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In this edition...
ChemGenex has finally struck a deal for Omapro for the European region. The deal now puts the company in a position to fund the roll-out of Omapro in the US, where it retains full rights.
Pharmaxis has released 12 month efficacy data for Bronchitol with very positive results emerging. BioMD is overseeing a second trial of its ADAPT tissue treatment technology in pelvic floor reconstruction surgery. And a major milestone for Antisense Therapeutics is imminent as its partner Teva Pharmaceuticals decides whether to proceed with a Phase II dosing study of an MS drug, ATL/TV1102.
We also provide coverage of CSL's R&D Day. CSL has achieved at least a dozen product registrations over the last twelve months and made 20 forward transitions in its pipeline over the same period.
The Editors
Companies Covered: ANP, BOD, CSL, CXS, PXS

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.0%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.3%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.3%
Year 9 (May '09 - Current)	75.5%
Cumulative Gain	**241%**
Av Annual Gain (9 yrs)	**21.4%**

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Bioshares

11 December 2009
Edition 341

Delivering independent investment research to investors on Australian biotech, pharma and healthcare companies.

Breaking News - Monday 14 December 2009

ChemGenex Strikes $137 Million Deal for Omacetaxine

ChemGenex Pharmaceuticals has delivered on its promise to sign a European partner for the commercialisation of omacetaxine for chronic myeloid leukemia (CML), and including marketing and development of the drug in indications outside of CML, before the end of 2010.

Omacetaxine (also known by its trade name as Omapro) has been licensed to **Hospira Inc** for the European region, the Middle East and certain African countries.

For the indication of CML alone, ChemGenex stands to receive $17.8 million in an upfront payment, followed by another $119.4 million in milestone payments that are based on achieving (sub) indication approvals and various sales targets. The royalty rate covering the license was not disclosed, however, in our view, a rate in the high teens to the mid twenties would not be unusual.

According toChemGenex CEO Greg Collier, Hospira was the right partner for Europe because it is in the earlier stages of building an oncology franchise and omacetaxine should serve as a product that can demonstrate the company's emerging capabilities in oncology.

Oncology drug portfolios continue to remain as financially attractive assets for pharmaceutical firms because pricing pressures are less intense relative to many other drug classes.

A European Medicines Agency decision on omacetaxine is expected in 2010 H2.

Commentary

ChemGenex is now in a position to support the roll-out of omacetaxine in the USA under its own steam, with cash supplied through the deal with Hospira. At its last capital raising, the company had said it would not need to go back to the market for further funding and it looks as though this is can now be confirrmed.

What must be made clear from the Hospira deal is that milestone payments for other indications *outside of* CML, such AML and MDS, *are yet to be disclosed*. Progress in taking these indications forward in the territories assigned to Hospira would further support the financial position of ChemGenex.

ChemGenex has continued to meet investor expectations, which is a reflection of a passionate and hardworkding management team. ChemGenex is capitalised at $272 million, based on its last trade of $0.96 at 11.00 AM.

Bioshares recommendation: **Speculative Buy Class A**

Pharmaxis – Strong 12 Month Efficacy Data

Last week Pharmaxis (PXS: $2.72) released a further six months of safety and efficacy data from the company's Phase III cystic fibrosis trial with its drug candidate Bronchitol, following the initial six month results which reported in May. The results were very impressive from an efficacy standpoint.

At six months, the Bronchitol treatment group showed a mean improvement in lung function of 6.5%. After treatment for a following six months, lung function continued to improve, delivering a mean lung improvement of 8.0% at 12 months. For the patients who were in the placebo arm in the first six months, when they were switched to Bronchitol, their lung function increased by a substantial 10.3% after six months of Bronchitol treatment.

Of interest is the take-up rate of patients in the Bronchitol arm for the first six months who elected to continue with the trial for another six months on Bronchitol. A total of 111 patients (from the initial 177 patients who started the trial in the Bronchitol arm) completed treatment with six months of Bronchitol. Of these patients, 97 (87%) elected to accept another second six months of treatment of Bronchitol, with 81 (83%) completing the second six months treatment.

