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**In this edition...**
Benitec Biopharma's fortunes have changed rapidly this year all because the company was able to acquire a company it had licensed its gene silencing technology to, Tacere Therapeutics, in a move akin to restoring a very large, in fact, two very large jewels to a crown. Tacere's HCV and AMD programs represent very large market opportunities which sit right in the sweet spot for Benitec's ddRNAi technology. Validation of the platform in HCV patients could be as soon as year away but before then, the company must raise funds. However, that may be less of a challenge when the market examines the opportunities in HCV and AMD. pSivida is poised to see revenues flow from Alimera's launch of Iluvien in Europe next year. Alchemia's pricing of Audeo Oncology ascribes it a pre-money value of 42 cps.
**Companies Covered: ACL, BLT, PVA**

| | 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 - current) | -10.1% |
| **Cumulative Gain** | **210%** |
| **Av. annual gain (11 yrs)** | **17.8%** |

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# Bioshares

**16 November 2012**
**Edition 481**

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

## Benitec's Big Hepatitis C Play

Benitec Biopharma (1.6 cents) followed its recent AGM with an R&D update session. Dr David Suhy delivered an outline of Benitec's Hepatitis C (HCV), HBV and Age-related Macular Degeneration (AMD) programs. Professor David Yeomans, from Stanford University, discussed the company's approach to intractable cancer-associated pain. Per Lindel, from Novadigm Consulting, discussed aspects of the company's licensing strategy. Below we focus on the HCV, HBV and AMD presentation made by Dr David Suhy.

In addition to the HCV, AMD and pain programs, Benitec has internal programs in lung cancer (in collaboration with the UNSW), Hepatitis B (Biomics, China) and oculopharyngeal muscular dystrophy (Royal Holloway, University of London). Its out-licensed programs include HIV/AIDS with Calimmune and retinitis pigmentosa with Genable.

A brief description of Benitec's gene silencing technology can be found on the following page.

### HCV Program

The HCV program is a recent inclusion in Benitec's therapeutics product development pipeline, courtesy of its acquisition Tacere Therapeutics in October.

Tacere originally licensed ddRNAi IP from Benitec in October 2006 and was working on Hepatitis C and eye disease applications of the technology.

Suhy briefly described the history of the HCV program which commenced in September 2003, with Tacere being founded in 2004. In December 2007, Tacere licensed the programs to **Pfizer** which committed substantial resources to the program.

A first generation HCV product (TT-03X) was developed but was found to have an unsatisfactory therapeutic window, with too much transcription of RNA taking place.

In October 2009, an improved HCV construct was developed (TT-034) and the over-transcription problem was resolved.

From January to April 2010, a pre-IND meeting was held with the FDA as were similar meetings with the MHRA, the AFSSAPS and Swiss Medic.

However, Pfizer decided to close its operations in Sandwich, UK and to shut down the program, as part of a company-wide business restructure.

Tacere spent nine months negotiating with Pfizer to hand the program back. Suhy said that 'Pfizer really believed in the program and promised to pay for the completion of GLP tox studies', that needed to be completed ahead of human clinical studies.

In July 2012, the draft reports from the toxicology studies were released with favourable results reported.

*Cont'd over*

TT-034 is a construct that is designed to transcribe three short hairpin constructs, each targeted at separate highly conserved regions of the HCV genome. The inclusion of three constructs means the construct has the potential to be more broadly applicable, including more applicable across the different strains of HCV but also applicable against mutational changes to the virus.

The highly conserved regions were identified through analysis of publicly curated databases of the HCV genome.

***AAV Vector***

TT-034 uses an adeno-associated virus (AAV) vector, which means among other things, that the therapy (and all Benitec therapies) is regulated as a gene therapy by regulators. AAV vectors have been evaluated in many clinical trials, in hundreds of patients, and is regarded more favourably than other vectors because of its low pathogenicity.

