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Bioshares

30 May 2014
Edition 553

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

Companies covered: BLT, IMC, VHL

	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-36%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - May '14)	26.6%
Year 14 (May '14 -)	-2.7%
Cumulative Gain	**338%**
Av. Annual gain (14 yrs)	**15.9%**

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Benitec Biopharma Doses First Patient in Phase I/II HCV Trial

Benitec (BLT: $1.20) this week announced it had treated its first patient with its unique RNAi treatment for patients chronically infected with Hepatitis C (HCV). The treatment uses a gene therapy approach to achieve an RNAi effect on the Hepatitis C virus.

The main aim of the trial is to assess the safety and tolerability of the treatment. The first patient received a non-therapeutic dose of the treatment, called TT-034. However secondary endpoints include evidence of efficacy. Evidence of whether the therapy is functioning as designed, by generating the expression of short hairpin RNA, will be looked at in the first three weeks through a liver biopsy.

Safety of the therapy can initially be judged, by investors, by whether the trial progresses to the next patient cohort. Six weeks after the first patient is treatment, the second patient can be treated with the same dose once the safety profile is assessed by an independent Data Safety Monitoring Board.

The next three patients will receive a dose three times as high as the first dose as early as six weeks after the second patient is treated. It will take at least 18 months to treat all 14 patients, according to the schedule. However, being an open label study, it can be expected that some efficacy data can be released as the trial progresses.

Endpoints

The main endpoint is safety and to establish the maximum tolerable dose. The fifth and highest dose will be 100 times higher than the first dose. Patients will only be able to receive the one dose and the therapy can not be withdrawn once it is given.

Secondary efficacy endpoints for the trial include changes in viral load (over six months), detection of mutations of the virus against the therapy (over six months), looking at whether the short hairpin RNA (shRNA) is expressed in the liver as a result of the therapy to effect RNA interference (neutralizing) of the virus (after three weeks) as well as the DNA levels delivered by the therapy, using the adeno-associated virus (AAV).

TT-034 works by a gene therapy approach, whereby DNA is delivered into the liver by a safe virus (adeno-associated virus). This DNA then generates the expression of the shRNA which then silences the Hepatitis C virus using RNA interference. The idea is that the liver will continue to produce the shRNA once its genetic make-up has been changed using the therapy.

The AAV that Benitec is using has been previously used in a gene therapy for the treatment of hemophilia.

Cont'd on page 6

The Essential Australian Biotech Investment Event

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Bob Atwill – CEO Cytomatrix
David Blake – Editor, Bioshares
Matt Callahan – Director, Orthocell
Rick Carreon – CEO Impedimed
Bob Crane – CFO GI Dynamics
Jackie Fairley – CEO Starpharma
David Fisher – Exective Director, GI Therapies
Neil Frazer – CEO Oncosil Medical
Peter French – CEO Benitec Biopharma
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Immuron's Opportunity with NASH

Melbourne-based Immuron (IMC: $0.005) is a potential turnaround story in the making. The company has been through a number of board, management and strategy changes since its listing in 1999. However, the company's objective of developing and commercializing therapeutic products by immunising dairy cattle and then harvesting the antibodies rich colostrum, the first but very immunologically beneficial milk that mammals provide for newborns, has not changed.

Travelan, the company's product for the management of traveller's diarrhea, is approved in many territories, starting in Australia in 2004. Travelan prevents infection from enterotoxigenic escherichia coli. Sales of the product have shifted to a more positive track in Australia now that the company has taken on a direct-to-wholesale role.

The company recently raised just under $10 million. This is a transformational capital raising for the company because it means it can now move forward with an IND backed Phase II trial of IMM-124E to treat a stage in the progression of liver disease called non alcoholic steatohepatitis (NASH), which is the more severe subset of non alcoholic fatty liver disease (NAFLD).

IMM-124E is forumulated from colostrum powder, which contain antibodies to lipopolysaccharide, an endotoxin and a stimulant of the immune system. The hypothesis for the therapy is that a cell-mediated response is induced which dampens inflammation in the liver.

Immuron marked out NASH as a therapeutic market opportunity some years ago but a lack of cash has stymied plans to date. The company had submitted a protocol to the FDA for the Phase II trial, but has since submitted a revised protocol. The company now expects to commence the Phase II trial later in 2014.

The incidence of NASH in the US adult population is estimated to be between 2% and 5%, with NAFLD occurring in 25% of the adult population. There are no therapies which have been approved to specifically address either of these conditions.

