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Bioshares

5 September 2014
Edition 567

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

Companies covered: ANP, BLT, IPD, Hatchtech

	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 - current)	22.9%
Cumulative Gain	**421%**
Av. Annual gain (14 yrs)	**17.7%**

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Impedimed Gains Expanded Reimbursement Status for L-Dex

The American Medical Association has expanded the Category I CPT code for Impedimed's (IPD: $0.455) bioimpedance spectroscopy technology to include lymphedema from all relevant cancer types, from an earlier, more specific focus on breast cancer related lymphedema.

This is a significant event for Impedimed because it expands the addressable market for the company's L-Dex product to 940,000 patients in the US, up from 230,000 breast cancer patients. The expanded addressable market includes lymphedema relating to other cancers such as melanoma, colorectal and gynecologic cancers.

The improved code descriptor for bioimpedance spectroscopy follows the bringing forward of an effective date for the CPT1 code to January 1, 2015 from January 1, 2016. And in fact, the company believed that gaining an expanded descriptor was more likely to have also occurred in 2016.

A first round effect of the granting of a CPT1 code is that it means that Impedimed can move towards gaining coverage under the US government's Medicare insurance program, which cover Americans aged 65 and over, but also 100 million Americans in total. More than half of all breast cancers occur in women aged over the age of 65 so access to Medicare is of commercial importance in that regard. We expect progress with other insurers will take longer.

One consequence of the expansion of the code to include all related cancers is that the company now has the potential to work with 20 patient advocacy groups. Such groups can play an important role in advocating the benefits of new technologies to health insurance groups, physicians and to patients themselves who are seeking to understand what constitutes best practice in treating various conditions or diseases.

The company will also increase its efforts to work with medical oncologists, who act as principal care managers for cancer patients and coordinate both pre- and post-care activities. The key link here is that regular monitoring of lymphedema is arguably an important long term activity for medical oncologists and their patients.

Both the medical oncologists and the patient advocacy groups will form part of Impedimed's efforts to work on having its bioimpedance spectroscopy technology included in the National Comprehensive Cancer Networks guidelines.

Impedimed has a commenced a 1,100 patient study which will evaluate the benefits of its L-Dex assessment over a five year period.

Cont'd on page 3

Benitec Biopharma's HCV Trial

Benitec Biopharma (BLT: $1.025) dosed the first patient in May with its novel ddRNAi therapy in its Phase I/II Hepatitis C (HCV) trial.

The company is currently screening for the next patient into this trial. But due to the strict entry criteria into the trial, and the health status of the patients being screened, there have been delays in recruiting the second patient. The company has added a second site to screen patients for the trial and has appointed an internal clinical trial manager to work in conjunction with the CRO that is coordinating the study.

Results from the first patient were positive at the six week follow-up point. There were no treatment-related side effects. And of particular importance was that there was evidence of the ddRNAi therapy correctly activating the liver cells as measured through a liver biopsy.

Benitec's DNA was found in the liver, and was also found to have produced the short hairpin RNA, albeit in small quantities, from the very small starting dose.

The next patient will receive the same dose and will be monitored for six weeks, at which point the company will be able to recruit the third patient, if all goes well. The third patient will receive a dose three times as high. If the treatment is still shown to be safe, then patients four and five will be treated in parallel.

Six weeks after patients four and five are cleared, the company will screen for patient number six, with that patient to receive a dose 10 times higher than the first patient, with what is expected to be a therapeutic dose. A total of 14 patients are to be treated in this trial and the company has the option to recruit more patients into this study. Subsequent studies may involve less stringent entry criteria, once the safety and efficacy profile of the therapy becomes better known.

Update From Benitec's Head of R&D

Recently, Benitec's Senior VP of R&D, David Suhy, provided investors with an update on Benitec's HCV program. Suhy said that Benitec is a company that is based on gene therapy to deliver its RNAi treatment.

However 'gene therapy' is no longer a longer a dirty word, with the first gene therapy product approved by European regulators for UniQure. In November 2012, UniQure received approval for Glybera, which uses the same vector as Benitec, the adeno-associated virus, to deliver a treatment for a rare metabolic disorder called Lipoprotein Lipase Deficiency.

The difference between Benitec's technology and other RNAi players is that Benitec's treatment may only needs to be given once. This compares to Alnylam's technology which Suhy said needs to injected every three to four weeks. Alnylam now has a market value of US$5 billion, which has increased from US$1 billion two years ago. A limitation however of Alnylam's technology is that it only works with liver specific diseases.

Suhy stressed the point that this is no longer a preclinical technology. There are more hurdles for Benitec's approach than for siRNA, particularly in moving through the regulatory process. "There are not many trials using gene therapy," said Suhy.

