1 μg/ml)
- 2 MIC (2 μg/ml)
- 4 MIC (4 μg/ml)
DC-159a cures severe respiratory tract infection

DC-159a has potent inhibitory effects on RFP-Resistant Mycobacterium and MAC

<table>
<thead>
<tr>
<th>MIC(_{90}) ((\mu) g/mL)</th>
<th>(M.\text{tuberculosis Wild}) (n=21)</th>
<th>(M.\text{tuberculosis RFP-R}) (n=12)</th>
<th>(M.\text{avium AIDS associated}) (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC-159a</td>
<td>0.06</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>MFLX</td>
<td>0.25</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>LVFX</td>
<td>0.5</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>RFP</td>
<td>0.13</td>
<td>&gt;128</td>
<td>128</td>
</tr>
</tbody>
</table>

MFLX: Moxifloxacin  
LVFX: Levofloxacin  
RFP: Rifampicin  

[Res.Inst.Tuberculosis]
CS-023

- A novel parenteral carbapenem for bacterial infections
- Best in class can be expected based on:
  - Broad spectrum and superior activity against pathogens
  - Longer half-life than competitors
  - High safety
- Target indications are moderate to severe infections such as:
  - Nosocomial pneumonia
  - Systemic infections
  - Surgical or soft tissue infections etc.
- Longer half life (2-fold) than other carbapenems and good safety profile were demonstrated in Phase 1 studies
- License-out to Roche in US/EU: Phase 2 studies on-going
- Phase 2 studies on-going in Japan

CS-023 efficacy depends on *in vitro* activity (=MIC) and length of half life

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS-023</td>
<td>8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>32</td>
</tr>
<tr>
<td>Meropenem</td>
<td>16</td>
</tr>
</tbody>
</table>

* Imipenem MIC: ≥16 µg/mL

**CS-023 PK in human**

- CS-023, 500 mg
- Imipenem, 500 mg
- Meropenem, 500mg

**MIC<sub>90</sub> for IPM*-resistant *P. aeruginosa***

- Longer time above MIC than competitors
- "Stronger Efficacy"
CS-8958

- Novel neuraminidase inhibitor as an anti-flu drug
- Inhaled formulation (dry powder inhaler & nebulizer)
- Longer-acting than existing drugs
- Could possibly use for influenza treatment and prophylaxis
- Single dosing for treatment and once a week dosing for prophylaxis are expected based on exploratory clinical study
- Collaborate with Biota to find appropriate partner in US/EU
- In-house development in Japan: Preparation for Phase 1 study is on-going

Human PK results in exploratory clinical study
- Efficacy of CS-8958 was expected to be longer-acting than Relenza

Urinary excretion after administration of CS-8958 and Relenza to human at a dose of 10 mg (inhalation).

- CS-8958
- R-125489 (Active Metabolite)

Dosage regimen:
- 10 mg/every 6 days or more

10 mg/day · 5 days
(twice a day, 5 mg/12 hr)

(from published data)
Glucose Metabolic Diseases

WelChol DM
CS-011
CS-917

WelChol® contains colesevelam hydrochloride, a non-absorbed, polymeric, lipid-lowering agent intended for oral administration.

WelChol DM : Expansion of indication for diabetes in the US

Preliminary data suggest WelChol® may have a beneficial effect on blood glucose levels in patients with type2 diabetes.

To be used as an adjunct to diet and exercise to lower blood glucose for type 2 diabetes not responding to current therapy.

Phase 3 studies are on-going for inadequately controlled type 2 diabetes patients.

One of the Phase 3 studies suggests 0.5% in HbA1c decrease in diabetic patients on insulin.

Submission Target: 4Q 2006
CS-011/ Rivoglitazone

Product Description
- Potent selective PPAR-γ agonist for treatment of diabetes
- Greater glycemic and non-glycemic effects than demonstrated by pioglitazone or rosiglitazone
- Goal is to achieve superior glycemic control and safety compared to pioglitazone (Best in Class)
- Dose-dependent efficacy on plasma glucose and lipid parameters superior to pioglitazone were demonstrated in Phase 2b study
- Carcinogenicity studies are on-going
- License agreement of development for the purpose of dry eye treatment was concluded with Santen

CS-917

Product Description
- First in class, the fructose 1-6 bisphosphatase (FBPase) inhibitor
- FBPase is a rate-limiting enzyme that regulates hepatic glucose production
- Potential to treat a majority of type 2 diabetic patients as monotherapy or in combination with other therapies
- Completed Phase 2a studies Dose-dependent reductions in levels of fasting plasma glucose (FPG) was demonstrated and proof of concept was established
- Phase 2b study with low dose range for the sake of safety is on-going after re-evaluation of lactic acidosis elicited in patients taking concomitant metformin
Immunology
CS-0777

CS-0777

- Novel immunomodulator
- Unique mechanism of action:
  - CS-0777, converted to phosphorylated form in vivo, is an agonist of sphingosine 1-phosphate receptor 1 (S1P1).
  - CS-0777 causes peripheral lymphopenia through lymphocyte retention in secondary lymphoid organs.
- Target indications are autoimmune diseases such as RA, Psoriasis and MS, as well as organ transplantation.
- First in class or Best in class
- IND submission in March 2006
The forecasts and other figures included in these materials are derived from our assessments and assumptions based on information available and are subject to risks and uncertainties. Actual earnings may differ from these forecast values.