ISSN 1443-850X

In this edition...
Interest is returning to the stock market with a share rally starting last week. How long it can be sustained remains to be seen, however interest in the biotech sector has been picking up for a number of months.
Australia is on the verge of finding out how much money can be made from selling technology enabled generics with Alchemia and Acrux both passing major milestones this week.
With Arana releasing positive results from its Phase II trial of ART621 in psoriasis patients, the timing of Cephalon's bid for Arana looks exquisite.

The Editors
Companies Covered: AAH, ACR, ACL

	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 - current)	-32%
Cumulative Gain	**41%**
Av Annual Gain (7 yrs)	**17.8%**

Bioshares is published by Blake Industry & Market Analysis Pty Ltd.

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Individual Subscriptions (48 issues/year)
$320 (Inc.GST)
Edition Number 303 (13 March 2009)
ISSN 1443-850X

Bioshares

13 March 2009
Edition 303

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

Alchemia's Partner Files ANDA As A Share Market Rally Starts

There were some positive signs emerging that a share market rally may have started following signs of containment of the global financial crisis. **JP Morgan Chase** and **Citigroup** this week announced profitable results for the months of January and February and with a profit forecast from **Bank of America** for 2009, the Dow Jones Industrial Average increased by 9% for the week, after falling 54% from its October 2007 high of 14,167 points. Whether the rally is sustainable or not remains to be seen.

Biotech stocks look to have bottomed a number of months ago, with strong gains seen in number of stocks since December. These include: **Alchemia** (up 142%), **Biota Holdings** (up 75%), **Peplin** (up 107%), **Nanosonics** (up 75%), **Pharmaxis** (up 27%) and **Sirtex Medical** (up 28%). The market rally coincides with very positive news from Alchemia, with its marketing and manufacturing partner, **Dr Reddy's**, having filed Alchemia's generic fondaparinux for approval (ANDA) with the FDA.

Being the first generic on the market to the branded drug Arixtra, sold by **GlaxoSmithKline**, the FDA should assess the application within six months, which means the drug should be selling in the US by year's end.

There is currently no second generic manufacturer that has yet surfaced. The fondaparinux drug is extremely difficult to manufacture. It normally takes around 50 manufacturing steps to make. As a comparison, some small molecule drugs have only three or four steps in the manufacturing process. Alchemia brings to the table proprietary manufacturing technology for carbohydrate compounds (where functional groups on the sugar scaffold ring can be capped and therefore assisting in directing chemical bonding between the sugar chains). Using Alchemia's process, the number of steps is halved, to an estimated 25 steps.

Everything seems to be falling in place for Alchemia. The last 12 months has seen the fondaparinux market move from a medium sized market to a semi-blockbuster market (anything over US$1 billion a year in sales is defined as a blockbuster market). Based on the most recent quarter results (annualised), Arixtra is generating sales of US$360 million and growing at 62% over the year. In the USA – which is the important figure to look at as this is where Alchemia/Dr Reddy's will start selling their generic in 2010 or late 2009 – Arixtra sales are tracking at US$208 million and heading towards US$300 million by the time Alchemia's generic is scheduled to reach the market.

At current Arxitra sales, our estimate is that Alchemia should generate a profit share of at least $23 million. On a fondaparinux market worth US$300 million, Alchemia's profit share should be at least $33 million in the USA, based on current exchange rates. This assumes a 20% price drop, capturing 40% of the fondaparinux market, and a 50-50 profit share with Dr Reddy's. (Note, Alchemia's profit share could reach as high as 60% based on sales

Cont'd over

volume, there could be only a 10% price drop, and Alchemia/Dr Reddy's could get as high as a 50% market share in the US).

The main risk at this stage is that the product will not be approved by regulators. We rate this as a low risk. The other risk is from a new Factor Xa inhibitor Xarelto (**Bayer**). While this drug will start to take away market share from the anticoagulant market – Bayer is forecasting peak sales of US$2 billion – it will be not happen immediately, and it will not all be smooth sailing, with previous concerns, albeit in a very small number of patients, regarding potential liver toxicity. And widespread adoption of the drug will take time. The market leader is Lovenox, which has a strong grip on its US$4 billion market. Xarelto will be reviewed by the FDA on March 19. It received approval in the second half of 2008 in Europe and Canada. We expect the anticoagulant market for injectable hospital use following surgery will be more difficult to break into whilst Xarelto will have stronger appeal for use at home.