AAV is attractive for use in the HCV setting because it has a high affinity to liver tissue; 90% of TT-034 vector product migrates to liver tissue, which is the organ infected by HCV. Benitec (Tacere) has found that TT-034 is capable of transfecting 100% of hepatocytes (liver cells).

With 180 day toxicology studies now complete, and with no toxicology issues having emerged in mouse, human or cynomolgus monkey liver cells, TT-034 is ready for clinical studies in human subjects.

***TT-034 Clinical Trial***

While Benitec has not finalised the design of an initial HCV clinical trial, Suhy said that patients enrolled in the trial would be those who have failed treatment with the current standard of care (SOC) which includes Interferon, ribavarin and a protease inhibitor class drug.

The company's expectation is that once the therapy is shown to be safe then the restriction to patients who have failed SOC would be lifted.

The principle advantage of a ddRNAi therapy in HCV patients would be that it confers protection (viral elimination) with *one injection* in contrast to drug therapies that last for months and confer side effects that lead to non-compliance.

The company's ability to conduct clinical trials will be governed by its ability to access medical centres that have developed a familiarity with the use of AAV vectors, have investigators familiar with gene therapy, and also conduct significant work with HCV patients in order to access a robust population for recruitment purposes.

In the initial trial, the company will also restrict patient enrollees to those that are HCV Type 1 positive, presumably to produce a clearer picture of the effect of the therapy.

The company expects to see a multi-log drop in viral titre. It will compare viral load before and after treatment. It will also monitor patients who might have experienced a re-bound in viral load and then seek to understand why that might have occurred, based on the type of HCV infection.

**Benitec's Gene Silencing Technology**

Benitec is commercialising gene silencing technology which is potentially applicable to diseases and medical conditions where a permanent 'knock out' effect of aberrant protein production or viral elimination is warranted.

Benitec's approach uses a viral vector to deliver a genetic construct into a cell. The construct migrates to the nucleus of the cell where transcription takes place and a double stranded RNA molecule known as short-hairpin RNA (shRNA) is produced. Furthermore the shRNA is expressed continuously in the nucleus. The hairpin serves as a clip for joining like strands of RNA together.

The hairpin construct is later cleaved ('cut') by an enzyme called DICER. The double stranded RNA is then cut into sequence specific RNA, one half of which is paired with its complement on a gene and by doing so modifies gene expression or more bluntly so stops the production of protein involved in the disease state. Benitec's technology is regulated as a gene therapy in part because it makes use of viral vectors to deliver DNA into cells which go on to continually express shRNA.

## HBV Program

The HBV program is very similar to the HCV program in that the same vector will be loaded with constructs that target three highly conserved regions of the HBV genome. Pfizer also complete substantial work on this program. However, the pre-clinical studies in animal models have yet to be completed.

## Age-Related Macular Degeneration

The Age-related Macular degeneration program, while less advanced than the HCV program, is exciting because of the large market opportunity and the tractability of a potential gene target that could be selected for the therapy.

Although the company has not disclosed a gene target, the characteristics of macular degeneration are such that the area of biological interest is likely that addressed by the antibody therapies which include Lucentis and Avastin, which is the VEGF-A protein, or in the case of Benitec (Tacere), the corresponding gene.

These therapies stabilize vision in 95% of patients and marginally improve vision in 29% to 40% of patients. However, the antibody therapies have a half life of 9 days, resulting in the need for injections on a monthly basis, which in itself is negative feature. A consequence is that the annual treatment costs of the antibody drugs are very high. (Lucentis costs ~US$1,600 per injection).

(Global sales of therapies for AMD totalled US$ 4 billion in 2011.)

*Cont'd over*

## Commentary

### Funding Challenge

The most immediate challenge for Benitec is funding. The company's cash is not sufficient to support the prospective Phase I/II trial of TT-034. However, the company is in the best position it has been for many years to build a better funding base. The company held cash of $2 million at September 30, which would only support operations (based on previous spending) for a little over six months.