Suhy believes that the data from the first patient has de-risked the program significantly. However, the challenge is that it is a complex product that is not 'withdrawable'. "One IV injection has been able to transduce most, if not all, liver cells and produce short hairpin RNA," said Suhy. But once Benitec's loop sequence is cleaved, it is essentially identical to siRNA said Suhy.

What appealed to clinicians about Benitec's approach was the technology's capability to produce multiple short hairpin RNA's that hit multiple targets in the virus. "It's multiple combinations that really control the disease," said Suhy.

Gilead Science's new but very expensive HCV therapy, Sovaldi, has set the bar very high, said Suhy. With a cure rate of between, 95%-100%, nothing short of complete removal of the virus will be sufficient believes Suhy. But the high price of Sovaldi, at US$84,000 per treatment, is leaving gaps in the market with less than 10% of insurers in the US currently approving payment.

Another benefit from Benitec's once only treatment is that it takes compliance out of the equation, said Suhy, which is something that pleases insurers. This will also be important in applying the treatment for hepatitis B, which is more common in Asia where compliance is an issue.

Suhy said that so far extensive preclinical data from Benitec's therapy, TT-034, has aligned with what has been seen with the first patient treated. Benitec's CEO Peter French said he is highly confident that this trial should meet its primary and secondary endpoints.

Other Programs

Benitec's Chief Business Officer, Carl Stubbings, said the company's $31.5 million capital raising in February this year was a very smart move because it allows the company to advance its other programs as well.

The next program after HCV is in the treatment of chemotherapy-resistant lung disease, with toxicology studies to be conducted next. After that is the company's wet AMD program. The Hepatitis B (HBV) program is less advanced. However this program could be accelerated if there is early clinical success in HCV.

In AMD, the standard of care is an injection into the eye every six weeks, which leaves open a more patient friendly treatment option. In HBV, there is no current cure.

Arrowhead Research Corporation is currently conducting an RNAi treatment Phase II trial in eight patients with data expected in this quarter. However Stubbings said that you need to keep administering this treatment. Arrowhead is currently valued at US$837 million.

Cont'd over

Bioshares Model Portfolio (5 Sept 2014)

Company	Price (current)	Price added to portfolio	Date added
Actinogen	$0.050	$0.050	September 14
Benitec Biopharma	$1.025	$1.025	September 14
LBT Innovations	$0.130	$0.130	July 14
pSivida	$5.150	$3.800	May 14
Invion	$0.080	$0.089	February 14
Impedimed	$0.455	$0.245	December 13
Analytica	$0.038	$0.025	December 13
Imugene	$0.016	$0.022	November 13
Oncosil Medical	$0.120	$0.155	September 13
IDT Australia	$0.250	$0.260	August 13
Viralytics	$0.265	$0.300	August 13
Tissue Therapies	$0.400	$0.255	March 2013
Somnomed	$1.99	$0.94	January 2011
Cogstate	$0.275	$0.13	November 2007

Portfolio Changes – 5 September 2014

IN:
Actinogen, Benitec Biopharma

OUT:
No changes

– Impedimed cont'd

Summary

The receipt by Impedimed of an expanded descriptor for bioimpedance spectroscopy for the assessment of lymphedema changes the Impedimed business because it will place new growth-based demands on the business ahead of time. But those demands are linked to a greatly expanded market opportunity.

Revenues from L-Dex can be expected to increase in 2015, but we suggest, however, that calendar year second half financials will be more meaningful in terms of evidence of any expanded CPT1 code driven growth in sales. The widespread adoption of L-Dex (or bioimpedance spectroscopy) for detecting lymphedema at the subclinical stage will still take time to achieve because the technology must be incorporated into medical policy and treatment guidelines. In the long run, it has the potential to become a standard of care technology.

Impedimed recorded sales of $3.3 million for FY2013 and posted a net loss of $8 million. The company retained cash of $10.8 million at June 30, 2014.

Impedimed is capitalised at $108 million.

Bioshares recommendation: **Speculative Buy Class A**

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Addendum: Virax Holdings

In last week's edition of *Bioshares,* we held over our recommendation for Virax Holdings, pending assessment of the company's patent position covering its GGTI-2418 program. The US patent covering this molecule expires in 2022, but the company states that a three year extension exists for this patent.

Bioshares recommendation: **Speculative Hold Class B**

Bioshares

– Benitec Biopharma cont'd

Benitec said that there is renewed interest in RNAi and gene therapy from the pharmaceutical industry. Going forward an item to look out for may be a licensing deal with a major pharmaceutical company for access to the Benitec technology.

French believes that the outcome from the HCV trial will be very predictive for another of the company's programs, in HBV. "Positive results will provide real support for HBV and other programs in the pipeline," said French.

Benitec also has four out-licensed programs. These are: in HIV (Calimmune), cancer vaccines (Regen BioPharma), ocular disease (Genable), and Huntington's disease (UniQure).