Of the 118 patients who started the trial in the placebo group, 89 completed the first six months, then when offered to take Bronchitol for six months, 73 (82%) accepted and 49 (67%) completed the second part of the trial.

Pharmaxis has previously indicated that around 60% of people with CF may be a realistic usage figure of the Bronchitol product, if approved. The above compliance rates are more conservative, given that patients failed to remain enrolled in the trials for various reasons, including failure to complete questionnaires correctly before receiving any treatment, dissatisfaction with the trial arrangement, and some considered the clinical trial protocol too troublesome.

Market Penetration

Bronchitol will be more effective in some patients than other. The above numbers would suggest that 50% - 60% market penetration is not unreasonable, given the sustained effect of the drug and the drug's ability to modify disease progress. At a 60% adoption rate, we estimate this equates to sales of $660 million a year.

The side effect profile of the Bronchitol was reasonably good. Most of the adverse events (in 40 patients) were mild to moderate and were related to the underlying disease. Introducing 400mg of powder is likely to aggravate responses such as coughing and wheezing, although this was only noted in four patients in the second part of the trial involving a total of 170 patients.

Path to Market

Bronchitol has been filed for approval with European regulators. If successful, approval should be received towards the end of 2010, allowing for a 2011 market launch in Europe. Pharmaxis has completed health economic studies for its product, and the company is confident it can justify reimbursement or payment from payors.

The CF community in the UK is excited about a new product being coming to market. However their concerns are that of pricing, with a previous CF drug, tobramycin having enjoyed limited commercial success in Europe due to perceived incorrect pricing. It would appear that Europe is comfortable with the price set for the competing drug Pulmozyme, of US$13,000 a year. Whether Pharmaxis likes it or not, this has become a benchmark for pricing.

Pharmaxis should be able to argue its case well, given the similar efficacy to Pulmozyme after six months, and the ability of the drug to provide a sustained effect and modify disease progression.

By the end of February Pharmaxis will receive initial feedback from the European regulators, which will give the company some idea of how its submission is progressing.

At the end of this month, a decision is expected from the FDA on the company's first product, Aridol, a lung function test. At the Advisory Committee last month, Pharmaxis had prepared responses to 200 potential questions relating to Aridol, with a slide accompanying each potential question. This level of preparation impressed and surprised the Committee, with every question asked accounted for in its response dossier.

Aridol could be launched in the US in early 2010. Pharmaxis will market and sell the test directly. The decision for Pharmaxis is how much it will invest into commercialising the product. Initially the product may be marketed to 30-40 major asthma centres. We expect Aridol to generate only modest sales for Pharmaxis. However the product has proven to be an excellent practise run from commercialising the key product for the company, Bronchitol. In the US, setting up the supply chains and distribution for Aridol will be useful preparation for the expected launch of Bronchitol in 2012 in the US.

The second Phase III CF trial has completed enrolment with results due out in Q2 2010. The company expects to file its NDA in the US for Bronchitol in late 2010. Pharmaxis currently has 115 employees, with 12 based in the US.

Pharmaxis is capitalised at $ 610 million.

Bioshares recommendation: **Speculative Hold Class A**

Bioshares

Antisense Therapeutics Update

Antisense Therapeutics (ANP: 5.8 cents) has licensed its Phase II multiple sclerosis drug candidate to **Teva Pharmaceutical Industries**. The deal with Teva was signed in early 2008 just prior to completion of a positive Phase II trial in MS by ANP. The trial showed a 54% reduction in cumulative new active brain lesions that underlie the disorder. The trial enrolled 77 patients.

Following the trial Teva moved quickly to conduct additional toxicology trials with the compound, ATL/TV1102. Under the deal Antisense has received US$6 million with potentially US$100 million more in milestone payments plus royalties from sales of any products. One third of all payments received by ANP go to Isis Pharmaceuticals, which designed and manufactured the drug candidate.