The company should be aiming to lift its cash resources so that it can *comfortably* support the Phase I/II trial, *comfortably* invest in the AMD programs, and *comfortably* address licensing opportunities.

A related challenge for the company is to strengthen its register with investors who are capable of supporting the company through further additional rounds.

### FDA RAC Meeting in 2013

The HCV clinical trial has to pass several regulatory thresholds before it can commence. It must be cleared by the FDA's Recombinant DNA Advisory committee (RAC), which meets next on March 12-14, 2013. Submissions for this meeting must be made by January 15, 2013. The next meeting of the RAC is then in June, with submissions made by April. Benitec (Tacere) must also have its IND accepted by the FDA before it can commence its clinical trial.

### Technology Class Still Unvalidated

Gene silencing technology remains unvalidated clinically and commercially. The siRNA approach championed by Sirna and Alnylam has not paid off and has suffered because certain siRNA constructs were found to initiate undesirable immuno-stimulatory responses.

### Long Term Risk from Rival Approaches

A long term risk for Benitec is that passage of therapies in the RNAi class of therapies will be subjected to subtle interference at the regulatory and clinical level by companies with strong franchises in HCV and AMD. This is because this emerging class of therapy is disruptive to revenue models that benefit from administration of drugs on a repeat basis (chronic dosing). This risk will increase as all oral regimes that dispense with the co-administration of ribavarin and interferon emerge.

### The Pfizer Investment

Investors would do well to appreciate the investment made by Pfizer in Tacere, which while not public would easily have been in the multi-millions of dollars and represent a significantly undervalued aspect of Benitec's pipeline of therapeutic opportunities. We understand that one stage Pfizer had somewhere between 85 to 90 people working on the HCV project.

RNAi therapies such as Benitec's ddRNAi approach are limited to diseases where a permanent gene silencing effect can be tolerated. Chronic viral infections such as HCV and HBV fit this rule. AMD is also suitable because the eye is a protected organ and the risk of negative systemic effects should be low.

### Summary

After a long period of being a less than attractive investment opportunity, while working through patent litigation challenges (now clearly resolved in Benitec's favour), Benitec has moved into a centre stage position where high risk but high reward opportunities are gathered. The Tacere acquisition is a potential game changing event for Benitec because it brings several large market opportunities, namely HCV and AMD into the investment proposition. HCV is especially attractive, with 170 million people infected with the virus worldwide and 3-5 million infected each year.

The investment appeal of the Benitec's initial HCV clinical trial is that it would yield both safety and efficacy results in the first instance and has the potential to validate the entire Benitec platform. An additional attraction for investors is that proof of concept in HCV could be evident as early as this time next year, although a 2014 data yield is more likely.

Benitec is capitalised at $17 million, holding cash of $2 million at September 30, 2012.

*Bioshares* recommendation: **Speculative Buy Class A**

**Bioshares**

***Changes to Subscription Rates for Bioshares***

The cost of a 12 month subscription to Bioshares has been increased from $375 to $400.

The prices for other subscription categories have been increased by a similar rate. These new rates can be found on the back page of this edition.

# *Alchemia Spin-out Audeo Oncology Files S-1 with the SEC*

Alchemia's (ACL: $0.595) proposed spin-out, Audeo Oncology, has filed its S-1 registration statement with the US SEC. The company is now out of its 'quiet period', able to promote the proposed new listing. This week the company was on a roadshow in Australia and it will start a US roadsahow on November 22. The offer is expected to close on 5 December and list after that.

The S-1 is an interesting document for a couple of reasons. Firstly it gives an indicative pre-money valuation for the Audeo Oncology business, and secondly, it spells out how much the company is seeking to raise.

### Pricing – US$14-$16 per Share

The IPO is priced at US$14-$16 per share. It is offering 3.25 million shares, which translates to raising between US$45.5 - US$52 million. Since 2006, $47 million has been spent on the Audeo assets .