Untreated NASH leads to fibrosis, liver cancer and/or liver failure. The prevalence of the condition is being fuelled by the prevalence of diabetes and obesity. The condition can often be asymptomatic and can be found in patients in who are lean.

A timely strategy for investors is to wait for Immuron to receive clearance from the FDA for its Phase II trial design before taking a position in the stock.

Immuron is capitalised at $15 million.

Bioshares recommendation: **Speculative Hold Class B (Revisit when FDA clearsPhase II trial protocol)**

Several Recent Events in NASH Drug Development

In January, Intercept Pharmaceuticals, halted its Phase II trial of obeticholic acid (OCA), having reached its endpoint early, when the trial exceeded a pre-defined efficacy endpoint threshold of $p < 0.0031$. The primary endpoint was defined as a decrease in the NAFLD score of at least 2 points.

Intercept shares jumped from around US$70 to US$497 and the stock is currently trading at US$236. It is capitalised at US$5 billion.

Obeticholic acid targets the nuclear receptor farnesoid X and which regulates bile acid synthesis and clearance from the liver.

Lumena Acquired by Shire Pharmaceuticals

In mid-May, Shire Pharmaceuticals acquired Lumena Pharmaceuticals, to access its late stage rare liver disease compound, LUM001, as well LUM-002 for NASH. Both molecules inhibit the apical sodium dependent bile acid transporter (ASBT) which blocks bile reabsorption. LUM-002 has cleared a Phase I trial.

Shire Pharmaceuticals paid an upfront of US$260 million in cash. What makes the deal remarkable was that Lumena has only just raised US$45 million in a Series B round in March and was intending to conduct a Nasdaq listing.

Other Clinical Programs

On the following pages we have tabled a select number of clinical trials underway or planned for NASH/NAFLD, which gives an idea of the competitive landscape faced by companies such as Immuron.

Outside of Lumena (now with Shire Pharmaceuticals) and Intercept Pharmaceuticals, there are nine companies with NASH/NAFLD clinical programs and an equal number of academic programs as well. Some of these programs are focused on applying approved drugs, for example, testosterone, atorvastatin, sitagliptine and ezetimibe to treating the condition. Only one drug, Oltipraz (Pharmaking, Korea), is in a Phase III trial. A large number of both the commercial and academic programs will read out later in 2014 or in 2015, making the next 18 months are key period for NASH drug development.

Of interest is that Gilead Sciences, which has a major franchise in the Hepatitis C drug space, is investigating the use of simtuzumab in treating NASH induced fibrosis. Simtuzumab is the only antibody in development to treat NASH or related conditions, which Gilead has also been evaluating to treat idiopathic pulmonary fibrosis. And apart from Takeda and Abbott Laboratories, the absence of major pharmaceuticals from the drugs in development roll call for NASH is a sign of a drug market that is open for acquisition plays, as typified by Shire Pharmaceuticals purchase of Lumena Pharmaceuticals.