The MS market is very large, valued at US$6 billion at present, and expected to increase to US$10 billion by 2012. A drug that inhibits the same target as the ANP/Teva drug candidate, Tysabri, is currently generating sales of US$800 million a year and growing at 20%. Teva has a very large presence in the MS market, selling the market leading drug Copaxone. Copaxone sales jumped 38% in the last quarter over the previous corresponding period, now generating a massive US$3.1 billion of annual income for Teva.

For ANP, a major milestone is approaching, with Teva due to decide on whether it will proceed with a dose ranging Phase II study with ANP's drug candidate. That will trigger a milestone payment if Teva moves forward and should see an improved revaluation of ANP's share price.

For ANP, the short term issue is whether the company can fund the planned Phase I study with its next compound in development, ATL1103. This is potentially a very promising program. The compound is being designed to treat a growth disorder, called acromegaly, and also diabetic retinopathy. ANP is currently conducting final toxicology tests which should be done by year's end.

What makes the program appealing is that the end point can be measured very easily and clearly (IGF-1 levels in the blood), preclinical primate studies have shown that IGF-1 levels were successfully reduced with ATL1103, and also that antisense drugs have shown to work particularly well in the liver, where the growth hormone receptor is located.

ANP anticipates gaining regulatory clearance to proceed with the Phase I trial in the first half of 2010 and to start the trial in the second half of 2010. To fund the trial, ANP can either raise the funds now, or wait for a decision from Teva as to whether it will proceed to Phase IIb studies, triggering a likely milestone payment and share price revaluation.

Increased interest in drugs based on antisense

Antisense technology has yet to deliver a blockbuster drug to the market from any company. Only one antisense drug is approved, Vitravene from **Novartis**, although it has not achieved commercial success. Interest in antisense spiked when **Genzyme** signed a major deal with **Isis Pharmaceuticals** for up to US$1.9 billion in 2008, including an initial US$325 million payment (upfront and equity). That drug candidate (mipomersen) is currently being tested in four Phase III trials aimed at reducing high cholesterol levels in patients with a genetic disorder who are unable to correctly metabolise LDL cholesterol. The drug candidate yielded stunning Phase II results. That drug candidate also works on the liver. Data from four Phase III trials is emerging, with positive efficacy (25% reduction in cholesterol at 26 weeks) in the first Phase III trial although some evidence of liver toxicity was noticed, which was reversed after treatment. Genzyme plans to file the drug candidate for approval in Europe and the US by mid 2011. The remaining three Phase III trial results are due to be released in the next six months.

Another antisense company, **Oncogenex Pharmaceuticals,** has seen its share price take off since March this year, from $3 a share to over $30, now valuing the company at US$189 million. Oncogenex is at a similar stage of development to ANP although the leads are in different fields. Oncogenex has now delivered positive results in overall survival in three PhaseI/II cancer trials with its antisense inhibitor drug candidate, OGX-011.

Other programs

ANP has a third drug candidate, ATL1101, which the company will seek to test against prostate cancer. The target is IGF-IR, and this target (though not with antisense drugs) is being investigated by **Pfizer** and **Insmed** in Phase III and Phase II trials respectively. ANP will likely partner this program before it enters the clinic.

Summary

ANP is capitalised at $34 million. It has the potential to see significant growth in its share price if Teva begins a large Phase IIb clinical program with the MS drug candidate. ANP could also see significant value creation from progressing its acromegaly program, with very promising signs to date that this drug candidate could be effective. However the company will need to show it can fund the earlier clinical program. The company could also benefit from a strengthening of its board.

At the end of September, ANP had $3.7 million in funds.

Bioshares recommendation: **Speculative Buy Class B**

Bioshares

BioMD – Second Clinical Trial Progressing Well

BioMD (BOD: 4.1 cents) has developed a proprietary technology (ADAPT) to reprocess bovine pericardium tissue that can be used as a medical patch with wide ranging applications.

The first clinical trial with the ADAPT technology was completed in South Africa in October this year, repairing heart deformities in 30 children. The trial was completed successfully. At six months, there was no calcification of the patch or immune response seen to the patch. At least 10 patients have now progressed past 12 months and full 12-month data is expected to be available next year.