The fondaparinux program has been in development for more than five years, even prior to the company's listing in 2003. The company is now very close to realising a return from that investment. Whether that return will be $5 million a year or $35 million a year remains to be determined by how the anticoagulant market will play out over the next decade.

Alchemia is capitalized at $37 million with $11 million in cash at the end of last year. We have upgraded our recommendation to a **Speculative Buy Class A**

Bioshares

Correction:
In Bioshares 302, the recommendation was ommitted from our discussion of Circadian (CIR).

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

Acrux – Don't Forget The Main Event

The problems Acrux (ACR: 45 cents) has been having with some of its development and marketing partners has blind-sighted investor attention away from the main game at Acrux, as far as future potential value is concerned. Sales of the company's first product on the market, Evamist (spray-on estradiol), have been slower to build than expected, tracking at around 50% of expected. The company selling that product, **KV Pharmaceutical,** has experienced major issues (see *Bioshares* 298) and future development programs with KV Pharmaceutical have been cancelled, as have programs with **Organon**, for unrelated reasons.

There is still the expectation at Acrux that original peak sales forecasts of Evamist (US$125 million) will be achieved although it will take longer. Currently Evamist script sales are around 2,500 per week, which translates to an estimated US$5.5 million in sales a year. By our estimates this translates to a royalty stream of only $500,000 a year to Acrux. Acrux has already received a number of royalty payments from KV, which are paid quarterly. This is nowhere near the expected $24 million in annual royalty income should the expected peak sales be achieved. However, growth in Evamist sales continues to be linear. The production shut down at KV Pharmaceutical does not affect Evamist, which is made under contract by a third party and KV remains committed to Evamist product.

However, the main game at Acrux, the product that is shaping up as holding the greatest potential for the Acrux delivery technology, is the male testosterone gel, which has been named Axiron. This week Acrux announced it had completed enrolment in its pivotal trial involving 150 men. The aim of the trial is to establish that Axiron can maintain testosterone levels within a normal range.

The trial is open label, which means results are not blinded. The first 60 men have completed treatment and the remainder will finish treatment within four months, allowing the company to report results in the third quarter of 2009. Acrux is expected to file an NDA in the last quarter of this year with the product to reach the market in the US in early 2011 if all goes well.

Acrux has been able to make very rapid progress with this program. There has already been strong interest in licensing when the company completed its Phase II trial. However Acrux decided it could keep more of the value if it finished development of Axiron on its own and either sell or license the product once an NDA has been filed.

The market for male testosterone is large and accessible. Global sales are estimated at US$1 billion a year, with about three quarters of that in the US and US$650 million in testosterone gels. The Acrux product could seek to achieve sales of US$300 million if it is well accepted. Market research conducted indicates that users (67%) and prescribing physicians (87%) overwhelmingly would use or offer the Axiron product.

The drawbacks with existing gels on the market is the volume of gel that needs to be applied over a large area on the upper torso, an unpleasant odour, the length of time to dry, and the risk of passing the gel on to others, including infants, through body contact. Axiron is applied to a much smaller area, under the arms, with an applicator, and has been designed with a 'pleasant smell'.

Value of Axiron

The overriding focus for Acrux, aside from completing the Phase III Axiron trial, is licensing or selling the product. At possible peak sales of US$300 million, the product could be sold outright for US$150 million - US$300 million. Alternatively it could be licensed, where Acrux could receive a sizeable payment well in excess of

Cont'd on page 4

Arana Produces Some Positive Phase II Psoriasis Results

Arana Therapeutics released the results of the Phase II trial of ART621 in psoriasis patients this week, following closely on the heels of a bid by US pharmaceutical firm Cephalon to acquire Arana for $1.40 per share, with a further 5 cents to follow if more than 90% of acceptances are received. Arana's two independent directors have recommended acceptance of the bid in the absence of a superior offer. Cephalon moved to take a pre-bid 19.8% stake in Arana, securing stock from Start-up Australia and Rockwell Securities.