Patents: Benitec's core patents are granted and run out to 2019. The company has further protection around composition of matter of its therapies (granted for HCV, protection to 2026), its multiple promoter expression cassettes for HCV (granted, protection to 2025) and tissue specific promoters for hepatitis (granted, protection to 2026). Patents pending around HBV will give protection to 3031 if granted, pain treatment to 2033 and wet AMD out to 2034 if granted. With Benitec's therapies classified as biologics, they should receive 12 years market exclusivity in the USA for any approved product.

Cash: $31.3 million at June 30, 2014

Capitalisation: $118 million

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Antisense Therapeutics Delivers Positive Phase II Data in Acromegaly Trial

Antisense Therapeutics (ATL:$0.125) has achieved a positive result from its Phase II trial with drug candidate ATL1103 in patients with acromegaly.

Acromegaly is a disease that is characterised by excessive limb and organ growth. IGF-1 plays a key role in this disease and reducing IGF-1 levels in the blood is an effective way to bring this disease under control.

There are two main drug treatment options for acromegaly. The first line treatment is with a drug called Octreotide, which is a depot injection. This drug is effective in about 60% of patients. Those who do not respond to this drug can be treated with Somavert, which is a genetically engineered protein.

Somavert generates sales of around US$200 million a year. However the drug is very expensive, around US$60,000 a year, needs to be injected daily, needs to be reconstituted from powder, and has shown to elevate liver enzymes. The deficiencies with this drug open up a market for a drug that achieves a similar therapeutic benefic but which is more patient friendly and less expensive.

Phase II Results for ATL1103

The clarity with Antisense's acromegaly program is that the biomarker that is measured, serum IGF-1 levels, is also the primary endpoint. In this trial, patients were divided into two groups to receive either 200mg a week or 400 mg a week for 13 weeks (with an initial dose of 600mg over a week in the first week in both groups).

In this trial, it was shown that at the higher dose (400mg per week), IGF-1 levels were reduced by average 30% at the end of treatment. This compares to a Phase II study with Somavert which saw a 31% reduction in IGF-1 levels.

A week after treatment stopped, average IGF-1 levels were still 26% lower than at the start (which was statistically significant, $p<0.0001$), and around 20% lower five weeks after treatment had ended.

In the lower dose group (200mg per week), there was no average change in IGF-1 levels. However four of the 13 patients receiving this lower dose achieved a greater than 20% reduction in IGF-1 levels.

The other positive outcomes from this trial is that there was a clear dose response with the treatment, between the lower and higher doses, as well as a distinctly better result in smaller patients (i.e. those receiving a higher dose effectively per kg of weight).

There was a clear downward trend in the IGF-1 levels the longer the patients received therapy, suggesting that IGF-1 levels should continue to fall the longer treatment continues. In this trial patients' IGF-1 levels were very high, at 2.6 times normal levels. This compares to 1.8 times normal levels in a published study with another drug for acromegaly. IGF-1 levels were normalised in two of the patients in the higher dose and in one patient in the lower dose. In a Phase II study with Somavert, three out of 15 patients were stabilised.

The comments from the Principal Investigator in the study are of interest. Dr Peter Trainer said: *"There are limited therapeutic options for patients with acromegaly and there is an acknowledged need for new therapies. The results achieved in this Phase II study suggest ATL1103 with appropriate dose adjustment should be capable of achieving disease control in a significant proportion of patients with acromegaly. ATL1103's profile as a potentially efficacious and well tolerated, conveniently dosed therapy strongly supports its move into Phase III stage of development."*

ATL1103 is dosed weekly as a subcutaneous injection.

With respect to the safety profile of ATL1103, elevated liver enzymes were seen in two patients (one in each of the doses), but the company said this was not clinically meaningful, with patients continuing with treatment.

Next Stage for ATL1103

Antisense now plans to partner this program, for it to move into a Phase III study. Additional material would need to be manufactured from a contract manufacturing group, which Antisense does not intend fund.

However, while licensing discussions are in process, Antisense intends to conduct a small study with ATL1103 in a higher dose.

Chronic toxicology studies will also need to be conducted with ATL1103 in one or two species, which may take six to 12 months.

In a Phase III trial, the end point would be disease stabilisation. For ATL1103, that would likely mean higher doses, in at least some patients, or a higher dose per weight, over a longer period.

Future Treatment Options

If ATL1103 does reach the market as a treatment for acromegaly, it may be that patients will receive a higher dose of the drug initially to normalize IGF-1 levels, and then a lower maintenance dose. As with other drugs on the market, treatment is titrated at times, escalating drug dose to achieve stabilisation of IGF-1 levels.