Pelvic Floor Reconstruction

These positive results spiked the interest of surgeons in Sydney, with a trial recently started for pelvic floor reconstruction in women. The first of two patients have been implanted with ADAPT treat bovine tissue. The remaining 20 patients are due to be implanted with similar tissue by the end of March next year.

The problem with materials used in existing pelvic floor reconstruction procedures is the high level of post-operative complications, in around 20% of patients. A polypropylene-based mesh is generally used, which can result in fibrosis, shrinkage after six months and adhesions.

The BioMD collagen scaffold does not become fibrotic, it does not shrink, and trials to date have shown that it offers more similar properties to that of human tissue. It is derived from living (bovine) tissue that has been reprocessed to prevent any immune response to that normally seen with foreign material placed in the body.

Other applications of the technology include use as a hernia mesh, breast reconstruction, in orthopedics and for stem cell delivery. In separate laboratory studies, the company has shown that its collagen scaffold has provided a suitable framework to enable mesenchymal stem cells to be grown. In 2010, BioMD is also aiming to start a ventral hernia study with its technology.

There are 26,000 pelvic floor reconstructions conducted each year in Australia. That translates to a market size worth around $30 million in Australia for biologic products. Globally, the market is expected to reach US$1.5 billion by 2011.

Funding

For BioMD, the challenge is to fund the commercialisation of this technology. The company had just over $900,000 in cash at the end of September, which is about nine months funding. The company is currently seeking to raise additional funds.

If the Sydney pelvic floor trial is successful, there should be demand for the technology from surgeons and from potential partners looking to commercialise the technology internationally. The technology may become available to surgeons next year through a Special Access Scheme, and BioMD is aiming to file its first product for approval in Australia by the end of 2010. Interim results from the pelvic floor trial are expected in the second quarter of 2010.

Summary

BioMD is capitalised at only $5 million. The company has the challenge to build the infrastructure to commercialise this technology. However if the company is successful in its second clinical trial next year, there is scope for considerable appreciation in the company's share price over the coming 12 months.

Bioshares recommendation: **Speculative Buy Class C**

Bioshares

Bioshares Model Portfolio (11 December 2009)

Company	Price (current)	Price added to portfolio	Date added
Biodiem	$0.20	$0.15	October 2009
QRxPharma	$0.82	$0.25	December 2008
Hexima	$0.48	$0.60	October 2008
Atcor Medical	$0.19	$0.10	October 2008
CathRx	$0.65	$0.70	October 2008
Impedimed	$0.84	$0.70	August 2008
Mesoblast	$1.30	$1.25	August 2008
Circadian Technologies	$0.70	$1.03	February 2008
Patrys	$0.12	$0.50	December 2007
Bionomics	$0.37	$0.42	December 2007
Cogstate	$0.32	$0.13	November 2007
Sirtex Medical	$6.70	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.30	$0.66	September 2007
Starpharma Holdings	$0.57	$0.37	August 2007
Pharmaxis	$2.72	$3.15	August 2007
Universal Biosensors	$1.85	$1.23	June 2007
Probiotec	$2.54	$1.12	February 2007
Chemgenex Pharma.	$0.93	$0.38	June 2006
Acrux	$2.10	$0.83	November 2004
Alchemia	$0.62	$0.67	May 2004

Portfolio Changes – 11 December 2009

IN:
No changes.

OUT:
No changes.

CSL R&D Briefing

CSL (CSL: $30.48) held its annual R&D review this week. Dr Andrew Cuthbertson, CSL's R&D Director and Chief Scientific Officer, began the briefing by saying he believed the company had a high quality pipeline with the company being obsessed with focus, ensuring there is coherence in the portfolio and making sure all product candidates have commercial relevance.

Cuthbertson emphasised that in the context of wider industry developments that CSL needed to "chart its own path". "We believe our R&D investments are appropriate and carefully crafted", he said.

R&D Strategy, which has not changed from a year ago, is in two parts. CSL develops, makes and sells high quality complex biological medicines and conducts R&D to extract maximal value from existing assets, as well as supporting and improving the product portfolio. However, the company is also committed to developing new protein based medicines for treating serious life threatening diseases. Cuthbertson said that "in our industry, novelty should translate into product margin", adding that "investing in our portfolio is good value".