The Phase II Psoriasis Trial

The Phase II trial of ART621, a modified antibody molecule, was designed to primarily study dosing and safety and secondarily explore efficacy, immunogenicity and pharmacokinetics. ART621 was delivered by subcutaneous injection, with three doses administered (0.5 mg/kg, 1 mg/kg or 2 mg/kg) in addition to a placebo. The study included 57 patients, typically suffering from psoriasis for 18-20 years. The treatment period lasted for 12 weeks, with doses administered on six occasions at fortnightly intervals. On the dosing front, ART621 was generally well tolerated, with two serious adverse events reported, both at the 1 mg/kg dose. The SAE's for these patients were a case of pneumonia and one case of an intentional antidepressant overdose.

For protein based drugs, the development of antibodies against the therapeutic antibody or protein is unwelcome, leading to a limiting of potential therapeutic effect. In the case ART621, no antibodies to ART621 were detected for up to four weeks after the last injection.

From an activity point of view, ART621 revealed a small degree of activity (not statistically significant) with four subjects in the ART621 group achieving greater than 50% reduction in their PASI scores (a measure of psoriasis severity).

Overall, the Phase II trials has delivered positive news for Arana, confirming that the drug candidate acts within reasonable safety parameters and there are good enough hints that the drug is biological active at a therapeutically useful level. How therapeutically useful is a task best left to the more important rheumatoid arthritis trial which is ongoing, as well as further potential Phase III trials. In our view this trial, was designed to deliver an early 'kill point' for the drug, based on the delivery of negative safety data and a clear sign of biological inactivity. However, the trial has delivered clear 'go ahead' signal.

Cephalon's exquisite timing

It would appear that Cephalon has exquisitely timed its bid for Arana and its most advanced and arguably attractive asset ART621, coming in just a few days prior to the release of important clinical data.

A continuing issue

A continuing issue for Arana shareholders is the behaviour of the independent directors in respect of their efforts to obtain a superior bid for Arana. Our view is that the offer is a low ball bid, valuing Arana on a technology or enterprise basis of US$44 million, and does not take into consideration the potential for ART621, the other products in development or other assets held by Arana.

We would argue that at the very least that Cephalon should increase its bid price, following the release of positive Phase II data for ART621.

A comparison of sorts can be made with the **Roche** bid for **Genentech** for the 44% Roche did not already own, which concluded this week with an offer accepted by the Genentech board of US$95 per share. The Genentech board, over an eight month period, worked the price up from an initial bid by Roche of US$89 per share. The Genentech board originally sought US$112 per share but came to the conclusion that a compromise price needed to be reached, no doubt influenced by falls. Another important factor to remember is that the Genentech board would have been mindful of is Roche's majority 56% shareholding.

Genentech's Independent Directors Went to Work

What stands out about the Genentech board is the strenuous efforts it went to argue for a higher price and the length of time (eight months) it spent on the task, with Genentech establishing a special committee of three independent directors to review the proposal in July 2008.

As an example, at a recent investor meeting the board showed a chart of the Roche product pipeline, of which the total number of projects in mid-to-late stage development was 78. However, if Genentech-managed projects were deleted the number fell to 21, suggesting that a greater source of significant future value was to be found in Genentech. The board also developed and presented updated and longer-range sales projections for Genentech products. Genentech forecast sales in the US would increase by 79% by 2015 (to US$17 billion) and that the company would deliver a 16% compound annual growth rate in earnings per share from 2010 to 2015. And to round it out, the Genentech CEO Art Levinson flagged as many as 15 new drug approvals on the books by 2015. (seehttp://www.gene.com/gene/ir/webcasts/2009_icm_slideaccess.html)

The Genentech independent directors obtained an additional $6 per share for minority shareholders, which equates to a firm-level figure of US$6.3 billion.

As yet, to our knowledge, no arguments have been put forward by the independent directors of Arana that support a higher price than that offered by Cephalon. It is also worth noting that there are very few synergies between the Arana and Cephalon businesses. Cephalon is predominantly a small molecule company focusing on the areas of cancer, pain and CNS disorders. This would suggest that Cephalon is acquiring Arana purely for the standalone value of the company and potential of the Arana business.