Bioshares

Survey of NASH Clinical Trials

Selected Non Alcholic Fatty Liver Disease /NASH Trials

Company/ Organisation	Product/Program	Mechanism of Action	Phase	Num. Pts	Design	Endpoints	Start	End
Commercial								
Abbott Laboratories	S-adenosyl-L-methionine (SAMe)	A naturally occurring molecule; addresses methionine deficiency	Phase II	120	SAMe 1000mg, 1500mg, 2000mg; dosing study; randomized; open label	Methionine elimination half-life measured in blood, 6 weeks	Dec-12	Sep-14
Conatus Pharmaceuticals Inc	IDN-6556 (emricasan)	Pan-caspase inhibitor	Phase II	40	25 mg BID for 28 days/Randomized /double blind	? in AAT	May-11	May-14
Galectin Therapeutics	GR-MD-02	Inhibition of galectin proteins (galectin-3)	Phase I	24	Dose escalation , 3 cohorts / Partially blinded	Safety/PK profile ; ? in ALT, and AST		Apr-14
Galmed Pharmaceuticals [ISRAEL]	Aramchol	Conjugate of Cholic Acid and Arachidic (Fatty acid /Fatty bile acid conjugates)	Phase IIb	240	400mg or 600mg or placebo, for 12 months (once daily)/ Randomized /double blind /placebo	reduction in liver fat concentration of more than 10%		2015 ?
Gilead Sciences	Simtuzumab (GS-6624) [for Cirrhosis due to NASH]	Monoclonal Antibody Against Lysyl Oxidase-Like 2 (LOXL2)	Phase II	225	200mg or 700mg, for up to 240 weeks (by IV every 2 weeks); Randomized /double blind, plus open label exten.	Mean change from baseline in hepatic venous pressure gradient (HVPG)		Nov-22
Gilead Sciences	Simtuzumab (GS-6624) [for fibrosis due to NASH]	Monoclonal Antibody Against Lysyl Oxidase-Like 2 (LOXL2)	Phase II	225	75mg or 125mg, for up to 96 weeks (by sc weekly);Randomized /double blind,	Change from baseline in morphometric quantitative collagen on liver biopsy at 96 weeks	Dec-12	May-16
KT&G Life Sciences Corp [KOREA]	MB12066	ß-lapachone, a natural compound, modulates epxn of genes assoc. with mitochondrial biogenessis and fatty acid metabolism	Phase II	50	MB12066 200mg (100 mg twice daily), 12 weeks; Randomised; Double blind	? in hepatic steatosis, fibrosis, lobular inflammation	Nov-13	Jan-15
Pharmaking [KOREA]	Oltipraz	Inhibits fatty acid synthesis through AMPK-S6K1 pathway and LXRg-SREBP-1c pathway	Phase III	276	3X30g or 3X40g day/ Randomized /double blind	? in liver fat at 24 weeks	Feb-14	Jul-15
Phenex Pharmaceuticals AG	Px-104	Farnesoid X Receptor (FXR) Agonist (Novel fully synthetic)	Phase II	12	28 days, pilot study	Safety	Oct-13	Mar-14
Takeda	Roflumilast (DAXAS) plus Pioglitazone (ACTOS)	Roflumilast - a selective, long-acting inhibitor of the enzyme PDE-4 (anti-inflammatory)	Phase II	75	Randomized /double blind	Safety and efficacy; ? in ALT at 4 months	Jun-13	Feb-14
Completed								
Shire Pharmaceuticals (acq. Lumena Pharmaceuticals)	LUM022	apical sodium dependent bile acid transporter (ASBT) inhibitor (blocks bile reabsorption)	Phase Ib					

Sources: Clinicaltrials.gov, company filings and announcements

– Cont'd over

Survey of NASH Clinical Trials (cont'd)

Selected Non Alcholic Fatty Liver Disease /NASH Trials

Company/ Organisation	Product/Program	Mechanism of Action	Phase	Num. Pts	Design	Endpoints	Start	End
Commercial								
Trial Halted Early								
Intercept Pharma-ceuticals/ NIKDD	Obeticholic Acid	farnesoid X receptor, a nuclear receptor that regulates bile acid synthesis and clearance from the liver	Phase II	283	25 mg daily for 72 weeks/ Randomized/ Double Blind/ Placebo controlled	Hepatic histological improvement in NAFLD Activity Score at 72 weeks	Mar-11	Sep-14
Pre-clinical								
Cempra Pharma-ceuticals	Oral solithromycin	anti-inflammatory						
Academic/Non-commercial								
University of Aarhus	Resveratol	anti-oxidant polyphenol	NA	48	Randomised; Double blind	? hepatic steatosis and inflammation	Sep-11	Oct-14
University of California, San Diego	Sitagliptin (JANUVIA)	dipeptidyl peptidase-4 (DPP-4) inhibitor	Phase II	50	Sitagliptin 100 mg orally daily versus placebo; Randomised	Safety/Efficacy	Jan-14	Jan-16
University of California, San Diego	Ezetimibe (EZETROL)	Niemann-Pick C1-Like 1 (NPC1L1) receptor (manages intestinal uptake of cholesterol and phytosterols)	Phase II	50	10 mg daily; 24 weeks	Liver Biopsy and MRI at week 24	Jan-13	Jan-14
University of Malaya	Sillymarin (complex of silybins A and B, isosilybins A and B, silychristin, and silydianin)		Phase II	120	Silymarin 700mg TID/ Randomised; Double blind; placebo controlled	? in NAS score by at least 30%, 12 months; ? in ALT and AST	Jun-12	Jun-15
University of Michigan/ NIDDK	Metreleptin (MYALEPT)	synthetic analog of the hormone leptin	Phase II	20	Open label	Safety/Efficacy Study	Oct-12	Sep-15
University of Michigan	Amlexanox (discontinued in the US as a treatment for mouth ulcers) (dev. In Japan for asthma)	selectively inhibits TBK1 and IKK-e	Phase II	40	25mg titrated to 50mg daily(12 weeks in total); randomized; double blind; placebo controlled	improvement in HbA1c; improvement in hepatic steatosis by MRI, at 12 weeks	Jan-14	Jan-16
Sheba Medical Center	Atorvastatin	Statins (i.e.) Atorvastatin inhibits HMG CoA reductase	NA	150	Randomised; Open label	? liver steatosis at 6 mo; ? baseline in liver fibrosis at 6 mo	Dec-13	Jul-15
Sheffield Teaching Hospitals NHS Foundation Trust	Testosterone	Hypothesis is that low testosterone causes insulin resistance	Phase II	10	1 mg as a single intramuscular injection at 0, 6, 18, 30 and 42 weeks; open label	steatohepatitis improvement assessed by liver biopsy; 12 months	Jul-13	Sep-15
Tehran University of Medical Sciences	L-Carnitine With Atorvastatin	Statins (i.e.) Atorvastatin inhibits HMG CoA reductase;L-Carnitine modulates inflammation	Phase II	440	Atorvastatin 20mg, L-carnitine 1000mg - daily; Randomized /double blind	improvement in liver stiffness at 2 years; improvement in liver enzymes	Jan-13	Dec-15