Prior to listing, there will be 7.592 million shares that will be owned by Alchemia shareholders. This translates to a pre-money valuation of US$106 - US$121 million (A$103 - A$118 million), or 36.7 - 42 cents per ACL share (based on AUD/USD = 1.03). The stock will trade under the stock code AURX on the Nasdaq. The stock will also trade on the ASX under CDIs, a decision that is bound to be appreciated by many of Alchemia's Australian shareholders.

Of the funds to be raised, around half will go towards funding the completion of the current Phase III HA-Irinotecan program, a filing of approval for the drug candidate, and also sufficient funds to stay in a strong position for licensing negotiations.

Some of the funds will also go towards expanding manufacture. At the moment the company only has sufficient capacity for making product for clinical studies. Some of the funds will be used to expand into other indications if this Phase III trial result is positive, and it will also spend a small amount of the funds on the company's carbohydrate drug library (VAST).

The company will have a predominantly US focus, with all four recently appointed non-executive directors based on the east coast of the US, and management expected to be based in the US eventually.

CEO Pete Smith described the company's HyACT technology as an evolution in cancer treatments, not a revolution. All of the toxicities from chemotherapy drugs occur outside of the tumour. HA (hyaluronic acid) is a naturally occurring product found in the body, in the extracellular matrix. The company is using a 'Trojan horse' approach, where cancer cells have a high affinity for HA, and so will bring in an additional quantity of the chemotherapy drugs attached to the HA. The problem with chemotherapy drugs is they can't hit the cancer cells hard enough, said Smith.

Smith is very pleased with the way the trial is progressing. To date, over 280 patients have been enrolled, with 60 in the last month alone. The company is seeking to have full recruitment in January. The end point is when 350 patients have progressions in their cancers after treatment, which is expected within six months. Smith expects the results from the Phase III trial to be 'black or white'. If they are positive, the company will look to get other existing oncology drugs onto the market using the same HyACT approach.

The company's Phase II trial in small cell lung cancer is progressing slowly. It started enrolment in September 2011. It is a physician sponsored trial. It is a very aggressive and difficult cancer to treat, with an average life expectancy of only about two months. The important aspect to this trial will be whether the drug will show an effect against stem cells. If so, the company will then be able to support the claim that it's drug is effective against cancer stem cells.

### Funding

The capital rasing for Audeo is expected to see investors participate in the US, Australia and Europe. If the spinout and funding does not occur, Alchemia may still be able to fund the current Phase III trial from existing cash reserves and from fondaparinux income.

The group had $8.9 million at the end of September. The company should receive $1.4 million from an Australian R&D tax rebate (possibly $2.5-$3.0 more if overseas spending is rebated – an ATO decision is pending). If the IPO does not occur, funds will be tight. A small rasing is one option, or there are other alternatives. (Our view is debt financing will also be an option).

Smith said the IPO window is open a bit. The appeal for potential investors in Audeo is that a major value inflection point is less than one year away.

### Fonda Revenue

Alchemia receives a profit share from the generic fondaparinux (fonda) sales in the US. Its manufacturing and marketing partner is **Dr Reddy's**. Gross sales at the moment are around US$100 million a year. Alchemia receives quarterly profit share payments. The September should see the first payment come through (due this month), which we expect to be low.

Revenue should ramp up in the December quarter with significantly higher production yields. We expect the company will start to see sales from December quarter of to be annualised at $15 million (based on revenues of $3.75 million a quarter). We estimate peak sales should occur in the next three years. Sales should increase from growth in market share in the US hospital market, and from a launch in Europe in 2013. We expect peak profit share to Alchemia to be between $20 - $23 million a year for the fonda product.

Alchemia is capitalised at $167 million.