CSL has a major interest in new products derived from waste fractions from each litre of plasma that is fractionated. This means that while there are conversion costs, it also means that the raw materials are essentially free.

CSL also has a strong emphasis on IP, including patents and know how, with R&D being an integral part of its phased growth strategy. Cuthbertson said CSL recognises the importance of investing invest in early-stage, mid-stage and late-stage projects.

"I get paid to look at the whole portfolio and intelligently determine where to place our money", said Cuthbertson. "You want to have some relatively near term low risk projects, but also long term higher risk investments that are tough but if you can make it work you can get a big return". Gardasil was high risk in the beginning, he noted.

R&D Allocations

CSL spends about $100 million a year on life cycle management and on continuous product improvement. Spending in this area has generally remained constant. Spending on market development has increased and is devoted to expanding geographical registrations, with FY2009 spending including flu vaccine registrations in various territories.

The third segment is new product development, including, for example, recombinant coagulation factors and the reconstituted high density lipoprotein product.

Cuthbertson said it was important to note that spending in the market development segment over the last few years was distorted by new flu vaccine development, and CSL will complete this in the next 12 months which will then give the company further capacity to invest in new product development or new market development.

Overall CSL expects to spend $350 million on R&D in this fiscal year (FY2010), compared to $311 million 2009. As a guide, this could be expected to increase by 10% each year, assuming CSL has high quality opportunities to invest in, Cutherberston stated.

By way of clarification, CSL has since April spent $40-$50 million on development and trials of the AH1N1 (swine flu) vaccine but that spending was not included in the R&D figures since the expenditure was reimbursed by governments. However, the R&D numbers do include spending on Afluria (seasonal flu vaccine).

A key principle underpinning the management of R&D at CSL was that of focus. "Focus is extraordinarily important", said Cuthbertson. "There is risk involved in R&D activities so the only way to make high quality judgment calls is to work in focused areas where you are truly world class. We work in areas where we can have clarity of thinking and where every decision can be related to data."

Plasma Proteins

Val Rohmberg, CSL's Senior Vice President of Research and Development, discussed progress of the CSL plasma proteins portfolio.

Rohmberg described two groups of products in the plasma products are; marginal products and infra-marginal products. Marginal products are the products that are taken from every litre of plasma that is processed. CSL derives three marginal product lines; Factor VIII products (Heamate/Humate, Monoclate), albumin (Albuminar) and Immunoglobulins (Carimune, Privigen, Vivaglobin) from every litre of blood. This means the cost of plasma is spread across at least three product areas.

The inframarginal products are those that are not derived from every litre of plasma e.g. Berinert, Zemaira, Riastap and Cytogam. The challenge is that if use of these products can be driven up, then the cost is almost free. The relative cost of additional sales of inframarginal products is very low.

The focus on development in the inframarginal area is on driving up use and identifying new medical use. In the marginal products area the strategy is have a 'balanced litre' strategy and continue to have three products per litre but also identify medical value, which helps improve margin.

Privigen

Privigen was approved two and a half years ago in the US, with several approvals rolled out in other regions since then. Privigen is the only room temperature stable IVIG. In the last year, a new manufacturing facility for Privigen was approved, which has allowed the company to successfully roll the product out in the US and Europe. The company is in the process of building a second manufacturing facility, which will come on line in 2010. CSL is aiming to make Privigen a global brand, and have it approved in an additional 33 countries.

Cont'd over

Hizentra
Currently CSL markets Vivaglobin, a 15% subcutaneous immunoglobulin, which is the only s.c product of that type on the market in the US. IgPro20 is a 20% subcutaneous immunoglobulin which has now been named Hizentra. The advantage is the higher concentration (e.g. at 20%) the lower the volume that needs to be infused, with a patients experiencing a more quicker infusion experience.

The clinical development of Hizentra has been completed and a submission was filed with the FDA in April 2009. A European Primary Immune Deficiency Phase III study has been completed and a European submission is planned for 2010 H1. Rohmberg expected competitors in the s.c IVIG area will emerge in the next few years. However, the competitive threat will not be as significant as one might expect as these competitor products will only be 10% formulations.