Market for Acromegaly

The CEO of Antisense Therapeutics, Mark Diamond, said there are around 15,000 patients failing first line treatment for acromegaly, and only around 3,000 patients are being treated with Somavert, based on annual sales numbers.

Roche Pulls out of Octreotide Deal

In February 2014 Roche signed a major deal with biotech group Chiasma to gain access to Chiasma's oral Octreotide program. Roche paid US$65 million up front. However in August this year Roche pulled out of the deal citing data emerging from Phase III trials as well as feedback from regulators. Octreotide generated around US$640 million in sales in 2013 for Novartis for the treatment of acromegaly.

One of the negatives with the oral version of octreotide being

Cont'd over

Private Company Update

Convincing Phase III Trial Results for Hatchtech's Head Lice Treatment

Hatchtech has successfully completed the two US Phase III trials of its head lice treatment, Xeglyze (abametapir), which was formerly known as DeOvo and also as Ha44. The clinical trials achieved the primary endpoint that had been agreed with the US FDA under a Special Protocol Assessment.

A single, 10 minute application of Xeglyze (0.74% w/v), resulted in 81.5% of subjects being free of lice at the 14 day follow-up, without any nit combing. This figure is the average of the results for the two studies of 81.1% and 81.8% for studies 001 and 002 respectively.

The trials also showed that Xeglyze was safe and well tolerated, with no treatment related adverse events observed.

Secondary endpoints were the proportion of subjects free of lice at day 1 and day 7 following the treatment. The result was that 90% of subjects were free of lice at day 1 and 88% were free at day 7.

Hatchtech's goal was to exceed a 75% clearance rate, with 80% standing as the clearance rate for commercial differentiation i.e. a labelling claim.

By way of comparison, the most recently approved head lice treatment Sklice, achieved 76.1% and 71.4% in the two Phase III trials conducted for its drug submission.

Pre-NDA Meeting

The company's next step will be to hold a pre-NDA (New Drug Application) meeting with the FDA. While Hatchtech would ideally like to hold this meeting before the end of the calendar year, it is more likely that it will take place early in 2015, with a filing to take place in the first half of 2015.

Guidance and information the company gains from the meeting will then be used by the company in partnering discussions. Hatchtech will run its partnering activities in parallel with its drug application. Hatchtech's objective is to achieve either a sale of the company or licensing arrangement in 2015.

Hatchtech expects that it will take 3-4 months to put its NDA package together.

Patents

The granted Australian and US patents covering Xeglyze run to 2024 and 2026 respectively, with other patent applications covering formulations potentially enabling the product to be protected to 2036.

Other Studies

Hatchtech expects to obtain the results of its 'egg counting' Phase II study at the end of September. Recruitment for this trial has now been completed. This study is evaluating the proportion of hatched eggs pre-treatment relative to the proportion of hatched eggs post treatment for the Xeglyze and control treated eggs, after 14 days of incubation. The purpose of this study is to provide additional claims for the Xeglyze product label.

Comments

Hatchtech's Phase III trials would appear to place Xeglyze comfortably ahead of its closest rival Sklice (Sanofi) in terms of lice clearance at two weeks post treatment. Most head lice products require two treatments, with the exception of Sklice, which was approved in the US in February 2012 and launched six months later. However, Sklice is not ovicidal, but is neurotoxic, acting on its nervous system and shutting down its ability to breathe. Sklice is a re-purposed lotion formulation of the anti-parasitic compound ivermectin.

There is an attractive market opportunity for a superior head lice treatment both in the US and in many other countries. The US CDC estimates that while there may be anywhere from 6 to 12 million infestations in children a year in the US, the current approaches to treatment have many limitations and until now, none of the chemical approaches have targeted the eggs laid by the head lice and with the one treatment.

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– Antisense Therapeutics cont'd

developed is that it stabilises only 60% of patients who are effectively being treated with the depot injection of octreotide, thereby not being effective in 40% of patients.

The large Pharma interest in the acromegaly space, even though Roche has pulled out due to what appears to being program specific reasons, is a positive for Antisense and helps validate the commercial potential in its program.

Summary

Antisense Therapeutics has delivered positive Phase II data with its drug candidate ATL1103 for the treatment of acromegaly. According to the Principal Investigator in the trial, the program warrants moving into a Phase III setting, with the treatment options for acromegaly lacking and improvements needed.

For Antisense now the next phase is to license the program and more immediately to improve its funding position, with only $1.3 million in cash at June 30 with a further $1.2 million R&D tax refund due.

Patents: The core patents on ATL1103 go out beyond 2024 with additions on use patents and combination use.

Royalty obligations: Antisense is required to pay Isis Pharmaceuticals an undisclosed royalty on any revenue it receives from commercialization of ATL1103, not on net sales.

Capitalisation: $18 million

Bioshares recommendation: **Speculative Buy Class B**

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. 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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