*Bioshares* recommendation: **Speculative Buy Class A**

**Bioshares**

**Bioshares Model Portfolio (16 November 2012)**

| Company | Price (current) | Price added to portfolio | Date added |
|---|---|---|---|
| Psivida | $1.55 | $1.550 | November 2012 |
| Benitec | $0.016 | $0.016 | November 2012 |
| Nanosonics | $0.520 | $0.495 | June 2012 |
| Osprey Medical | $0.40 | $0.40 | April 2012 |
| QRxPharma | $0.77 | $1.66 | October 2011 |
| Somnomed | $0.83 | $0.94 | January 2011 |
| Cogstate | $0.330 | $0.13 | November 2007 |
| Sirtex Medical | $10.94 | $3.90 | October 2007 |
| Clinuvel Pharmaceuticals | $1.72 | $6.60 | September 2007 |
| Pharmaxis | $1.22 | $3.15 | August 2007 |
| Universal Biosensors | $1.01 | $1.23 | June 2007 |
| Alchemia | $0.595 | $0.67 | May 2004 |

### *Portfolio Changes – 16 November 2012*

**IN:**
pSivida and Benitec Biopharma have been added to the Model Portfolio.

**OUT:**
No changes

# *pSiVida Prospects Improve as Iluvien Edges to Market in Europe*

pSivida's (PVA: $1.55) partner **Alimera Sciences** is set to launch its first product, Iluvien, onto the European market in the first quarter of next year. It's very good news for pSivida which will receive between a 14%-15% net royalty from net sales.

More good news for pSivida is that Alimera is expected to refile Iluvien with the FDA for the approval of chronic diabetic macular edema (DME), also in the March quarter of next year. The drug candidate has been knocked back twice by the FDA. However the drug has shown to be more effective in patients with chronic disease, as this is the condition under which the drug was approved in Europe.

Also going pSivida's way is that Alimera raised $40 million earlier this year from some major biotech investment funds in the US, including Palo Alto Investors and Sofinnova Ventures. Palo Alto is also a shareholder in Psivida as is Allan Gray with a 14% stake.

Alimera will launch Iluvien first into Germany, the UK and France. The drug will go up against Lucentis from **Genentech**, and Eylea from **Regeneron**. Both Lucentis and Eylea work by inhibiting the growth of new blood vessels in the eye, targeting VEGF-A. Lucentius binds to the protein VEGF-A involved in new blood vessel formation, and Eylea is a VEGF trap, which is a soluble decoy that binds also to the VEGF-A protein.

Eylea is expected to be a blockbuster drug (over $1 billion in sales) in its first year. Regeneron has recently announced it will add 300 jobs in New York to expand its production capacity. The drug was approved by the FDA for the treatment of wet AMD in November last year, and more recently has been approved for the treatment of macular degeneration (after central retinal vein occlusion).

Both drugs are more effective than Alimera's Iluvien, however they need to be injected into the eye every four to six weeks. Iluvien is also injected into the eye but lasts three years, offering significant delivery advantages. Iluvien is a depot injection containing a corticosteroid.

The down side with Alimera's drug, is that while it improves eye sight in DME, 20% of patients need medication to treat increased ocular pressure. And 5% of patients need minor surgery to relieve the pressure build up in the eye.

pSivida is also planning to conduct two Phase III trials with its depot drug Medidur for the treatment of uveitis. The trial is expected to start towards the end of March next year. Medidur is effectively the same as Iluvien, containing the same corticosteroid. Psivida can use all of the safety data from the Phase III trials for Iluvien. The trials would take around 2.5 years to complete.

### Summary

pSivida is well funded with $17.6 million in cash at the end of September. It is capitalised at US$29 million. pSivida can expect to receive royalties from Iluvien sales in Europe starting next year, and if Iluvien is approved in the US, it will receive a US$25 million milestone payment from Alimera.

*Bioshares* recommendation: **Speculative Buy Class A**

**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***

***Sell***

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