Cytogam
Cytogam is administered to solid organ transplant patients, addressing the problem of where the donor organ patient has a CMV infection but the recipient doesn't. Generally there are no clinical signs of CMV infection. In a transplant situation, where the patient is immune-suppressed, the CMV infection can flare up. The product is currently contract manufactured but the process is being transferred to the Bern facility. A submission will be made to the FDA in mid 2010.

Zemaira
Zemaira is an alpha-1 proteinase inhibitor that is used to treat congenital deficiencies which result in a patient's lung function decline when middle age is reached. Zemaira is a protective agent for the lungs, and can successfully halt the decline in lung function

Zemaira was approved in the US in 2003. However, the company has been required to do an Phase III/IV study. The EMEA has agreed the US study will be suitable for a European application process. The Phase III/IV study is still recruiting patients, and CSL anticipates completing recruitment in 2010. The observation period lasts for two year, so a potential European approval is still some time away.

Berinert
Berinert is a C1 Esterase inhibitor used for treating hereditary angio-oedema, a very painful condition presenting as sudden swelling (acute attacks). Berinert was approved in the US in October 2009 and is also approved in 23 European countries. In Canada and Australia, marketing applications are under review.

Coagulation Products
According to Rohmberg, CSL is a leader in understanding the complex biochemistry of the coagulation cascade, has the broadest product line in coagulation in the world and has all the tools to work in the coagulation cascade.

Riastap
Riastap is a fibrinogen product and one of very few manufacturers of fibrinogen in the world. Riastap was approved by the FDA in January 2009 for congenital fibrinogen deficiency. In December 2009, approval was received in Germany. Full European approval is expected in mid 2010.

Potential for Riastap in New Indications
Riastap is the only fibrinogen approved in the USA and an opportunity exists to expand its take up in bleeding situations, for example in aortic surgery. Currently fibrinogen can be sourced from fresh frozen plasma (FPP) but it has limitations: it is relatively dilute, it takes 30 minutes to deliver from a hospital pharmacy to a theatre and FPP must be matched to the patient.

Use of Fibrinogen in Aortic surgery
If an aneurism develops during aortic surgery, a rupture could potentially occur resulting in death from massive bleeding. So when detected that part of the aorta (sometimes all the aorta) is replaced with Dacron. However, this kind surgery involves large quantities of blood.

In a retrospective study it was found that use of Riastat to manage clotting control delivered a 13.9 units of difference compared to FPP. CSL has initiated a Phase II placebo controlled study in aortic surgery. Recruitment is going well and results are expected in 2010. Riastat is an example of a CSL strategy to register a product to treat a congenital deficiency and then look more broadly in the acquired deficiency area.

Reconstituted High Density Lipoprotein (rHDL) Program

rHDL is a potential product for treating Acute Coronary Syndrome (ACS). The program, led by former **Merck** scientist, Dr Sam Wright, brings together a body of research on heart disease and the function of HDL. It marries it with CSL's unique ability to manufacture reconstituted HDL and bring it to market

Wright said that coronary heart disease is one on the great unmet medical needs of all time and is the largest killer in the industrialised world. In the US, ACS is the leading cause of death each year, causing 450,00 deaths per annum, and generating direct costs of US$164 billion. There are 1.255 million heart attacks (i.e. acute chest pain events) both new and recurrent occurring each year.

Cholesterol is the cause of the condition which commences as it builds up as plaque in the artery wall. The critical step is when part of a large plaque ruptures, blocks the flow of blood to the heart, causing the chest pain which results in damage to the heart (heart attack).

The cholesterol deposited is LDL (low density lipoprotein) otherwise known as 'bad' cholesterol. The body has a process that opposes the accumulation of 'bad' cholesterol, the ability to carry cholesterol away from the artery wall and back to the liver. This function is performed by HDL, known as 'good' cholesterol.

Cont'd over

CSL's development program in this area aims to emulate the natural process that takes the cholesterol away from the lesion and reduces the risk of rupture. The medical hypothesis is that by adding CSL112 (rHDL) it will be possible to draw the cholesterol out and stabilize the plaque.