Bioshares Model Portfolio (30 May 2014)

Company	Price (current)	Price added to portfolio	Date added
pSivida	$3.900	$4.000	May 14
Invion	$0.065	$0.089	February 14
Impedimed	$0.200	$0.245	December 13
Analytica	$0.042	$0.025	December 13
Imugene	$0.011	$0.022	November 13
Oncosil Medical	$0.105	$0.155	September 13
IDT Australia	$0.230	$0.260	August 13
Viralytics	$0.290	$0.300	August 13
Tissue Therapies	$0.330	$0.255	March 2013
Somnomed	$1.45	$0.94	January 2011
Cogstate	$0.240	$0.13	November 2007

Portfolio Changes – 30 May 2014

IN:

No changes

OUT:

No changes

Recommendations:

Virax Holdings Acquires New Cancer Drug Candidate

Virax Holdings (VHL: $0.008) has a new focus having this week acquired a therapeutic cancer program through the acquisition of Pathway Oncology. The company has announced a new CEO, Rob Crombie, who was formerly at Evogenix and Arana Therapeutics. It has also appointed Paul Hopper as an executive director.

The core asset of Pathway is a cancer immunotherapy that inhibits the enzyme linked to tumour growth, called GGTI. The original technology was discovered at Yale University.

Hopper is building a track record in his involvement with Australian oncology companies. He is Chairman of Viralytics and Executive Chairman of Imugene. Hopper was a founder of Pathway Oncology, and was Chief Operating Officer of Biolife Science Qld, which was acquired by Imugene.

The lead compound that has been acquired, GGTI-2418, has been evaluated in a Phase I trial which showed that 30% of late stage patients with solid tumours achieved stable disease following treatment with GGTI-2418. Virax expects to start a Phase I/II trial in patients with breast cancer and multiple myeloma in the first half of next year. The company expects to re-open an IND with the FDA.

The acquisition price for Pathway Oncology is $2 million (240 million shares based on the achievement of milestones).

Bioshares recommendation: **Under Review**

– Benitec cont'd

Strict Entry Criteria

Selection of patients into this trial has been very well considered, with 26 exclusion criteria. This explains the delay in selecting the first patient, with this previously expected to occur in March this year. The most important criteria for patients entering the trial is that they need to have been infected with the Hepatitis C virus (genotype 1) for at least six months, and have failed the standard-of-care antiviral therapy or be unwilling to receive this combination therapy.

There are two trial sites in the US involved with this trial, with one of those sites actively recruiting at this stage.

Summary

Benitec has made excellent progress over the year in commercializing its novel therapy for chronic Hepatitis C infection. The company received a positive review from the NIH's Recombinant DNA Advisory Committee (regarding the gene therapy approach being used) in July last year, gained FDA IND clearance in January this year, raised $31.5 million in April, and this month treated its first patient.

Benitec's approach to treating Hepatitis C with its drug candidate TT-034 is a technically challenging project. The potential rewards are very high for the company, and success in the Hepatitis C program will be potentially leveraged across the company's platform, reflecting positively for its hepatitis B program in particular.

Benitec is capitalised at $138 million. The company has an estimated $32 million in cash.

Bioshares recommendation: **Speculative Hold Class A**

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. For both groups, the rating "Take Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

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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