Bioshares recommendation: **Reject the offer**

Bioshares

Acrux - from page 2

US$20 million (on approval of product) plus a royalty from sales as high as 25%.

Of interest to note is that KV Pharmaceutical acquired Evamist from Vivus for US$10 million up front with a further US$140 million paid once the product was approved in the US, with KV still required to maintain the royalty obligation to Acrux.

Easier sell than Evamist

It is expected the appeal of Axiron will make it an easier sell to end users than Evamist. Whilst Evamist has been successful in winning a high number of new users of HRT products, it has been more difficult to convert existing HRT product users. The product advantages of Axiron will assist breaking into the existing male testosterone market.

Is Acrux an acquisition target?

Acrux is currently valued by the market at a fraction of the potential value of this product. So might we see an opportunistic fire-sale offer for Acrux at a 70% premium, which translates to $122 million ($77 cents a share)? For that to happen, two of Acrux's major shareholders, **Orbis Funds Management** group and **Walker Group Holdings**, which own around 30% of the company, would need to sell. Both groups bought into Acrux at an estimated average price of between 90 cents a share to $1.00 a share. It is unlikely these groups will be forced sellers and at this stage the company appears to be secure from predatory suitors at less than $1.50 a share.

Share price weakness

Much of the selling over recent months in Acrux has come from **Queensland Investment Corporation**, not known for its delicate disposal of its biotech investments. The fund has sold most of its 10.7 million shares, much of it on market, since October last year. This should remove the overhang in the stock and may see some buying support from now.

Acrux is well funded with $25 million in cash at the end of last year. A steady stream of income can be expected now from milestone and royalty payments from sales of Evamist (KV Pharmaceutical and from other future partners outside of the US), animal health products (Eli Lilly), and from an Axiron licensing deal or product sale. It is offering exceptional value to investors. Acrux is capitalised at $72 million.

Bioshares recommendation: **Speculative Buy Class A**

Bioshares

Bioshares Model Portfolio (13 March 2009)

Company	Price (current)	Price added to portfolio	Date added
ASDM	$0.35	$0.30	December 2008
QRxPharma	$0.24	$0.25	December 2008
Hexima	$0.36	$0.60	October 2008
Atcor Medical	$0.17	$0.10	October 2008
CathRx	$0.37	$0.70	October 2008
Impedimed	$0.70	$0.70	August 2008
Mesoblast	$0.80	$1.25	August 2008
Cellestis	$1.90	$2.27	April 2008
IDT	$1.55	$1.90	March 2008
Circadian Technologies	$0.60	$1.03	February 2008
Patrys	$0.03	$0.50	December 2007
Bionomics	$0.21	$0.42	December 2007
Cogstate	$0.22	$0.13	November 2007
Sirtex Medical	$2.20	$3.90	October 2007
Clinuvel Pharmaceuticals	$0.20	$0.66	September 2007
Starpharma Holdings	$0.19	$0.37	August 2007
Pharmaxis	$1.40	$3.15	August 2007
Universal Biosensors	$0.44	$1.23	June 2007
Biota Holdings	$0.56	$1.55	March 2007
Probiotec	$1.42	$1.12	February 2007
Peplin Inc	$0.59	$0.83	January 2007
Arana Therapeutics	$1.43	$1.31	October 2006
Chemgenex Pharma.	$0.44	$0.38	June 2006
Cytopia	$0.10	$0.46	June 2005
Acrux	$0.45	$0.83	November 2004
Alchemia	$0.23	$0.67	May 2004

Portfolio Changes – 13 March 2009

IN:
No changes

OUT:
No changes

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
Sell

Corporate Subscribers: Pharmaxis, Cytopia, Arana Therapeutics, Starpharma Holdings, Cogstate, Xceed Biotechnology, Optiscan Imaging, Bionomics, ChemGenex Pharmaceuticals, Circadian Technologies, Biota Holdings, Stem Cell Sciences, Halcygen Pharmaceuticals, Peplin, BioMD, Impedimed, QRxPharma, Patrys, Labtech Systems, Hexima, Tyrian Diagnostics, Mesoblast, Atcor Medical

Subscription Rates (inc. GST)

48 issues per year (electronic distribution): **$320**

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