CSL is aiming to develop an acute treatment for an acute danger. The proposal is to deliver a short series of IV infusions straight after a heart attack (ACS event). There are very sharp rises in ACS events following that first heart attack. A goal will be to reduce the recurrent event that occurs in the months after the ACS. This is a product niche that is distinct from the classic oral statins and anti-hyperlipidemics drugs that are on the market today. These are oral products for chronic treatment, whereas CSL112 is designed as an acute IV treatment.

The statins don't work in the acute setting. They are designed to change the risk over a much longer period. The MIRACLE study showed that statins were relatively ineffective in the early stages post-ACS events.

Why will rHDL work?

According to Wright, large epidemiological data has connected HDL levels to coronary heart disease, and an enormous body of animal data research that started in the late 1980s showed that infusion of HDL in rabbits reduced the size of atheroma. These studies have been repeated many times.

More recently studies in genetic models have shown that ApoA1 is the active agent in HDL driving the reduction in LDL.

Wright said that to carry the animal findings into man you need a large amount of HDL, and that is one of the things that CSL is in a position do. CSL has pioneered the production and purification and re-constitution of HDL at scale, and has developed a two step process.

The first step involves taking ApoA-1, the dominant protein of HDL, from a waste fraction of plasma. Then it is pasteurized and combined with phosphatidyl choline (which is present on the membranes of cells) to form HDL.

A prototype was made some years ago (CSL111) and using that prototype gained proof of concept in the clinic and it was shown to reduce the size of atheroma in man.

The ERASE trial in ACS patents looked at the size of the atheroma using intravascular ultrasound and showed that infusion of CSL111 reduced the size of the atheroma.

A deficiency in the study was that the investigators could see that lesions were getting smaller, but didn't know which part was getting smaller.

A second study in Melbourne with a small number of patients focused in atherosclerosis in the leg, which allowed biopsies to be performed. After a single infusion and over seven days, there was a 60% decline in lipids in that region. This confirmed that rHDL had an effect on the lesions and that effect was focused on the lipids, and was acute in effect.

CSL111 was reformulated as CSL 112 because the original formulation was made before important pieces of knowledge about how cholesterol was transported were revealed through research. What was discovered was the role of a pump designated ABCA1. This protein is deficient in patients with Tangiers disease, a congenital defect that results in low HDL and gives rise to accelerated atherosclerosis.

The pump takes the cholesterol out of cells in artery walls and takes it to HDL. It doesn't deliver it equally to all forms of HDL, and some forms (pre beta forms) are much more able to accept ABCA1, so CSL112 is optimised to receive cholesterol from ABCA1. CSL has performed studies to show that CSL112 is a better receiver of ABCA1 than CSL111.

With CSL111 there were problems with excipients that caused dose limiting liver toxicities, so a reformulation to optimise safety was also required. With CSL112, the excipients were reduced and animal studies indicate that a three-fold decrease is in toxicities is achievable with CSL112.

The current status of CSL112 is that preclinical safety studies are ongoing, with a Phase I trial expected to commence in 2010 that will look at safety and pharmacokinetics and also evaluate ABCA1-dependent cholesterol efflux.

A Phase II would look at optimal dosing whereas Phase III trial would be a classical morbity and mortality study to demonstrate clinical benefit in ACS patents. A full program would take 7 years from now, which it was emphasised as a program CSL is committed to.

Therapeutic Proteins Portfolio

CAM3001

CAM3001 is an antibody (GM-CSFR alpha) being developed by partner **AstraZeneca.** for the treatment of rheumatoid arthritis.

The market opportunity is based on patients who do not respond to DMARDS such as methotrexate or biological medicines such as the TNF blockers. A Phase I study has been completed in patients with mild to moderate arthritis.

CAM3001 is a fully human recombinant monoclonal antibody that was developed at the time by **Cambridge Antibody Technology** working with **Zenyth Therapeutics**. However CAT was acquired by **Medimmune** which was the then acquired by AstraZeneca.

Results from the Phase I trial were presented at the American College of Rheumatology annual meeting in October 2009. A Phase II is expected to start early in 2010. Positive trends in CRP and erythrocyte sedimentation rates were recorded. Of 10/27 patients that had high erythrocyte sedimentation rates at the beginning of treatment, ESR was returned to normal levels in 9 subjects after treatment.

Cont'd over

The study found that the single intravenous doses up to 10mg/kg were safe and no anti-CAM3001 antibodies were detected.

CSL360

CSL360 is a chimeric antibody targeting the IL-3 receptor alpha chain, a receptor target implicated in acute myeloid leukemia (AML). This is the most common form of leukemia in adults. Although it can be treated by standard chemotherapies, remission occurs and survival rates are very poor as the age of patients increase.

AML occurs as a result of leukemic blast cells proliferating in the bone marrow and migrating into the blood. They then overwhelm the normal blood cells, pre-disposing patients to bleeding and infection, resulting eventually in death.

In the normal state, hemopoeitic stem cells (HSC) in the bone marrow differentiate into various normal blood cells. In AML, it is believed that mutations that occur in the HSC lead to leukemic stem cells, which are unable to differentiat into normal blood cells, only leukemic blast cells, which come to dominate cells circulating in the periphery.

Leukemic cells are characterised by possessing IL-3 receptors on their surfaces. The IL-3 molecule is important for maintaining the survival of leukemic stem cells. It was postulated that targeting the IL-3 receptor would halt the progression of the disease.

Phase I Study

In a Phase I study with 16 evaluable patients it was found that CSL360 bound to the target and had an effect on AML proliferation and survival. Importantly, investigators found that saturation of the targets on the cells occurred at the higher doses, and that CSL360 did interfere with signalling in the blast and stem cell populations. However and 'disappointingly' it did not have an impact on AML stem cell and blast cell numbers. The conclusion was blocking IL-3 signalling alone does not provide a therapeutic effect in AML patients.

CSL has developed a second generation antibody, CSL362, that targets IL-3R alpha but is optimised for tumour killing. CSL362 is a humanised antibody, whereas CSL360 was an chimeric antibody. CSL has accessed technologies from both **Biowa** and **Xencor** for the tumour cell killing capabilities. *In vitro* studies indicate greatly enhanced killing of tumour cells occurs and the expectation is to be in clinical trials around mid-2011

Periodontal Disease Vaccine

The periodontal disease vaccine program is being developed as a therapeutic vaccine but in time could become a prophylactic vaccine program. Periodontal disease leads to tissue destruction, bone loss and tooth loss. Treatments include scaling and root planing, aiming to get rid of the colonising bacteria, plaque and tarter. Treatment is painful, however, the main issue is that recurrence is common.

The condition is under-diagnosed yet about 17 million treatments occur in the US each year at an expenditure of US$6 billion. It is estimated that probably 30% of adults suffer from some sort of periodontal disease in Australia

Periodontal disease is associated with several bacteria, but the one necessary is *Porphyromonas gingivalis*. Antigenic material for use in a vaccine has been isolated from *P. gingivalis.*

Links appear to exist between periodontal disease and cardiovascular disease, oropharyngyal disease and pancreatic cancers and also with diabetes and pre-term births. So the potential is there for a vaccine to be used prophylatically in relation to these diseases although much more research must be conducted before this occurs.

CSL and the University of Melbourne Dental School have been collaborating since mid 1990s on the vaccine. The Dental School has developed a mouse model of *P. gingivalis*-mediated periodontal disease. Mice can now be infected and get bone loss similar to humans.

The next task is to identify the best antigens and identify a formulation to take forward into clinical studies. CSL has granted **Sanofi Pasteur** an option to an exclusive world-wide license for the technology.

Summary

In summarising CSL's 2009 R&D presentation Andrew Cuthbertson said that CSL had achieved 20 forward project transitions on its R&D pipeline, although a few went backwards. Using its R&D expertise, CSL had achieved 12-13 product registrations around the world.

Bioshares recommendation: **Accumulate**

Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, *Bioshares* divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, *Bioshares* grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

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